Health effects of nutrient intake from supplements during pregnancy

No. 2021/26-A3e, 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

In this background document, the current state of scientific knowledge is presented on the relation between nutrient intake from supplements 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 had been summarised in a systematic review. These specific conclusions are not recommendations; recommendations for pregnant women will be formulated in the advisory report.

The committee carried out systematic literature searches in PubMed to retrieve systematic reviews (with or without meta-analysis) on a priori selected exposures (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, publications missed by the search but known by the committee could be added. Also, a public consultation round took place in the autumn of 2019 asking explicitly for potentially missed publications. The committee, therefore, considers that it is reasonable to assume that the relevant publications until the autumn of 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*.[1]

The focus is on health effects. Intermediary measures of health (such as maternal blood pressure or head circumference of the infant) 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.

For some topics described in this background document, the available research has (almost) exclusively been carried out in low and middle-income countries, with too little research from high-income countries. This restriction was specified in conclusions with limited or strong evidence, but not specified if the committee concluded that there was too little research or that the findings were contradictory or inconclusive.

02
folic acid

This chapter describes the scientific evidence from systematic reviews of cohort studies and a few intervention studies on the relation between folic acid supplementation before and during pregnancy and the risk of perinatal mortality, congenital anomalies, twinning, preterm birth, an infant that is small for gestational age, pre-eclampsia, asthma in the offspring, wheezing in the offspring and autism in the offspring. For these outcomes, at least two cohort studies or two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies or two intervention studies.

2.1 Foetal loss, miscarriage and stillbirth

Summary: Folic acid supplementation and the risk of foetal loss, miscarriage and stillbirth.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[2]
Heterogeneity	Yes, for miscarriages.
Strength of the effect	Foetal loss RR = 1.00 (95%CI 0.75-1.24), more than 100 cases Miscarriage RR = 0.99 (95%CI 0.72-1.38), more than 100 cases Stillbirth RR = 1.03 (95%CI 0.51-2.09)
Study population	Pregnant women either or not giving previously birth to a child with a neural tube defect.

Conclusion 1:

Based on RCTs, an effect of periconceptional folic acid supplementation on the risk of foetal loss and miscarriage is unlikely.

Conclusion 2 (RCTs):

There is too little research to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of stillbirth.

Explanation

The committee found one systematic review by Balogun et al. (2016) of three RCTs on the effect of the use of folic acid with and without multivitamins on the risk of foetal loss, miscarriages and stillbirth and one systematic review of one RCT focusing only on the risk of stillbirth (Table 1).[2,3] As the one RCT described by Imdad et al. (2011) on stillbirth was also included in the meta-analysis by Balogun et al. (2016) together with two other RCTs, the committee describes the results from the meta-analysis by Balogun et al. (2016) (Table 1).[2] The committee did not find any more recent RCTs on folic acid supplementation and the risk of miscarriage, stillbirth and foetal loss.

Balogun et al. (2016) found no indications for an effect of folic acid supplementation on the risk of foetal loss, miscarriage and stillbirth. There was considerable heterogeneity in the effect on miscarriage, which was reduced when the trial including women previously giving birth to a child with a neural tube defect was excluded. This exclusion did not change the conclusion of the meta-analysis. The number of cases of stillbirth was small (31 in total), which limits the interpretation of this finding.[2]

The number of RCTs on the effect on miscarriage was only three, however, the number of cases in the meta-analysis was large (substantially higher than 100) and the relative risks for foetal loss and miscarriage were very close to one (relative risks were 0.99 and 1.00). Therefore, the committee concludes that an effect of periconceptional folic acid supplementation on the risk of foetal loss and miscarriage is unlikely. In view of the fact that the number of cases of stillbirth was small, the committee concludes that there is too little research to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of stillbirth.

Table 1. Results from the meta-analysis of Balogun et al. (2016) on the effect of 0.9 to 4 milligram / day folic acid with multivitamins versus trace element or placebo, supplemented prior to conception, periconceptional or during pregnancy on the risk of foetal loss, early or late miscarriage, and stillbirth.

Outcome	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
Foetal loss	3	368 / 3,511	324 / 3,372	1.00 (0.75-1.24)	46%
Early or late miscarriage	3	352 / 3,511	309 / 3,372	0.99 (0.72-1.38)	52%
Stillbirth	3	16 / 3,511	15 / 3,372	1.03 (0.51-2.09)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

2.2 Congenital anomalies

2.2.1 Neural tube defects

There is international scientific consensus on the conclusion that periconceptional folic acid supplementation of 0.4 milligram per day reduces the risk of neural tube defects. The committee considers this to be strong evidence.

The Health Council of the Netherlands concluded in 1993 that the use of folic acid from at least four weeks before until eight weeks after conception reduces the risk of neural tube defects by at least 50 percent.[4] This effect estimate was used by the Health Council in 2008 in another advisory report on policy options to ensure the optimal use of folic acid.[5] The conclusions in the 1993 report were based on risk reductions in one RCT, one cohort and several case-control studies preceding the RCT. The single RCT was initiated by Czeizel et al. (1994) in Hungary in 1984. They reported an odds ratio (OR) for neural tube defects of 0.13 (95%CI 0.03 to 0.65) in women receiving a vitamin supplement containing 0.8 milligram per day folic acid as compared with a trace element supplement. The multivitamin provided 12 other vitamins than folic acid, four minerals, and three trace elements. The trace element supplement provided the same three trace elements and a low dose of vitamin C.[6] Based on this RCT, it cannot be ruled out that the other vitamins influenced the finding. However, the association between folic acid supplementation and a lower risk of neural tube defects has been replicated in other studies. Furthermore, there is international

scientific agreement on the conclusion that periconceptional folic acid supplementation reduces the risk of neural tube defects.

The dosage advice of 0.4 milligram folic acid per day was based on the cohort and case-control studies.[4] After the publication of the RCT by Czeizel et al. (1994), the conduction of further RCTs was considered ethically irresponsible because of the clear benefits of folic acid supplementation.[7]

A recent systematic review by the U.S. Preventive Taskforce Services (2017) describes a Hungarian cohort study (publication by Czeizel et al., 2004) in combination with an American cohort study (publications by Milunsky et al., 1989 and Moore et al., 2003). In the Hungarian study, an RR of 0.11 (95%CI 0.01 to 0.91) was found for the use of a multivitamin supplement with 0.8 milligram folic acid per day. The American study reported a RR of 0.27 (95%CI 0.11 to 0.63) for the use of a multivitamin supplement providing 0.1 to 1.0 milligram folic acid per day in the first six weeks of pregnancy compared with no supplement use or use of multivitamins not containing folic acid in weeks seven and beyond. According to the U.S. Preventive Taskforce Services, no new RCTs or cohort studies on neural tube defects have been conducted since 1998 in developed countries.[7] In other countries, like China, cohort studies have been conducted (e.g. Berry et al., 1999). In line with earlier studies, Berry et al. (1999) found that periconceptional intake of 0.4 milligram per day is associated with a lower risk of neural tube defects.[8]

Therefore, the committee did not carry out additional literature searches on folic acid and neural tube defects. The committee subscribes to the earlier conclusion of the Health Council of the Netherlands from 1993 and considers that there is international scientific consensus on the conclusion that periconceptional folic acid supplementation of 0.4 milligram per day reduces the risk of neural tube defects. The committee considers this to be strong evidence.

2.2.2 Congenital anomalies in general (other than neural tube defects)

Summary: Folic acid supplementation and the risk of congenital anomalies in general (other than neural tube defects).

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs.[2]
Heterogeneity	No
Strength of the effect	RR = 1.69 (95%CI 0.81-3.53)
Study population	Pregnant women either or not giving previously birth to a child with a neural tube defect.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of periconceptional folic acid supplementation on congenital anomalies other than neural tube defects.

Explanation

The Health Council of the Netherlands concluded in 2008 that there was evidence from case-control studies, but not from cohort studies or RCTs, that additional folic acid is associated with a lower risk of congenital abnormalities other than neural tube defects.[5] Opposite to 2008, the current committee bases its conclusions in this background document on prospective studies only.

The committee found one systematic review of two RCTs on folic acid plus multivitamins compared with no folic acid or multivitamins (Table 2).[2]

In the Hungarian RCT, a vitamin supplement containing 0.8 milligram per day folic acid was compared with a trace element supplement.[6]
In the British RCT, a multivitamin with folic acid was compared with a multivitamin without folic acid and placebo in women who had a previous pregnancy affected by a neural tube defect.[9] Neither RCT found a significant effect and confidence intervals were broad due to the small number of cases in the two trials (19 cases in the folic acid group and 12 cases in the control group).

In view of the small number of studies and cases, the committee concludes that there is too little research from RCTs to draw a conclusion on the effect of periconceptional folic acid supplementation on congenital malformations other than neural tube defects.

Table 2. Results of the meta-analysis of Balogun et al. (2016) on the effect of folic acid supplementation on the risk of congenital anomalies in general (other than neural tube defects).

Intervention	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
0.8 milligram / day folic acid with multi-vitamins[a]	Multivitamin without folic acid, placebo or trace elements	Peri-conceptional	2	19 / 2,932	11 / 2,845	1.69 (0.81-3.53)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).
[a] In the British study, the amount of folic acid was not specified.

2.2.3 Congenital cardiovascular defects

Summary: Folic acid supplementation and the risk of congenital cardiovascular defects.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[10]
Heterogeneity	No
Strength of the effect	RR = 0.57 (95%CI 0.24-1.33)
Study population	Pregnant women either or not giving previously birth to a child with a neural tube defect.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of congenital cardiovascular defects.

Explanation

There are two systematic reviews of prospective studies on the effect of periconceptional use of folic acid supplements and the risk of congenital cardiovascular defects.[10,11] De-Regil et al. (2015) summarised three RCTs.[10] One of these RCTs is also summarised in the systematic review by Feng et al. (2015) in combination with one cohort study and 16 case-control studies.[11] They found a statistically significant association with a reduced risk of congenital cardiovascular defects in their meta-analysis (RR 0.72; 95%CI 0.63-0.82). However, exploring case-control studies is outside of the scope of this advisory report. As De-Regil et al. (2015) performed a meta-analysis of the RCTs, the committee focuses on this publication (Table 3).

De-Regil et al. (2015) found a lower but statistically non-significant effect of folic acid supplementation in the periconceptional period on the risk of congenital cardiovascular defects. The number of cases was small.

In view of the small number of cases, the committee concludes that there is too little research from RCTs to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of congenital cardiovascular defects.

Table 3. Results of the meta-analysis of De-Regil et al. (2015) on the effect of periconceptional folic acid supplementation on the risk of congenital cardiovascular defects.

Intervention	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
0.4, 0.8 or 4.0 milligram / day folic acid	no intervention, placebo or trace elements	Peri-conceptional	3	8 / 2,869	14 / 2,743	0.57 (0.24-1.33)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

2.2.4 Oral clefts

Intervention studies

Summary: Folic acid supplementation and the risk of oral clefts.

Aspect	Explanation
Selected studies	Cleft palate: One meta-analysis of three RCTs.[10] Cleft lip: One meta-analysis of three RCTs.[10]
Heterogeneity	No
Strength of the effect	Cleft palate: RR = 0.73 (95%CI 0.05-10.89) Cleft lip: RR = 0.79 (95%CI 0.14-4.36)
Study population	Pregnant women either or not giving previously birth to a child with a neural tube defect.

Conclusion (RCTs):

There is too little research from RCTs to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of oral clefts.

Explanation

The committee found one systematic review summarising RCTs on the use of periconceptional folic acid supplements and the risk of oral clefts (Table 4).[10]

De Regil et al. (2015) described two RCTs in which three babies in total were affected with cleft palate and one trial in which no cleft palates occurred. In addition, they summarised three trials on cleft lips. Two in which eight babies in total had a cleft lip (four in the treatment group and four in the control group) and one trial in which no cleft lips occurred.

In view of the small number of cases, the committee concludes that there is too little research from RCTs to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of oral clefts.

Table 4. Results from the meta-analysis of De-Regil et al. (2015) on the effect of periconceptional folic acid supplementation (0.4, 0.8 or 4.0 milligram / day) versus no use and the risk of oral clefts.

Outcome	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
Cleft palate	3 (2 with cases)	1 / 2,869	2 / 2,743	0.73 (0.05-10.89)	33%
Cleft lip	3 (2 with cases)	4 / 2,869	4 / 2,743	0.79 (0.14-4.36)	21%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Cohort studies

Summary: Folic acid supplementation and the risk of oral clefts.

Aspect	Explanation
Selected studies	One meta-analysis of five cohort studies[12], one additional cohort study[13] and one additional registry study.[14]
Heterogeneity	No
Strength of the association	Meta-analysis: RR = 0.76 (0.63-0.90)[12]
Study population	Europe, North America, and Asia.

Conclusion:

Based on cohort studies, periconceptional use of folic acid supplements is associated with a lower risk of oral clefts.

Level of evidence: Limited.

Explanation

In the initial literature search, there were two systematic reviews of cohort studies on the association between the use of folic acid supplements and the risk of oral clefts.[15,16] Johnson and Little (2008) combined case-control studies and cohort studies, but did not provide separate estimates for cohort studies, and therefore is not further considered.[16] Badonivac et al. (2007) summarised four cohort studies and one RCT on the use of folic acid supplements or multivitamins containing folic acid.[15] Therefore, the committee describes the findings by Badonivac et al. (2007) below (Table 5a). The authors show a non-significant lower risk of oral clefts; none of the individual studies showed a significant association. Heterogeneity was

not significant. However, the meta-analysis is limited by the small number of cases.

The committee found one additional prospective study and one registry study published after the meta-analysis of Badonivac et al. (2007) (Table 5b).[13,14]

In a case-cohort study on the Danish National Birth Cohort, Bille et al. (2007) found a non-significant association between use of folic acid supplements in the first term of pregnancy and a lower risk of oral clefts (RR=0.72); for lower doses, the risk estimate was not significant either and close to 1.00 (RR=0.95).[13]

The committee also found one registry study. Gildestad et al. (2015) used data of the Norwegian Medical Birth Registry on all births in Norway. 21.5% of the women reported use of folic acid or multivitamins supplements containing folic acid before pregnancy. There was no significant association between the use before conception and during pregnancy of supplements containing 400 microgram of folic acid and/or multivitamins supplements (generally containing up to 200 micrograms folic acid) and the risk of oral clefts (RR = 0.90).[14]

Table 5a. Results from the meta-analysis of Badonivac et al. (2007) on the association between folic acid supplementation versus no use and the risk of oral clefts.

Timing exposure	N cohorts	n exposure	n control	N participants	RR estimate (95%CI)	Heterogeneity I^2
During pregnancy	5[a]	18	109	10,709	0.60 (0.35-1.04)	n.s.[b]

CI: confidence interval; N: number; n: number of cases; n.s.: not significant; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Four cohort studies and one RCT. [b] Q-test.

Table 5b. Results from the additional Danish National Birth Cohort study by Bille et al. (2007) and Norwegian registry study Gildestad et al. (2012) on the association between folic acid supplementation versus no use and the risk of oral clefts.

Cohort name	Exposure	Timing exposure	n / N exposure	n / N control	RR estimate (95%CI)
Danish National Birth Cohort[13]	≥ 400 microgram / day folic acid	First trimester	28 / 148	81 / 508[a]	0.72 (0.46-1.22)
Danish National Birth Cohort[13]	1-399 microgram / day folic acid	First trimester	83 / 360	81 / 508[a]	0.95 (0.66-1.35)
Medical Birth Registry Norway[14]	400 microgram / day folic acid and / or multi-vitamins, most with 0-200 microgram / day folic acid	95% before conception and during pregnancy, 5% only before conception	328 / 189,217	742 / 380,273	0.90 (0.79-1.04)
Medical Birth Registry Norway[14]	400 microgram / day folic acid and / or multi-vitamins, most with 0-200 microgram / day folic acid	During pregnancy only	558 / 311,078	742 / 380,273	0.93 (0.83-1.05)

CI: confidence interval; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Case cohort study, 192 cases and 828 controls.

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One more recent meta-analysis was found on cohort studies: Jahanbin et al. (2018), presented in Table 5c.[12] They included the six cohort studies. All four cohort studies from the meta-analysis of Badonivac et al. (2007) were included, but not the RCT included in that meta-analysis. Jahanbin et al. (2018) added one small case-cohort study from Hungary and one very large cohort study from China (89% of all participants and 86% of all cases in the meta-analysis were from this study; the study had seven of a maximum of nine quality points). Jahanbin et al. (2018) found that daily use of 400 microgram folic acid (either alone or as a multiple micronutrient supplement containing folic acid) starting before conception was associated with a statistically significant lower risk of oral clefts (RR = 0.76, 95%CI 0.63-0.90).[12]

The additional studies presented in Table 5b were not included in the meta-analysis by Jahanbin et al. (2018). The risk estimate of the additional cohort study (RR=0.72) was close to the risk estimate in the meta-analysis (RR=0.76). The estimate from the registry study was somewhat higher, but also below 1.00 (RR=0.90). Therefore, the committee assumes that addition of these results to the meta-analysis of Jahanbin et al. (2018) would not have changed the statistical significance of the meta-analysis.

Table 5c. Results from the meta-analysis of Jahanbin et al. (2018) of cohort studies (including case-cohort studies) on the association between folic acid supplementation versus no use and the risk of oral clefts.

Timing exposure	N cohorts	n exposure	n control	N participants	RR estimate (95%CI)	Heterogeneity I^2
During pregnancy	6	111	318	78,235	0.76 (0.63-0.90)	0%

CI: confidence interval; N: number; n: number of cases; n.s.: not significant; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

The risk estimates in the most recent meta-analysis as well as the additional cohort study and registry study are consistent and the findings in the meta-analysis are statistically significant. There was no heterogeneity. The committee concludes that periconceptional folic acid supplementation is associated with a lower risk of oral clefts. The committee judges the evidence to be limited, because of: (1) the very large impact of one study on the meta-analysis by Jahanbin et al. (2018), and (2) the fact that this study was the only study from a non-western country, which may limit the applicability for the situation in the Netherlands.

2.3 Twinning

Conclusion (cohort studies and RCTs):

There is too little research to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of twinning.

Explanation

In 2008, the Health Council of the Netherlands concluded that periconceptional folic acid supplement use may be associated with a higher risk of bearing dizygotic twins (RR = 1.26; 95%CI 0.91-1.73), but not with overall twinning (RR = 1.02; 95%CI 0.85-1.24).[5,17] This suggestion was based on a systematic review of one prospective and five retrospective cohort studies.[17] As the current committee bases its conclusions on cohort studies in which folic acid supplement use is assessed before the outcome is measured, it re-evaluates this conclusion.

In a recent systematic review of the U.S. Preventive Services Taskforce, the same prospective cohort study is described in combination with one RCT.[7] Neither study found evidence of a statistically significant higher risk of twinning. After adjustment for maternal age, parity, and in vitro fertilization, an OR of twinning of 1.04 (95%CI 0.91-1.18) was found in the cohort study for use of a folic acid supplement.[18] In the RCT, an OR of 1.40 (95%CI 0.89-2.21) was found for twin gestations in the multivitamin group with folic acid as compared with the trace element group.[19] However, in addition to folic acid, the multivitamin provided 12 other vitamins, four minerals, and three trace elements in this RCT. Therefore, it cannot be ruled out that the other vitamins influenced the findings. The proportion of twin births (as opposed to pregnancies) was higher in the multivitamin group (OR 1.41; 95%CI 1.03-1.96). The trial found no difference in twinning between the two groups in a subgroup analysis of women receiving fertility drugs.[19]

In summary, there is too little research to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of twinning.

2.4 Preterm birth

2.4.1 Intervention studies

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of preterm birth.

Explanation

There are two systematic reviews of RCTs on the effect of periconceptional folic acid supplementation on the risk of preterm birth (< 37 weeks).[20,21] A Cochrane review by Lassi et al. (2013) did not find any RCTs reporting preterm birth, whereas Saccone et al. (2016) reported the findings of one RCT.[20,21] In this Nepalese RCT 929 women who received 0.4 milligram folic acid per day and 1,000 microgram RE vitamin A had a similar rate of preterm birth compared with 1,037 women who received 1,000 microgram RE vitamin A (22.6% versus 22.9%; RR = 0.99; 95%CI 0.82-1.18).[22]

In summary, there is too little research from RCTs to draw a conclusion on the effect of periconceptional folic acid supplementation on the risk of preterm birth.

2.4.2 Cohort studies

Summary: Folic acid supplementation and the risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of seven cohort studies[23], and four more recent cohort studies.[24-27]
Heterogeneity	No
Strength of the association	RR = 0.84 (95%CI 0.74-0.96)[23]
Study population	Europe, North America, and Asia.

Conclusion:

Periconceptional supplementation of 0.2 to 1.0 milligram folic acid per day is associated with a 16% (95%CI: 4-26%) lower risk of preterm birth in cohort studies.

Level of evidence: Strong

Explanation

There are two systematic reviews of the association between the periconceptional use of folic acid supplements and the risk of preterm birth.[23,28] Mantovani et al. (2014) summarised five cohort studies in a systematic review without meta-analysis. Zhang et al. (2017) summarised seven cohort studies in a meta-analysis. Three studies are described in both reviews. Because Zhang et al. (2017) provide a quantitative risk estimate, the committee describes their results below (Table 6a). Additionally, the remaining cohort studies from Mantovani et al. (2014) in combination with three more recent cohort studies are discussed (Table 6b).[24-27]

Zhang et al. (2017) showed that the use of folic acid supplements before or after conception is associated with a reduced risk of preterm birth. There was moderate heterogeneity in the size of the effect, and no heterogeneity in the direction. Heterogeneity was partly explained by the timing of the use of folic acid. The association was stronger in two studies with postconceptional use than in five studies with preconceptional use. However, as the number of cases in the postconceptional folic acid use studies is limited, the committee considers this an insufficient basis for drawing conclusions.[23]

The committee only included one out of the two additional cohort studies from the systematic review by Mantovani et al. (2014), as the other one did not report on the dose of folic acid. In the included study by Timmermans et al. (2009) a non-significant protective association was found in Dutch women using 0.4 or 0.5 milligram folic acid per day.[24]

There are three more recent prospective cohort studies.[25-27]

Two Chinese cohort studies show an association between periconceptional use of folic acid and a lower risk of preterm birth. The associations were stronger for preconceptional folic acid supplement use than for postconceptional folic acid use.[26,27]

A more recent American cohort study did not find a significant association comparing more than 0.2 milligram folic acid per day with less than 0.2 milligram folic acid per day. Differences with the other cohort studies are not only related to the fact that part of the women in the control group used supplements providing a low dose of folic acid, but also to the fact that folic acid intake in the American cohort was relatively high due to folic acid fortification.

Two cohort studies carried out additional analyses in BMI subgroups, showing that the protective effect of folic acid supplementation was reduced in women with overweight or obesity.[25,27] However, the number of cases in the subgroup analyses was small, which limits the interpretation of these findings.

In conclusion, periconceptional supplementation of 0.2 to 1.0 milligram folic acid per day is associated with a 16% lower risk of preterm birth in cohort studies. In view of the consistent findings and the fact that more recent cohort studies show associations in the same direction, the committee judges the evidence as strong.

Table 6a. Results of the meta-analysis of Zhang et al. (2017) on the association between periconceptional folic acid supplementation versus no use and the risk of preterm birth.

Exposure	Timing exposure	N cohorts	n / N exposure	n / N control	RR estimate (95%CI)	Heterogeneity I^2
0.2-1.0 milligram / day folic acid	Pre- and postconceptional	7	1,364 / 23,016	1,730 / 21,803	0.84 (0.74-0.96)	44%
0.2-1.0 milligram / day folic acid	Preconceptional	5	1,090 / 19,606	1,648 / 21,228	0.89 (0.80-1.01)	n.r.
0.2-1.0 milligram / day folic acid	Postconceptional	2	274 / 3,410	82 / 575	0.68 (0.52-0.90)	n.r.
> 1 milligram / day folic acid	Pre- and postconceptional	2	1,645 / 21,634	1,818 / 16,334	0.67 (0.63-0.72)	n.r.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Table 6b. Results from the four additional cohort studies on the association between periconceptional folic acid supplementation and the risk of preterm birth.

Cohort name	Exposure	Control	Timing exposure	n / N exposure	n / N control	RR estimate (95%CI)
Generation R[24]	0.4-0.5 milligram / day folic acid	No use	Periconceptional	n.r. [a] / 2,493	n.r. / 1,877	0.75 (0.55-1.02)
Generation R[24]	0.4-0.5 milligram / day folic acid	No use	Start before 8 weeks gestation	n.r. / 1,983	n.r. / 1,877	0.88 (0.63-1.21)
Asthma in Pregnancy Study & Nutrition in Pregnancy Study[25]	> 0.2 milligram / day folic acid	< 0.2 milligram / day folic acid	Month before conception	n.r. / 1,590	n.r. / 2,057	0.90 (0.60-1.10)
Asthma in Pregnancy Study & Nutrition in Pregnancy Study[25]	> 0.2 milligram / day folic acid	< 0.2 milligram / day folic acid	First trimester overall	n.r. / 346	n.r. / 3,301	1.30 (0.90-1.80)
Preconception care service cohort[27]	0.4 milligram / day folic acid	No use	Periconceptional	n.r.[b]	n.r.	0.60 (0.57-0.63) for normal weight 0.57 (0.51-0.64) for underweight 0.85 (0.73-0.98) for overweight 0.77 (0.65-0.91) for obese
Jiaxing Birth Cohort[26]	0.4 milligram / day folic acid	No use	Periconceptional	1,979 / 57,634	6,065 / 173,545	0.95 (0.90-1.01)
Jiaxing Birth Cohort[26]	0.4 milligram / day folic acid	No use	Preconceptional	843 / 25,260	6,065 / 173,545	0.92 (0.85-1.00)
Jiaxing Birth Cohort[26]	0.4 milligram / day folic acid	No use	Postconceptional	1,136 / 32,374	6,065 / 173,545	0.97 (0.91-1.04)

CI: confidence interval; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk. [a] The total number of cases was 128. [b] Total number of women was 172,206.

2.5 Small for gestational age

Summary: Folic acid supplementation and the risk of small-for-gestational-age infants.

Aspect	Explanation
Selected studies	One meta-analysis of six cohort studies[23] and five more recent cohort studies.[24-26,29,30]
Heterogeneity	No
Strength of the association	RR = 0.76 (95%CI 0.63-0.91)[23]
Study population	Europe, North America, and Asia.

Conclusion:

Periconceptional supplementation with 0.2 to 1 milligram folic acid per day is associated with a 24% (95%CI: 9-37%) lower risk of small-for-gestational-age infants in cohort studies.

Level of evidence: Strong.

Explanation

There are two systematic reviews of prospective and retrospective cohort studies on the association between periconceptional folic acid use and the risk of small-for-gestational-age infants.[23,31] Hodgetts et al. (2015) narratively reviewed three cohort studies. As these studies were combined

with three other cohort studies in the meta-analysis by Zhang et al. (2017), the committee focuses on the findings of Zhang et al. (2017) (Table 7a). Two of the cohort studies were prospective cohort studies and the other four retrospective according to Zhang et al. (2017). In the studies, folic acid supplementation was reported before birth in five out of six cohort studies. Small for gestational age was defined as below the 10th percentile in five cohort studies and two standard deviations below the mean of foetal growth curves in one study.

Zhang et al. (2017) showed that both pre and postconceptional folic acid supplement use is associated with a lower risk of small-for-gestational-age infants in six cohort studies. The association was independent of the starting moment of supplementation. The authors did not provide heterogeneity estimates for this analysis. However, the variation in risk estimates for small for gestational age is rather similar to preterm birth on the basis of visual inspection. Therefore, the committee assumes that heterogeneity is moderate, as was the case for preterm birth.[23]

In an additional analysis of three cohort studies in which small for gestational age was also defined as smaller than the 5th percentile instead of the 10th percentile, a similar association was found as in the overall analysis. Heterogeneity was considerable, but could not be further explored due to the small number of studies.

Five prospective cohort studies were not included in the meta-analysis by Zhang et al. (2017) (Table 7b).[24-26,29,30] In general, they indicate that periconceptional use of folic acid supplements is associated with a lower risk of small-for-gestational-age infants. Timmermans et al. (2009) showed that use of 0.4 or 0.5 milligram folic acid per day from at least four weeks before conception versus no use is associated with a 60% lower risk of small-for-gestational-age infants, whereas the association for starting within the first eight weeks of pregnancy was not significant (RR = 0.69).[24] Two Chinese cohort studies also found an association between periconceptional folic acid use and a lower risk of small-for-gestational-age infants.[26,30] One of the two cohort studies also looked into the timing of folic acid supplement use: the association was stronger for preconceptional use than for postconceptional use.[26] A third Chinese cohort study did not find any significant association of folic acid use in the second or third term of pregnancy. However, the confidence intervals around the estimates were broad, which limits the interpretation of this finding.[29] An American study found no significant association either, which might have to do with the fact that more than 0.2 milligram folic acid per day was compared with less than 0.2 milligram folic acid per day and the fact that American women have a high intake of folic acid from fortified products.[25] In the other studies, comparisons were made with no folic acid supplement use or conducted in countries in which no mandatory fortification is in place. In conclusion, periconceptional supplementation with 0.2 to 1 milligram folic acid per day is associated with a 24% (95%CI: 9-37%) lower risk of

small-for-gestational-age infants in cohort studies. In view of the large number of studies and the consistent findings, the committee judges the evidence as strong.

Table 7a. Results from the meta-analysis of Zhang et al. (2017) on the association between the exposure to 0.2 to 1 milligram folic acid supplementation versus no use and the risk of small-for-gestational-age infants.

N cohorts	Timing of exposure	Outcome[a]	n / N exposure	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
6	Pre- and postconceptional	Birth weight under P10	4,108 / 34,341	5,729 / 37,541	0.76 (0.63-0.91)	n.r.
5	Preconceptional	Birth weight under P10	911 / 9,998	2,983 / 19,988	0.70 (0.57-0.85)	n.r.
3	Postconceptional	Birth weight under P10	3,197 / 24,343	2,746 / 17,553	0.84 (0.81-0.89)	n.r.
3	Pre- and postconceptional	Birth weight under P5	2,252 / 45,222	2,009 / 28,986	0.74 (0.65-0.84)	62%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] P10 and P5: 10th and 5th percentile.

Table 7b. Results from the five additional cohort studies on the association between periconceptional folic acid supplementation and the risk of small-for-gestational-age infants.

Cohort name	Exposure	Control	Timing of exposure	n / N exposure	n / N control	RR estimate (95%CI)
Generation R[24]	0.4-0.5 milligram / day folic acid	No use	Pre-conception start	n.r.[a] / 2,493	n.r. / 1,877	0.40 (0.22-0.72)
Generation R[24]	0.4-0.5 milligram / day folic acid	No use	Start before 8 weeks gestation	n.r. / 1,983	n.r. / 1,877	0.69 (0.42-1.14)
Asthma in Pregnancy Study & Nutrition in Pregnancy Study[25]	> 0.2 milligram / day folic acid	< 0.2 milligram / day folic acid	Month before conception	n.r. / 1,590	n.r. / 2,057	1.10 (0.80-1.40)
Asthma in Pregnancy Study & Nutrition in Pregnancy Study[25]	> 0.2 milligram / day folic acid	< 0.2 milligram / day folic acid	First trimester overall	n.r./ 346	n.r. / 3,301	1.30 (0.80-2.10)
Ma'anshan-Anhui Birth Cohort[29]	0.4 milligram / day folic acid	No use	Second trimester and not third trimester	n.r. / 109	n.r. / 2,181	0.55 (0.23-1.27)
Ma'anshan-Anhui Birth Cohort[29]	0.4 milligram / day folic acid	No use	Third trimester and not second trimester	n.r. / 223	n.r. / 2,181	0.77 (0.45-1.29)
Ma'anshan-Anhui Birth Cohort[29]	0.4 milligram / day folic acid	No use	Second and third trimester	n.r. / 131	n.r. / 2,181	0.90 (0.48-1.70)
Jiaxing Birth Cohort[26]	0.4 milligram / day folic acid	No use	Periconceptional	4,975 / 57,634	16,290 / 173,545	0.89 (0.80-1.00)
Jiaxing Birth Cohort[26]	0.4 milligram / day folic acid	No use	Preconceptional	2,165 / 25,260	16,290 / 173,545	0.81 (0.70-0.95)
Jiaxing Birth Cohort[26]	0.4 milligram / day folic acid	No use	Postconceptional	2,810 / 32,374	16,290 / 173,545	0.95 (0.83-1.09)
Cohort South China[30]	0.4 milligram / day folic acid	No use	Periconceptional	6,030 / 105,238	5,626 / 95,351	0.93 (0.89-0.96)

CI: confidence interval; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] The total number of cases was 128.

2.6 Pre-eclampsia

Summary: Folic acid supplementation and the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	One meta-analysis of eight cohort studies[32] and three more recent cohort studies.[25,33,34]
Heterogeneity	Yes
Strength of the association	RR = 0.88 (95%CI 0.76-1.02)
Study population	Europe, North America, Asia, and Middle East.

Conclusion:

Study findings from cohort studies on the association between periconceptional use of folic acid supplements and multivitamins containing folic acid and the risk of pre-eclampsia are inconclusive.

Explanation

There are three systematic reviews on the association between folic acid use and the risk of pre-eclampsia.[32,35,36] Hua et al. (2016), Shim et al. (2016) and Bulloch et al. (2018) defined the use of folic acid supplements as the use of folic acid alone or of multivitamins containing folic acid. The four cohort studies in the systematic review by Shim et al. (2016) were included in the systematic review by Hua et al. (2016) in combination with four other cohort studies.

Bulloch et al. (2018) combined six cohort studies with two cross-sectional studies.[36] Four of the six cohort studies were also summarised by Hua et al. (2016). As the publication of Hua et al. (2016) is the most complete, the committee describes their findings below (Table 8a). In addition, the two cohort studies from the meta-analysis by Bulloch et al. (2018), which were not summarised by Hua et al. (2016), are described separately (Table 8b).[25,33]

One more recent cohort study has been published on folic acid use and pre-eclampsia after the search date of Hua et al. (2016).[34] As Hua et al. (2016) defined folic acid use as the use of folic acid alone or of multivitamins containing folic acid, the committee could only draw a conclusion on this broad exposure measure.

The systematic review by Hua et al. (2016) summarised eight cohort studies on the association between periconceptional folic acid supplementation and the risk of pre-eclampsia. In two cohort studies, use of folic acid was recorded after birth, which might have biased the association with the risk of pre-eclampsia. However, the relative risks in the two studies did not differ from those in the six other studies. The folic acid dose ranged from 0.2 to more than 1.0 milligram per day, and was taken either from before conception or after conception.

Hua et al. (2016) showed that the use of folic acid was not significantly associated with a lower risk of pre-eclampsia (RR = 0.88; 95%CI 0.76-1.02). The associations in the cohort studies went largely into the same direction, whereas there was considerable heterogeneity in the size of the

association. In sensitivity analyses, exclusion of a Chinese study reduced heterogeneity to 49%. The authors did not investigate whether other factors such as dosage or publication year explained heterogeneity. Three studies were performed in countries that had a folic acid supplementation program in place at the time of study. No systematic differences in risk estimates were observed by the committee between studies that were performed in these countries and studies that were performed in countries without a fortification program.

Martinussen et al. (2015) found no significant association between the use of folic acid in the month before conception or in the first trimester of pregnancy with the risk of pre-eclampsia in American women. This cohort differed from other cohorts with respect to the intake of folic acid from supplements in the control group and from fortified foods in the total cohort. As 95% of the women used folic acid supplements, an average use of more than 0.2 milligram per day from one month before conception through the first trimester was compared with an average use of less than 0.2 milligram per day. In addition, American women have a high intake of folic acid from fortified products. The total number of cases was relatively small (N = 128). In subgroup analyses, they showed that in lean women (BMI < 25 kg / m^2) folic acid use in the month before conception, but not in the first trimester, might be associated with a lower risk. However, the upper limit of the confidence interval is 1.0 and the authors do not report how many cases occurred within the group of lean women. There was no significant association in overweight women (BMI > 25 kg / m^2).[25]

Wen et al. (2016) found a non-significant inverse association between the use of folic acid early in the second trimester of pregnancy and the risk of pre-eclampsia in Canadian women. The conclusion is limited by the small number of cases in women not using folic acid supplements (N = 17). The association went into the same direction for the use of folic acid alone. In subgroup analyses, the authors found a significant inverse association between folic acid use and the risk of pre-eclampsia in women at high risk of pre-eclampsia, but not in women at low risk. Again, this conclusion was limited by the small number of cases in the control group (8 at high risk and 9 at low risk).[33]

De Ocampo et al. (2018) found a non-significant association between starting folic acid supplementation at least 4 weeks before conception and a lower risk of pre-eclampsia. Whereas starting supplementation at least 4 weeks after the last menstruation was not significant.[34] Again, the small number of cases with pre-eclampsia in women not using folic acid supplements (N = 6) and in the group of late users (N = 29) limit the interpretation of the findings.

Taken together, the findings of three out of four cohort studies went into the same direction as the meta-analysis by Hua et al. (2016).

In view of the fact that the associations between the periconceptional use of folic acid supplements and a lower risk of pre-eclampsia are statistically not significant, but the risk estimates deviate substantially from 1.00, the committee concludes that the study findings on the periconceptional use of folic acid supplements and the risk of pre-eclampsia are inconclusive.

Table 8a. Results from the meta-analysis of Hua et al. (2016) on the association between periconceptional folic acid supplementation versus no use and the risk of pre-eclampsia.

N cohorts	Exposure	Timing exposure	n / N exposure	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
8	0.2 to > 1 milligram / day	Pre- or postconceptional	3,548 / 145,471	3,241 / 131,751	0.88 (0.76-1.02)	54%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RR, relative risk.

Table 8b. Results from the three additional cohort studies on the association between periconceptional folic acid supplementation and the risk of pre-eclampsia

Cohort name	Exposure	Control	Timing exposure	n / N exposure	n / N control	RR estimate (95%CI)
Asthma in Pregnancy Study & Nutrition in Pregnancy Study [25]	> 0.2 milligram / day folic acid	< 0.2 milligram / day folic acid	Month before conception	n.r.[a] / 1,590	n.r.[a] / 2,057	0.80 (0.60-1.20)
Asthma in Pregnancy Study & Nutrition in Pregnancy Study [25]	> 0.2 milligram / day folic acid	< 0.2 milligram / day folic acid	During first trimester	n.r. / 3,301	n.r. / 346	1.10 (0.60-2.10)
Oak Birth Cohort [33]	> 0 to 4 milligram / day folic acid versus no use	No use	Early second trimester pregnancy	228 / 7,265	17 / 404	0.58 (0.33-1.02)
MotherToBaby Network [34]	Use of folic acid	No use	Prior to conception	94 / 2,697	6 / 79	0.42 (0.17-1.05)
MotherToBaby Network [34]	Use of folic acid	No use	After conception	29 / 471	6 / 79	0.55 (0.21-1.46)

CI: confidence interval; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk. [a] The total number of cases was 128.

2.7 Asthma in the offspring

Summary: Folic acid supplementation and the risk of asthma in the offspring.

Aspect	Explanation
Selected studies	0.4 milligram per day: three meta-analyses of three to five cohort studies[37-39], one additional cohort study.[40] 1 milligram per day or more: one cohort study [41], and one registry study.[42]
Heterogeneity	No
Strength of the association	RR = 1.01 (95%CI 0.78-1.30)[37]; 1.04 (95%CI 0.94-1.16)[38]; 1.06 (95%CI 0.99-1.14)[39]
Study population	Europe, North America, and Australia.

Conclusion 1:

Based on cohort studies, an association between the periconceptional use of 0.4 milligram per day of folic acid and the risk of asthma is unlikely.

Conclusion 2 (cohort studies):

There is too little research to draw a conclusion on the association between a periconceptional use of a high dose (1 milligram per day or more) of folic acid and the risk of asthma.

Explanation

There are four systematic reviews of periconceptional folic acid supplementation and the risk of childhood asthma.[37-39,43] Brown et al. (2013) describe six cohort studies on asthma and / or wheezing in a narrative review, all of which have also been summarised in one or more of the other systematic reviews by meta-analysis. Crider et al. (2015), Wang et al. (2015) and Yang et al. (2016) each summarise five cohort studies on asthma by meta-analysis. The overlap between these three reviews was four studies. As the overlap is only partial, all three studies are discussed below (Table 9a).

The three meta-analyses of five cohort studies each (in total six cohort studies) on the association between use of folic acid supplements and the risk of asthma did not find evidence for an association.[37-39] As Wang et al. (2015)[38] and Yang et al. (2015)[39] used fixed-effects models their confidence intervals around the risk estimates were more narrow than the confidence interval for the estimate by Crider et al. (2013)[37] (which used a random-effects model). The age at which asthma was assessed varied: at 3.5, 5.5, 6, 6-7 or 7-8 years of age or annually at 1-8 years of age. Heterogeneity was low, which could be related to the small number of studies in each meta-analysis.

There are two recent birth cohort studies not included in the meta-analyses (Table 9b). In the studies, information on the use of folic acid before and during pregnancy was collected retrospectively. As the outcome measure was assessed prospectively, the committee did include these studies in its evaluation.[40,41]

In an American cohort, Veeranki et al. (2015) showed that the use of supplements containing 1 milligram folic acid was associated with a higher

risk of asthma in the offspring at age 4.5 to 6 years. The association was limited to women exposed in the first trimester or in the first trimester and beyond, and was not significant in women exposed after the first trimester.[41] In a Dutch cohort, Den Dekker et al. (2018) did not find any evidence for an association between the use of folic acid supplements during the periconceptional period and the risk of asthma in the offspring. The number of cases was too small to draw conclusions on timing of exposure.[40]

In other more recent cohort studies, the intake of folic acid from supplements, fortified foods, and dietary folate was combined.[44-46] It is therefore not possible to draw a conclusion based on these studies on the specific role of folic acid supplement use in asthma development in the offspring.

Finally, one study specifically explored the association between periconceptional high-dose folic acid supplementation and the use of asthma medication in offspring (Table 9b). They did their study using a Dutch population-based pharmacy prescription database.[42] Women at risk of having a child with a neural tube defect were dispensed high dose folic acid (5 milligram per day). The use of a high dose of folic acid during pregnancy was statistically significantly associated with a higher use of recurrent asthma medication and recurrent inhaled corticosteroids in offspring, but not significantly with any asthma medication.

In conclusion, an association between periconceptional use of 0.4 milligram folic acid per day and the risk of asthma in the offspring is unlikely. There is insufficient evidence to draw a conclusion on the association between periconceptional use of a high dose of folic acid (1 milligram per day or more) and the risk of asthma in the offspring.

Table 9a. Results from the meta-analyses of Crider et al. (2013), Wang et al. (2015), and Yang et al. (2015) and results from Generation R on the association between low-dose folic acid supplementation versus no use and the risk of asthma in the offspring.

Study type	N cohorts	Exposure	Timing of exposure	n / N exposure	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Meta-analysis[37]	3	0.4-0.5 milligram / day folic acid	Periconceptional through first trimester	n.r.[a]	n.r.	1.01 (0.78-1.30)	0%
Meta-analysis[38]	3	Folic acid use	Pre- and / or postconceptional	n.r.	n.r.	1.04 (0.94-1.16)	0%
Meta-analysis[39]	5	Folic acid use	Pre- and / or postconceptional	n.r.[b]	n.r.	1.06 (0.99-1.14)	0%
Cohort study	1	0.4 milligram / day folic acid	During pregnancy	180 / 3,213	43 / 597	0.99 (0.67-1.46)	n.a.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] The sample size was 4,823. [b] The sample size was 1,438.

Table 9b. Results from the two additional cohort studies on the association between high dose folic acid supplementation versus no use and the risk of asthma in the offspring.

Cohort name	Exposure	Timing of exposure	Outcome	n / N exposure	n / N control	RR estimate (95%CI)
Tennessee Medicaid cohort[41]	1 milligram / day[a] folic acid	First trimester	Asthma in the offspring	1,652 / 9,976	2,305 / 18,057	1.20 (1.10-1.30)
Tennessee Medicaid cohort[41]	1 milligram / day[a] folic acid	Second and/ or third trimester	Asthma in the offspring	3,738 / 29,159	2,305 / 18,057	1.00 (1.00-1.10)
Tennessee Medicaid cohort [41]	1 milligram / day[a] folic acid	First, second and third trimester	Asthma in the offspring	8,081 / 47,236	2,305 / 18,057	1.20 (1.20-1.30)
Pharmacy prescription database[42]	5 milligram / day folic acid	During pregnancy	Recurrent asthma medication	7,674 / n.r.	320 / n.r	1.14 (1.00-1.30)
Pharmacy prescription database[42]	5 milligram / day folic acid	During pregnancy	Recurrent inhaled corticosteroids	4,721 / n.r.	215 / n.r	1.22 (1.06-1.40)
Pharmacy prescription database[42]	5 milligram / day folic acid	During pregnancy	Any asthma prescription	11,344 / n.r.	436 / n.r.	1.03 (0.92-1.16)

CI: confidence interval; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] The median number of days the folic acid supplement was used was 30 for women exposed in the first trimester only, 40 for those exposed after the first trimester and 90 for those exposed in the first trimester and beyond.

Update July 2018 - July 2019

One additional meta-analysis was published between July 2018 and July 2019: Li et al. (2019).[47] However, since the studies included in the review by Li et al. (2019) are already included by the committee, this publication was not further considered by the committee.

2.8 Wheezing in the offspring

Summary: Folic acid supplementation and the risk of childhood wheezing.

Aspect	Explanation
Selected studies	One meta-analysis of three cohort studies[38] and one additional cohort study.[48]
Heterogeneity	No
Strength of the association	RR = 1.06 (95%CI 1.02-1.09)
Study population	Europe.

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between periconceptional folic acid supplementation and the risk of childhood wheezing.

Explanation

There are two systematic reviews of periconceptional folic acid supplementation and childhood wheezing describing the same three cohort studies.[38,43] As Wang et al. (2015) summarised the cohort studies by meta-analysis and Brown et al. (2013) did not, the committee focuses on the systematic review of Wang et al. (2015) (Table 10).

Wang et al. (2015) summarised three cohort studies on the use of folic acid early in pregnancy or in another period of pregnancy and the risk of childhood wheezing. The time wheezing was assessed varied between the studies: at 6-18 months, up to 4 years and until 6-7 years. There was a significant association between the use of folic acid supplements in the

first trimester of pregnancy and the risk of wheezing in the offspring (RR = 1.06). However, the estimate was largely determined by one large cohort study (weight 92%), and the other two smaller studies did not find any evidence for an association (RR = 1.00 and 1.02, respectively). In addition, a fixed-effects model was used to estimate the association, which results in a smaller confidence interval than if a random-effects model had been used. There was no significant association between folic acid supplementation in any other period of pregnancy and the risk of wheezing in the offspring.[38]

One birth cohort study retrospectively collected information on the use of folic acid during pregnancy. As wheezing was assessed prospectively, the committee includes this study in its evaluation.[48] In their analyses, Alfonso et al. (2018) compare late folic acid supplement initiation with use in the first trimester. Wheezing was defined as a reported wheeze in the past 12 months. The average age of the children at the time of assessment was 3.5 years. The authors show that compared with use in the first trimester, late initiation is not-significantly associated with a higher risk of wheezing (RR = 1.16; 95%CI 0.75-1.81).[48]

In conclusion, there is too little research to draw a conclusion on the association between periconceptional folic acid supplementation and the risk of childhood wheezing.

Table 10. Results of the meta-analysis of Wang et al. (2015) and the Environment and Child Health Outcome Survey on the association between periconceptional folic acid supplementation versus no use and the risk of wheezing in the offspring.

Study type	N cohorts	n / N exposure	N / N control	RR estimate (95%CI)	Hetero-geneity I^2
Meta-analysis[38]	3	n.r.	n.r.	1.06 (1.02-1.09) supplementation in early pregnancy 1.01 (0.98-1.03) supplementation in other periods of pregnancy	0%
Cohort study[48]	1	146 / 1,025	13 / 151	1.16 (0.75-1.81) supplementation late in pregnancy versus early in pregnancy	Not applicable

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

2.9 Autism in the offspring

Summary: Folic acid supplementation and the risk of autism spectrum disorders in the offspring.

Aspect	Explanation
Selected studies	One meta-analysis of five cohort studies[49], three more recent cohort studies.[50-52]
Heterogeneity	Not in the meta-analysis, but the results of two additional cohort studies are not consistent with the meta-analysis (note: the third additional cohort study is consistent with the meta-analysis).
Strength of the association	Meta-analysis: RR = 0.90 (95%CI 0.78-0.99) Three additional cohort studies: RR = 1.27 (1.01-1.60); RR = 1.06 (0.94-1.19); RR = 0.56 (0.42-0.74) for use before conception and 0.32 (0.26-0.41) for use during pregnancy.
Study population	Europe, North America, and Middle East.

Conclusion:
Study findings from cohort studies on the association between folic acid supplementation around the time of conception and the risk of autism spectrum disorders in the offspring are contradictory.

Explanation
A systematic literature search identified four systematic reviews and one review of systematic reviews (umbrella review) on the association between the use of folic acid supplements in the periconceptional period and the risk of autism spectrum disorders in the offspring.[49,53-56] The umbrella review by Modabbernia et al. (2017) used the findings by Castro et al. (2016). Castro et al. (2016) described one cohort study in their narrative review. Gao et al. (2016) described the same cohort study. Freedman et al. (2018) described another cohort study and an RCT (supplementing 5-methyltetrahydrofolate). The two cohort studies are summarised by Wang et al. (2017) in combination with three other prospective cohort studies. Therefore, the committee describes the findings by Wang et al. (2017) (Table 11a).[49]

Wang et al. (2017) found an association between the use of folic acid supplements during pregnancy and a 10% lower risk of autism spectrum disorders. In most studies, autism spectrum disorders were diagnosed with DSM-IV, occasionally in combination with other scales. The upper limit of the confidence interval was close to one. There was moderate heterogeneity both in the size and direction of the effect. Heterogeneity was not further explored, as the analysis of cohort studies itself was a subgroup analysis.[49]

More recent cohort studies show mixed results (Table 11b).[50-52] In these studies, autism spectrum disorders were diagnosed with DSM-IV and / or International Classification of Diseases. DeVilbiss et al. (2017) show that periconceptional use of folic acid supplements is associated with a higher risk of autism spectrum disorder in the offspring.[50] Strom et al. (2018) do not find a significant association for periconceptional folic acid supplement use. Associations were similar with early or late use of folic acid supplements and use of a low or a high dose in mid-pregnancy.[52] In contrast, Levine et al. (2018) show a protective association between periconceptional use of folic acid supplements and the risk of autism spectrum disorders. The number of cases, however, were smaller in this study than in the other two cohort studies.[51] In the countries where the three cohort studies were carried out, there was no folic acid fortification program in place.

The committee concludes that study findings on the association between periconceptional folic acid supplementation and the risk of autism spectrum disorders in the offspring are contradictory, as findings of two more recent cohort studies are in the opposite direction from the results of the meta-analysis.

Table 11a. Results from the meta-analysis of Wang et al. (2017) on the association between folic acid supplementation during pregnancy versus no use and the risk of autism spectrum disorders in the offspring.

N cohorts	n / N exposure	n / N control	RR estimate (95%CI)	Heterogeneity I^2
5	n.r.[a]	n.r.	0.90 (0.78-0.99)	43%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] The total number of cases was 2,794.

Table 11b. Results from the three additional cohort studies on the association of folic acid supplementation versus no use and the risk of autism spectrum disorders in the offspring.

Cohort name	Exposure	Timing of exposure	n / N exposure	n / N control	RR estimate (95%CI)
Stockholm County Cohort[50]	0.4 milligram / day folic acid	Periconceptional	78 / 2,798	2,045 / 91,895	1.27 (1.01-1.60)
Danish National Birth Cohort[52]	Use of folic acid	Periconceptional	749 / 52,822	485 / 34,388	1.06 (0.94-1.19)
Israeli case-cohort[51]	Use of folic acid	Before conception	19 / 3,066	469 / 25,863	0.56 (0.42-0.74)
Israeli case-cohort[51]	Use of folic acid	During pregnancy	55 / 11,686	469 / 25,863	0.32 (0.26-0.41)

CI: confidence interval; n.a.: not applicable; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

2.10 Summary of the findings on folic acid

In conclusion, this chapter is based on ten systematic reviews of cohort studies and a few intervention studies[2,7,10,21,23,32,37-39,49], one previous report of the Health Council of the Netherlands[4] and 12 additional cohort studies.[24-27,30,33,34,40,41,50-52] The committee subscribes to the earlier conclusions of the Health Council of the Netherlands from 1993 that periconceptional folic acid supplementation reduces the risk of neural tube defects. Further, strong evidence was found that periconceptional folic acid supplementation was associated with lower risks of preterm birth and of an infant that is small for gestational age.

The following overview presents all conclusions of the committee of this chapter on folic acid:

Committee's conclusion	Outcome
Strong evidence	• Neural tube defects: Based on RCTs and other study types, periconceptional folic acid supplementation of 0.4 milligram per day reduces the risk of neural tube defects. • Preterm birth: Based on cohort studies, periconceptional supplementation of 0.2 to 1.0 milligram folic acid per day is associated with a 16% (95%CI: 4-26%) lower risk of preterm birth. • Small for gestational age: Based on cohort studies, periconceptional supplementation with 0.2 to 1.0 milligram folic acid per day is associated with a 24% (95%CI: 9-37%) lower risk of small-for-gestational-age infants.
Limited evidence	• Oral Clefts: Based on cohort studies, periconception use of folic acid supplements is associated with a lower risk of oral clefts.
Unlikely	• Foetal loss and miscarriage: Based on RCTs, an effect of periconceptional folic acid supplementation on the risk of foetal loss and miscarriage is unlikely. • Asthma in the offspring: Based on cohort studies, an association between the periconceptional use of 0.4 milligram per day of folic acid and the risk of asthma is unlikely.
Contradictory	• Autism in the offspring (cohort studies)
Too little research	• Stillbirth (RCTs); • Congenital anomalies other than neural tube defects (RCTs); • Congenital cardiovascular defects (RCTs); • Oral clefts (RCTs); • Twinning (RCTs & cohort studies combined); • Preterm birth (RCTs); • Asthma in the offspring (≥ 1 milligram / day folic acid) (cohort studies); • Wheezing in the offspring (cohort studies).
Inconclusive	• Pre-eclampsia (cohort studies).

2.11 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 folic acid supplementation, this applies to a reduced risk of neural tube defects, preterm birth (evidence from cohort studies), and an infant that is small for gestational age (evidence from cohort studies). Additionally, there was one conclusion with a limited evidence level that was mentioned in the advisory report: an association with a reduced risk of oral clefts (evidence from cohort studies). This conclusion is in the same direction as the conclusion with a strong evidence level.

Based on cohort studies, the committee considers that it is unlikely that folic acid supplementation is associated with the risk of asthma. This type of conclusion (‘a relation is unlikely’) requires strong evidence.[1] The committee notes that the finding, also based on cohort studies, of a statistically significant association between folic acid supplementation and an increased risk of wheeze in the offspring is not consistent with the finding on asthma, but was based on too little research and therefore not taken into account.

Regarding folic acid supplementation, the committee is not aware of recent RCTs. It has been considered unethical to withhold folic acid supplementation from women ever since the beneficial effect on neural tube defects has become clear. The committee notes that folic acid supplementation may also be associated with a lower risk of other congenital anomalies other than neural tube defects, such as congenital cardiovascular anomalies, as has been reported based on case-control studies (see paragraphs 2.2.2 and 2.2.3). Case-control studies may indicate additional associations with rare outcomes, but this was not further explored by the committee, considering that a higher evidence level is required for establishing dietary recommendations.[1] Furthermore, the committee considered that the conclusions with a strong evidence level are amply sufficient to strongly recommend the periconceptional use of folic acid supplements.

03 multiple micronutrients

This chapter describes the scientific evidence from systematic reviews of intervention studies and cohort studies on the relation between multiple micronutrients supplementation before and during pregnancy and the risk of miscarriage, stillbirth, perinatal mortality, congenital malformations, preterm birth, growth measures at birth, delivery with a caesarean section, maternal mortality, pre-eclampsia, maternal anaemia, offspring mortality, cognitive functioning of the offspring, autism spectrum disorders in the offspring, childhood growth measures, and blood pressure in the offspring. For these outcomes, at least two intervention studies or two cohort studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies or two intervention studies.

Often, multiple micronutrient preparations contain folic acid, which is recommended in the periconceptional period. Therefore, the committee decided to use the same focus as was done for folic acid, i.e. incorporate studies on periconceptional supplementation in addition to studies on the supplementation during pregnancy.

In the systematic reviews which were identified by the committee, multiple micronutrient supplements were almost always defined as supplements with at least three micronutrients in one supplement. Often, the United Nations International Multiple Micronutrient Preparation (UNIMMAP) was studied versus a combination of folic acid and iron. The UNIMMAP supplement contains one recommended daily allowance of vitamin A, vitamin B_1, vitamin B_2, vitamin B_{12}, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium, iodine with 30 milligram of iron, and 15 milligram of zinc.

In total, 27 systematic reviews were identified (published before July 2018). Twenty-five were found via the literature search,[2,3,35,57-78] two were identified via snowballing.[79,80]

Twelve systematic reviews were excluded because they were outdated and more recent reviews / versions were available.[2,3,69-78]. Hence, 15 systematic reviews were considered for inclusion in this chapter.[35,57-68,79,80]

Smith et al. (2017)[61] aimed to “identify subgroups of pregnant women and infants who might experience greater benefit or harm from multiple micronutrient supplements”. They selected nine subgroups for which they stratified the analyses: gestational age at randomization, parity, maternal age, maternal underweight at randomization, maternal anaemia at randomization, maternal stature, education, infant sex, and adherence to the trial regimen. They state briefly that the subgroups were chosen based on biological plausibility and inclusion in previous meta-analyses. However, all subgroups are considered for all outcome measures in the study (preterm birth, stillbirth, neonatal mortality, infant mortality, low birth weight, small for gestational age, and large for gestational age). Authors do not explain the biological plausible mechanism underlying these subgroups,

nor limit subgroup analyses to occasions where heterogeneity in the overall analysis was high. Therefore, the committee only included the overall analyses from this meta-analysis.

Update July 2018 - July 2019

An update of the search was done in July 2019, retrieving six potentially relevant systematic reviews.[12,81-85] The publications of Iqbal et al. (2017) and Medley et al. (2018) based their results on reviews that were already included by the committee and were therefore left out of the evaluation.[84,85] The publications of Guo et al. (2019) and Jahanbin et al. (2019) reported on outcomes that were not discussed by earlier systematic reviews.[12,81] Based on these reviews, the outcome autism spectrum disorders and cleft lip with or without cleft palate were added to the evaluation of the committee. The publication of Sudfeld et al. (2019) presented a meta-analysis on the effect of multiple micronutrient supplementation on the risk of neonatal mortality.[83] As its results are in line with the results of Haider et al. (2017) this meta-analysis was not discussed separately. Lastly, the meta-analysis of Keats et al. (2019) is an update of the meta-analysis of Haider et al. (2017).[82] They included four new trials and removed two trials from the analyses. However, as this did not lead to different conclusions, the committee did not include the updated meta-analysis in the evaluation.

3.1 Miscarriage

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy and the risk of miscarriage.

Aspect	Explanation
Selected studies	One meta-analysis of eight RCTs.[67]
Heterogeneity	No
Strength of the effect	RR = 0.91 (95%CI 0.80-1.03)
Study population	Pregnant women predominantly from low and middle-income countries.

Conclusion:

Study findings from RCTs on the effect of multiple micronutrient supplementation on the risk of miscarriage are inconclusive.

Explanation

Haider et al. (2017) was the only systematic review reporting on the outcome miscarriage (Table 12).[67]

They summarised eight RCTs and found a non-significant reduction of the risk of miscarriage in women who took multiple micronutrient supplements during pregnancy. There was no heterogeneity. Sensitivity analyses using only high-quality studies (six out of the eight studies) showed similar results.

In view of the large number of studies in combination with an effect estimate that is not close to one, but not statistically significant, the committee concludes that study findings on the effect of multiple

micronutrient supplementation during pregnancy on the risk of miscarriage are inconclusive.

Table 12. Results of the meta-analysis of Haider et al. (2017) on the effect of multiple micronutrient (including iron and folic acid) supplementation versus iron and folic acid alone on the risk of miscarriage.

N RCTs	Start intervention	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
8	Before 37 weeks of gestation	n.r. / 24,506	n.r. / 24,749	0.91 (0.80-1.03)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

3.2 Stillbirth

3.2.1 Intervention studies

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of stillbirth.

Aspect	Explanation
Selected studies	Two meta-analyses of 15[67] and 16[61] RCTs.
Heterogeneity	No
Strength of the effect	RR = 0.97 (95%CI 0.87-1.09)[67] RR = 0.97 (95%CI 0.85-1.11)[61]
Study population	Pregnant women predominantly from low and middle-income countries. Some at increased risk of pregnancy complications.

Conclusion:

Based on RCTs, the effect of multiple micronutrient supplementation during pregnancy on the risk of stillbirth is unlikely.

Explanation

Three systematic reviews reported on stillbirth.[58,61,67] Haider et al. (2017)[67] and Smith et al. (2017)[61] are the most complete and recent reviews, and are therefore considered by the committee. Haider et al. (2017) performed a meta-analysis of study level data on 15 RCTs, and Smith et al. (2017) included individual patient data from 16 RCTs. The two reviews focus on supplementation during pregnancy and overlap by 13 RCTs. As the overlap is only partial, both are discussed by the committee (Table 13).

Haider et al. (2017) found no statistically significant effect of multiple micronutrient supplementation during pregnancy on the risk of stillbirth in a random-effects model. Haider et al. (2017) classify the quality of their results as ‘high’ according to GRADE criteria, meaning that further research is very unlikely to change the authors’ confidence in the effect estimate. Haider et al. (2017) reported moderate heterogeneity (I^2 26%), which was not explained.

Smith et al. (2017) found no statistically significant effect of multiple micronutrient supplementation during pregnancy on the risk of stillbirth in a random-effects model (RR 0.97; 95%CI 0.85-1.11). No measure of heterogeneity was reported for this random-effects model.

The studies included in the meta-analysis were predominantly from low and middle-income countries.

In view of the large number of studies, the effect estimates that were close to one in both meta-analyses, with a relative narrow confidence interval, the committee concludes that an effect of supplementation with multiple micronutrients during pregnancy on the risk of stillbirth is unlikely.

Table 13. Results of the meta-analyses of Haider et al. (2017) and Smith et al. (2017) on the effect of multiple micronutrient supplementation with iron and folic acid during pregnancy on the risk of stillbirth.

First author	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Haider[67]	Iron, with or without folic acid[a]	Before 37 weeks of gestation	15	n.r.[b]	n.r.[b]	0.97 (0.87-1.09)	29%
Smith[61]	Iron with folic acid	Before third trimester	16	n.r.[c]	n.r.[c]	0.97 (0.85-1.11)	n.r.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One out of 15 studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid [b] Total N: 120,946 [c] Total n / N was estimated at 4,152 / 112,753.

3.2.2 Cohort studies

Summary: Cohort studies on the association between multiple micronutrient supplementation before and during pregnancy and the risk of stillbirth.

Aspect	Explanation
Selected studies	One systematic review of two cohort studies.[57]
Heterogeneity	Not applicable.
Strength of the association	No summarised risk estimate.
Study population	Pregnant women or women who want to become pregnant in Europe.

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between multiple micronutrient supplementation before and during pregnancy and the risk of stillbirth.

Explanation

Wolf et al. (2017) was the only systematic review of prospective cohort studies on multiple micronutrient supplementation before and during pregnancy in relation to birth outcomes in high-income countries.[57] They summarised two cohort studies on stillbirth. As the number of studies in the meta-analysis is low, the studies explored different timing of exposure, and the risk estimates of the individual studies are in opposite direction, the cohorts are discussed separately (Table 14).

A Danish cohort study analysed whether periconceptional multiple micronutrient use (most commonly containing vitamin A, B_1, B_{12}, riboflavin, B_6, folic acid, niacin, pantothenic acid, vitamin C, D and E, iron, zinc, copper, iodine, manganese, chromium, selenium, and molybdenum) was associated with foetal death during gestation. They controlled their analyses for age, parity, prepregnancy BMI, smoking, social status, waiting time to pregnancy, infertility treatment, and previous miscarriage. As a comparison group, they used women who reported no use of multivitamins, folate, or any other single supplementation during the periconceptional period. Data from 1996-2002 from the Danish National

Birth Cohort (total N = 33,678) showed a higher risk of late foetal death (≥ 20 weeks of gestation) in the case of multivitamin use for 5-6 weeks within the six weeks preconception (4 weeks before last menstrual period until 2 weeks after) (adjusted HR 1.83 95%CI 1.11-3.03) and a lower risk in the case of postconceptional use (3 until 8 weeks after last menstrual period) (adjusted HR 0.55 95%CI 0.32-0.95).[86]

Czeizel et al. (2004) compared a supplemented cohort (n = 3,059) with an equivalent of unsupplemented matched controls; data were collected between 1993 and 1996. The supplemented cohort received multivitamins containing vitamin A, vitamin B_1, vitamin B_2, nicotinamide, vitamin B_6, folic acid, vitamin B_{12}, calcium pantothenate, biotin, vitamin C, D and E, calcium, magnesium, phosphorus, iron, copper, manganese, and zinc. The authors only report the number of cases, which is almost equal in both groups, but do not present an adjusted risk estimate.[87]

In view of the limited number of cohort studies available, there is too little research to draw a conclusion on the association between multiple micronutrient supplementation before and during pregnancy and the risk of stillbirth.

Table 14. Results from the cohort studies included in Wolf et al. (2017) on the association between multiple micronutrient supplementation versus no use and the risk of stillbirth.

Cohort name	Timing of exposure	n / N exposure	n / N control	RR estimate (95%CI)
Danish National Birth Cohort[86]	Preconceptional	n.r. / 8,397	n.r. / 10,959	1.83 (1.11-3.03)
Danish National Birth Cohort[86]	Postconceptional	n.r. / 12,334	n.r. / 10,959	0.55 (0.32-0.95)
Cohort from Hungarian Periconceptional Services[87]	Periconceptional	7 / 3,056	8 / 3,056	n.r.

CI: confidence interval; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

3.3 Perinatal mortality

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy and the risk of perinatal mortality.

Aspect	Explanation
Selected studies	One meta-analysis of 13 RCTs.[67]
Heterogeneity	Yes, partly explained by differences in start moment of supplementation.
Strength of the effect	RR = 1.01 (95%CI 0.91-1.13)
Study population	Pregnant women, predominantly from low and middle-income countries.

Conclusion:

Study findings from RCTs on the effect of multiple micronutrient supplementation on the risk of perinatal mortality are contradictory.

Explanation

Haider et al. (2017) was the most complete and recent review that reported on perinatal mortality and is therefore summarised by the committee (Table 15a).[67]

The authors found no indications for an effect of multiple micronutrient supplementation on the risk of perinatal mortality based on a meta-analysis of study level data of 13 RCTs. The authors classify the quality of their results as 'high' according to GRADE criteria, meaning that further research is very unlikely to change the authors' confidence in the effect estimate. There was moderate but statistically significant heterogeneity present in the direction and size of the effect. Heterogeneity was not used by the authors to downgrade evidence. The timing of supplementation partly explained the heterogeneity. Subgroup analyses revealed that the risk of perinatal mortality was statistically significantly lowered with multiple micronutrient supplementation starting after 20 weeks of pregnancy (three studies, low heterogeneity), while it was non-significantly increased with multiple micronutrient supplementation starting before 20 weeks of gestation (ten studies, substantial heterogeneity) (Table 15b). However, the authors of the meta-analysis do not provide a rationale for the cut-off point of 20 weeks of gestation, and the included trials are not designed to explore the difference in effectiveness when starting before or after 20 weeks of gestation.

Summarised estimates were based on a large number of studies. However, there was substantial heterogeneity in the direction of the effect, and it remained unclear what influence the timing of supplementation had on the outcome. Therefore, the committee concludes that study findings on the effect of multiple micronutrient supplementation on the risk of perinatal mortality are contradictory.

Table 15a. Results of the meta-analysis of Haider et al. (2017) on the effect of multiple micronutrient supplementation with iron and folic acid during different phases of pregnancy on the risk of perinatal mortality.

N RCTs	Control	Start intervention	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
13	Iron, with or without folic acid[a]	Before 37 weeks of gestation.	n.r.[b]	n.r.[b]	1.01 (0.91-1.13)	46%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One out of 13 studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid [b] Total N: 115,607.

Table 15b. Subgroup analyses by timing of intervention in Haider et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy on the risk of perinatal mortality.

Start intervention	N RCTs	Control	n / N Intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
≥ 20 weeks of gestation	3	Iron, with or without folic acid	n.r. / 21,410	n.r. / 20,408	0.88 (0.80-0.97)	0
< 20 weeks of gestation	10	Iron, with or without folic acid[a]	n.r.[b]	n.r.[b]	1.13 (0.96-1.33)	51%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One out of ten studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid. [b] Total N: 73,789.

3.4 Congenital anomalies

The committee found four systematic reviews in which the relation between multiple micronutrient supplements and the risk of congenital anomalies (multiple congenital anomalies, neural tube defects, recurrent neural tube defects, cleft lip and cleft palate defects, recurrence of clefts, cardio-vascular defects, urine tract defects, limb deficiencies, hydrocephalus and trisomy 21) was described.[57,59,65,67] Wolf et al. (2017) was the most complete and recent review and was therefore described by the committee in the evaluation in the next subparagraphs.[57] Goh et al. (2006) was excluded since they did not specify their definition of the intervention and control situation and they combined results from cohort studies and RCTs in their meta-regression.[59] Also, the review of Dean et al. (2014) was excluded since they combined results of cohort studies and RCTs.[65] Haider et al. (2017) included only one RCT and was therefore not further discussed.

The meta-analysis of Wolf et al. (2017) included no RCTs and only one cohort study on the outcomes cleft lip and cleft palate defects, cardiovascular defects, urine tract defects, limb deficiencies, hydrocephalus and trisomy 21. Since the committee focused on outcomes on which at least two RCTs or cohort studies are summarised in a systematic review, these outcomes are not further discussed.

3.4.1 Recurrent neural tube defects

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of recurrent neural tube defects and recurrent neural tube defects.

Aspect	Explanation
Selected studies	One systematic review of two RCTs.[57]
Heterogeneity	Not applicable.
Strength of the effect	No summarised effect estimate.
Study population	Women with previous pregnancy affected with a neural tube defect in Australia, Asia, North America, and Europe.

Conclusion (RCT):

There is too little research to draw a conclusion on the effect of multiple micronutrient supplementation during pregnancy on the risk of recurrent neural tube defects.

Explanation

The committee found one systematic review of two RCTs on the effect of pre and periconceptional multiple micronutrient supplementation on the risk of recurrent neural tube defects (Table 16).[57]

In these trials, supplementation started before conception until approximately 12 weeks of gestation. Wolf et al. (2017) compared multivitamin use with or without folic acid with folic acid alone or no supplementation. This comparison is not as relevant in the Dutch situation where the use of folic acid supplements is recommended to women in the periconceptional period. Therefore, the results of the comparison of multivitamins with folic acid versus folic acid alone from the separate trials are described below.

Kirke et al. (1992) started a trial in 1981 on the prevention of recurrent neural tube defects in Ireland in women with a previously affected pregnancy.[88] They compared multivitamin use (containing vitamin A, calciferol, thiamine, hydrochloride, riboflavin, pyridoxine hydrochloride, nicotinamide, ascorbic acid, calcium phosphate and ferrous sulphate with folic acid) with folic acid alone (daily dose of 0.36 milligram). No infants in the folic acid only group (n = 115) and the multivitamin with folic acid group (n = 120) had a neural tube defect.

A larger RCT in seven countries (United Kingdom, Hungary, France, Israel, Australia, Canada, Russia) compared multivitamin use (containing vitamin A, D, B_1, B_2, B_6 C, and nicotinamide with folic acid) with folic acid alone (4 milligram / day) in women with a previous pregnancy affected by a neural tube defect.[9] Four cases of neural tube defects occurred in the multivitamin group with folic acid, and two cases in the folic acid alone group. No risk estimate was presented.

Because of the low number of studies and cases, the committee concludes that there is too little research to draw a conclusion on the effect of multiple micronutrient supplementation on the risk of recurrent neural tube defects.

Table 16. Results from the RCTs included in Wolf et al. (2017) on the effect of multiple micronutrient with folic acid supplementation versus folic acid alone during the periconceptional period on the risk of recurrent neural tube defects.

First author	n / N intervention	n / N control
Kirke[88]	0 / 120	0 / 115
Wald[9]	4 / 295	2 / 298

n / N: number of cases / total number of participants.

3.4.2 Cleft lip with or without cleft palate and recurrent clefts

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between multiple micronutrient supplementation before and during pregnancy on the risk of cleft lip with or without cleft palate and on the risk of recurrent clefts.

There is one systematic review on the association between multiple micronutrient supplementation containing folic acid before and during pregnancy and the risk of cleft lip with or without cleft palate.[12]

The authors included five cohort studies on multivitamin use which were of interest to the committee and one on folic acid only supplementation, which was left out of the consideration as this chapter is on multiple micronutrient use. Furthermore, the committee only uses risk estimates from cohort studies that are adjusted for confounders. According to Jahanbin et al. (2018), only one of the five studies presented adjusted risk estimates (Conway et al. (1958)). Two cohort studies (Czeizel et al. (1999) and Czeizel et al. (2004)) on multivitamins presented unadjusted risk estimates according to Jahanbin et al. (2018). However, the authors of these studies matched the unsupplemented group and multivitamin group on possible confounding factors in their analysis, and it is therefore not necessary to adjust the estimates. From the two remaining studies that presented unadjusted risk estimates according to Jahanbin et al. (2018), no original data could be retrieved (Brigg et al. (1976) and Tolarova et al. (1995)). Therefore, the committee relied on the information in the systematic review and considers the estimates from these studies as unadjusted and thus excluded them from the evaluation.

Hence, three relevant cohort studies remained for the evaluation of the committee. None of the studies found statistically significant risk estimates: Czeizel et al. (1999) RR = 1.71 (95%CI 0.28-10.21); Czeizel et al. (2004) RR = 1.00 (95%CI 0.20-4.95); Conway et al. (1958) RR = 0.14 (95%CI 0.01-2.53).

In view of the fact that there are three studies available and none of them showed significant results, the committee concludes that there is too little research to draw a conclusion on the association between multiple micronutrient supplementation and the risk of cleft lip with or without cleft palate.

There are two meta-analyses on the association between multiple micronutrient supplementation before and during pregnancy and the risk of recurrent clefts.[12,57] Wolf et al. (2017) included two cohort studies and found a summarised risk estimate of 0.61 (95%CI 0.22-1.64). Jahanbin et al. (2018) included three cohort studies, the cohort studies included by Wolf et al. (2017) and one additional cohort study, and found a summarised risk estimate of 0.33 (95%CI 0.15-0.73). However, according to Jahanbin et al. (2018) the two overlapping studies presented unadjusted risk ratios; as the committee could not retrieve the original publications of these studies (Brigg et al. (1976) and Tolarova et al. (1995)), the committee relied on the information in the systematic review and considers the estimates from these studies as unadjusted and thus excluded them from the evaluation. Hence, one study remained for the evaluation of the committee; this is considered as too little research to draw a conclusion.

3.5 Preterm birth (< 37 weeks)

3.5.1 Intervention studies

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of preterm birth (< 37 weeks of gestation).

Aspect	Explanation
Selected studies	Two systematic review of 16 RCTs with meta-analyses of 15 and 16 RCTs.[61,67]
Heterogeneity	Yes, explained by prepregnancy BMI.
Strength of the effect	RR = 0.93 (95%CI 0.87-0.98) [61] and RR = 0.96 (95%CI 0.90-1.03) [67]
Study population	Pregnant women predominantly from low and middle-income countries (Asia, Africa, Central-America, and one study from Europe). Some at increased risk of pregnancy complications.

Conclusion 1 on < 37 weeks:

Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of preterm birth in low and middle-income countries.
Level of evidence: Limited.

Conclusion 2 on < 37 weeks:

Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of preterm birth in low and middle-income countries in women with a low prepregnancy BMI with 15% (-20% to -10%).
Level of evidence: Strong.

Explanation

There are two systematic reviews with meta-analyses on multiple micronutrient supplementation and the risk of preterm birth.[61,67] Haider et al. (2017) included 16 studies in their systematic review. All but one study compared multiple micronutrient supplementation with a combination of iron and folic acid. The RCT by Brough et al. (2010) was the only one comparing the supplement with a placebo and was not incorporated in the overall meta-analysis, but described separately by Haider et al. (2017).[89] Hence, 15 trials were summarised in the meta-analysis of study level data.[67] Smith et al. (2017) included 16 studies in their pooled analyses of individual patient data. The meta-analyses overlapped each other by 12 RCTs. Since the overlap is only partial, both reviews are discussed by the committee (Table 17a).

The pooled analysis of Smith et al. (2017) showed a statistically significant reduced risk of preterm birth. No measure of heterogeneity was reported, but visual inspection of the forest plot of the fixed-effects model suggested no heterogeneity in the direction of the effect.

Haider et al. (2017) found a risk estimate that favoured the multiple micronutrient group in their meta-analysis, but the effect was not statistically significant. The study of Brough et al. (2010), which was not included in the meta-analysis, found no effect on preterm birth.[89] Haider et al. (2017) reported substantial heterogeneity, which was explained by maternal BMI: women with a prepregnancy BMI lower than 20 kg / m^2 had a reduced risk of preterm birth when taking multiple micronutrient supplementation during pregnancy (based on four studies), while supplementation showed no

effect on the risk of preterm birth in women having a BMI of 20 kg / m^2 or higher (11 studies) (Table 17b).

Subgroup analyses by Smith et al. (2017) showed a significant protective effect both in women with prepregnancy BMI< 18.5 and ≥ 18.5; the risk estimate for the lower-BMI-group was lower than the estimate for the higher-BMI-group.

The committee formulates a conclusion for low and middle-income countries because there is too little research from high-income countries. Multiple micronutrient supplementation during pregnancy reduced the risk of preterm birth in low and middle-income countries. Although the direction of the effect was consistent in both reviews and the number of studies and cases was sufficient to conclude strong evidence, one meta-analysis showed a significant effect while the other showed a non-significant effect. Therefore, the committee judges the level of evidence for pregnant women from low and middle-income countries in general as limited.
In view of the heterogeneity that was present in the study of Haider et al. (2017) and that was explained by women with a low prepregnancy BMI, the committee judges the level of evidence for women with low prepregnancy BMI as strong.

Table 17a. Results from the meta-analyses of Haider et al. (2017) and Smith et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy on the risk of preterm birth.

First author	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Haider[67]	Iron, with or without folic acid[a]	Before 37 weeks of gestation	15	n.r.[b]	n.r.[b]	0.96 (0.90-1.03)	52%
Haider[67]	Placebo[c]	Before 13 weeks of gestation	1	n.r. / 207	n.r. / 195	1.10 (0.41-2.95)	n.a.
Smith[61]	Iron with folic acid	First to third trimester	16	n.r.[d]	n.r.[d]	0.93 (0.87-0.98)	n.r.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.a.: not applicable; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio);. [a] One out of 15 studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid. [b] Total N estimated at 120,946. [c] control group advised to take folic acid. [d] Total n / N estimated at: 21,695 / 110,575 (number of cases in Zagre et al. (2007)[90] not reported, thus total n must be interpreted as 'at least 21,695 cases').

Table 17b. Subgroup analyses of maternal BMI in Haider et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy (started < 37 weeks of gestation) on the risk of preterm birth.

Maternal BMI	Control	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Maternal BMI < 20 kg / m^2	Iron, with folic acid	4	n.r.[a]	n.r.[a]	0.85 (0.80-0.90)	0%
Maternal BMI ≥ 20 kg / m^2	Iron, with or without folic acid[b]	11	n.r. / 35,020	n.r. / 33,982	1.02 (0.97-1.04)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Total N estimated at 51,944, [b] One out of 11 studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid.

3.5.2 Cohort studies

Summary: Cohort studies on the association between multiple micronutrient supplementation before and during pregnancy and the risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of four cohort studies.[57]
Heterogeneity	Yes, mainly in the size of the effect.
Strength of the association	RR = 0.84 (95%CI 0.69-1.03)
Study population	Pregnant women or women who want to become pregnant in Europe and the USA.

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between periconceptional multiple micronutrient supplementation as compared with no vitamin use and the risk of preterm birth.

Explanation

Wolf et al. (2017) is the only meta-analysis that summarises four cohort studies on the association between periconceptional multiple micronutrient supplementation on the risk of preterm birth (Table 18).[57] They found a lower risk, but non-significant compared with no vitamin use. The authors classify the quality of evidence as very low. Heterogeneity was substantial and not explained in the paper. Visual inspection of the forest plot revealed that heterogeneity was mainly present in the size of the effect.

In view of the relatively low number of studies, the risk estimate that is neither close to one, nor statistically significant, and with substantial heterogeneity, the committee concludes that there is too little research to draw a conclusion on the association between periconceptional multiple micronutrient supplementation as compared with no vitamin use and the risk of preterm birth.

Table 18. Results of the meta-analysis of Wolf et al. (2017) on the association between the exposure to multiple micronutrient supplementation (three or more vitamins or minerals in a tablet) versus no vitamin use during the periconceptional period and the risk of preterm birth.

N Cohorts	n / N exposure	n / N control	RR estimate (95%CI)	Heterogeneity I^2
4	1,375 / 26,797	905 / 15,795	0.84 (0.69-1.03)	73%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

3.6 Preterm birth (< 34 weeks)

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of early preterm birth (< 34 weeks of gestation).

Aspect	Explanation
Selected studies	One meta-analysis of 14 RCTs.[61]
Heterogeneity	No
Strength of the effect	RR = 0.87 (95%CI 0.79-0.95)[61]
Study population	Pregnant women from low and middle-income countries (Asia, Africa). Some at increased risk of pregnancy complications.

Conclusion on < 34 weeks:

Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of early preterm birth by 13% (95%CI 5%-21%) in low and middle-income countries.

Level of evidence: Strong.

Explanation

Smith et al. (2017) was the most complete review reporting on the effect on early preterm birth (i.e. after < 34 weeks of gestation), they included individual patient data of 14 RCTs for this analysis (Table 19).[61]

Smith et al. (2017) found a statistically significant effect of multiple micronutrient supplementation on the risk of early preterm birth. Only fixed-effects models were available for this analysis. There was no heterogeneity.

The committee restricts the conclusion to low and middle-income countries, because there is too little research from high-income countries. The committee concludes that multiple micronutrient supplementation during pregnancy reduces the risk of early preterm in low and middle-income countries by 13% (95%CI 5% to 21%). In view of the large number of studies and the absence of heterogeneity, the committee judges the level of evidence as strong.

Table 19. Results from the meta-analysis of Smith et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy versus iron and folic acid on the risk of early preterm birth (< 34 weeks of gestation).

Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
start first to third trimester	14	n.r.[a]	n.r.[a]	0.87 (0.79-0.95)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Total n / N estimated at 2,885 / 106,564 (total number of cases from Zagre et al. (2007) not reported, thus total n must be interpreted as 'at least 2,885 cases').

3.7 Small for gestational age

3.7.1 Intervention studies

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of a small-for-gestational-age infant.

Aspect	Explanation
Selected studies	Two systematic reviews of 15 RCTs[67] and 16 RCTs[61] with meta-analyses of 14 and 16 RCTs.
Heterogeneity	Yes, in the size of the effect. Explained by maternal height and prepregnancy BMI.
Strength of the effect	RR = 0.92 (95%CI 0.86-0.98) [67], 0.94 (95%CI 0.90-0.98)[61]
Study population	Pregnant women, predominantly from low and middle-income countries (Asia, Africa, Central-America, and one study from Europe). Some at increased risk of pregnancy complications.

Conclusion:

Based on RCTs, supplementation with multiple micronutrients containing iron and folic acid starting during pregnancy reduces the risk of a

small-for-gestational-age infant by 6% (95% CI 2%-10%) in low and middle-income countries.
Level of evidence: Strong.

Explanation

Four systematic reviews reported on the effect of multiple micronutrient supplementation during pregnancy on the risk of a small-for-gestational-age infant.[61,63,64,67] Smith et al. (2017) and Haider et al. (2017) were the most complete and recent reviews and are therefore described by the committee. Smith et al. (2017) included individual patient data of 16 RCTs, and Haider et al. (2017) included study level data of 15 RCTs (14 of which were summarised in the meta-analysis). The two studies overlap by 12 RCTs. Since the overlap is only partial, the results of both systematic reviews are discussed below (Table 20a).

Haider et al. (2017) found a statistically significant effect of supplementation with multiple micronutrients containing folic acid and iron during pregnancy on the risk of a small-for-gestational-age infant when compared with supplementation with iron with or without folic acid.[67] Haider et al. (2017) identified one study which compared multiple micronutrients containing folic acid and iron with a placebo. This UK study was not incorporated in the meta-analysis but showed an effect estimate very similar to the overall analysis; however, not statistically significant. The authors classify the quality of the evidence as moderate and reported moderate but statistically significant heterogeneity, mainly in the size of the effect. This heterogeneity was explained by maternal BMI and height: in mothers with a BMI of at least 20 kg / m^2 and mothers with a height of at least 154.9 cm, supplementation with multiple micronutrients showed a greater reduction in the risk of a small-for-gestational-age infant than in women with a lower BMI or height (Table 20b).

Smith et al. (2017) found a similar overall effect in their meta-analysis.[61] They did not report a measure of heterogeneity. However, visual inspection of the forest plot revealed no heterogeneity in the direction of the effect. Smith et al. (2017) also reported subgroup analysis for prepregnancy BMI and maternal height. These analyses point in the same direction as the subgroup analysis of Haider et al. (2017). For the subgroup of women with BMI < 18.5 kg / m^2: RR = 1.00, 95%CI 0.94-1.06, and for the subgroup with BMI ≥ 18.5 kg / m2: RR =0.94, 95%CI 0.90-0.97. For the subgroup of women with maternal height < 150 cm: RR = 0.99, 95%CI 0.94-1.03, and for the subgroup with maternal height ≥ 150 cm: RR = 0.92, 95%CI 0.87-0.97.

The committee restricts the conclusion to low and middle-income countries because there is too little research from high-income countries. In view of the high number of studies and the consistency of the overall findings, the committee concludes that multiple micronutrient supplementation containing iron and folic acid during pregnancy as compared with iron with

or without folic acid reduces the risk of a small-for-gestational-age infant by 6% (95%CI 2%-10%) in low and middle-income countries. The evidence level is strong. In these countries, it seems that the effect occurs specifically in women with normal or high BMI and in taller women.

Table 20a. Results of the meta-analyses of Haider et al. (2017) and Smith et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy on the risk of a small-for-gestational-age infant.

First author	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Haider [67]	Iron, with or without folic acid[a]	Before 37 weeks of gestation	14	n.r.[b]	n.r.[b]	0.92 (0.86-0.98)	48% significant
Haider [67]	Placebo[c]	Before 13 weeks of gestation	1	n.r. / 207	n.r. / 195	0.93 (0.53-1.63)	n.a.
Smith [61]	Iron with folic acid	Before third trimester	16	n.r.[d]	n.r.[d]	0.94 (0.90-0.98)	n.r.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One out of 14 studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid [b] Total N estimated at 108,432. [c] Control group advised to take folic acid. [d] Total n / N estimated at 35,079 / 110,575 (total number of cases from Zagre et al. (2007) not reported, thus the total n must be interpreted as 'at least 35,079 cases').

Table 20b. Subgroup analyses by maternal BMI and maternal height in Haider et al. (2017)[67] on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy (started < 37 weeks of gestation) on the risk of a small-for-gestational-age infant.

Maternal subgroups	Control	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
Maternal BMI < 20 kg / m^2	Iron with folic acid	4	n.r.[a]	n.r.[a]	1.00 (0.95-1.05)	27%
Maternal BMI ≥ 20 kg / m^2	Iron, with or without folic acid[b]	10	n.r. / 28,768	n.r. 27,720	0.86 (0.81-0.92)	0%
Maternal height < 154,9 cm	Iron, with or without folic acid[b]	8	n.r.[c]	n.r.[c]	0.99 (0.97-1.01)	0%
Maternal height ≥ 154,9 cm	Iron with folic acid	6	n.r / 10,949	n.r. / 10,155	0.82 (0.76-0.89)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Total N estimated at 51,944. [b] One out of the included studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid. [c] Total N estimated at 87,328.

3.7.2 Cohort studies

Summary: Cohort studies on the association between multiple micronutrient supplementation before and during pregnancy and the risk of a small-for-gestational-age infant.

Aspect	Explanation
Selected studies	One meta-analysis of three cohort studies.[57]
Heterogeneity	No
Strength of the association	RR = 0.77 (95%CI 0.63-0.93)
Study population	United States and Europe.

Conclusion:
Based on cohort studies, multiple micronutrient supplementation during the periconceptional period is associated with a lower risk of a small-for-gestational-age infant.
Level of evidence: Limited.

Explanation
Wolf et al. (2017) is the most complete and recent meta-analysis on cohort studies in which the association between multiple micronutrient supplementation in the periconceptional period and the risk of a small-for-gestational-age infant is explored (Table 21).

Summarising three cohort studies, two from the United States and one from Europe, the authors found a significant association with a reduced risk of a small-for-gestational-age infant. There was moderate heterogeneity, mainly in the size of the association. The largest study was from Denmark, and accounted for almost 80% of the cases. The risk of bias of the included studies was low. However, using GRADE, the authors of the meta-analysis classify the quality of the evidence as very low.

In view of the statistically significant lower risk and absence in heterogeneity in the direction of the association, the committee concludes that multiple micronutrient supplementation during the periconceptional period is associated with a lower risk of a small-for-gestational-age infant.

In view of the relatively low number of studies and the fact that the reviewers classify the evidence as very low, the committee judges the level of evidence as limited.

Table 21. Results of the meta-analysis of Wolf et al. (2017) on the association between multiple micronutrient supplementation (three or more vitamins or minerals in a tablet) during the periconceptional period versus no vitamin use and the risk of a small-for-gestational-age infant.

N Cohorts	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
3	799 / 24,069	614 / 12,896	0.77 (0.63-0.93)	43%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

3.8 Low birth weight

3.8.1 Intervention studies

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of a low birth weight infant.

Aspect	Explanation
Selected studies	Two systematic reviews of 16 RCTs[67] and 17 RCTs[61] with meta-analyses of 15 and 17 RCTs.
Heterogeneity	No
Strength of the effect	RR = 0.86 (95%CI 0.81-0.92)[61], RR = 0.88 (95%CI 0.85-0.91)[67]
Study population	Pregnant women predominantly from low and middle-income countries (Asia, Africa, Central-America, one study from Europe). Some at increased risk of pregnancy complications.

Conclusion:
Based on RCTs, supplementation with multiple micronutrient supplementation containing iron and folic acid during pregnancy reduces the risk of low birth weight in low and middle-income countries.
Level of evidence: Strong.

Explanation
Four systematic reviews were found on the effect of multiple micronutrient supplementation on the risk of low birth weight in the infant.[61,63,64,67] Smith et al. (2017) and Haider et al. (2017) were the most complete and recent systematic reviews and are therefore discussed by the committee.[61,67]
Smith et al. (2017) included individual patient data from 17 RCTs and Haider et al. (2017) included study level data of 16 RCTs (15 of which were included in the meta-analysis). The two studies overlap by 13 RCTs. Since the overlap is only partial, results of both systematic reviews are discussed below (Table 22).

Haider et al. (2017) reported a statistically significant reduction in the risk of low birth weight in women who took multiple micronutrient supplementation during pregnancy in their meta-analysis.[67] Additionally, they identified one study which compared multiple micronutrients containing folic acid and iron with a placebo, which was not incorporated in the meta-analysis. This UK study showed an effect estimate in the opposite direction of the result of the meta-regression, however, not statistically significant. There was no heterogeneity and authors classify the evidence as high quality.

Smith et al. (2017) also reported a statistically significant reduction in the risk of low birth weight. [61] They did not report an estimate of heterogeneity; however, visual inspection of the forest plot suggests no heterogeneity in the direction of the effect.

In both meta-analyses, the study of West et al. (2014)[91] contributed for around 75% to total weight of the overall effect estimate.

The committee restricts the conclusion to low and middle-income countries because there is too little research from high-income countries. In view of the large number of studies and the absence of heterogeneity, the committee concludes that the supplementation with multiple micronutrients containing folic acid and iron during pregnancy reduces the risk of an infant with a low birth weight in low and middle-income countries. In view of the fact that one study contributed almost three-quarters of the combined effect estimate, the committee does not quantify the effect.

Table 22. Results from the meta-analyses of Haider et al. (2017) and Smith et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy on the risk of a low birth weight infant.

First author	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Haider[67]	Iron, with or without folic acid[a]	Before 37 weeks of gestation	15	n.r.[b]	n.r.[b]	0.88 (0.85-0.91)	0%
Haider[67]	Placebo[c]	Before 13 weeks of gestation	1	n.r. / 207	n.r. 195	1.63 (0.66-4.03)	n.a.
Smith[61]	Iron with folic acid	First to third trimester	17	n.r.[d]	n.r.[d]	0.86 (0.81-0.92)	n.r.

CI: confidence interval; N: number; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One out of 15 studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid. [b] Total N estimated at 120,946. [c] Control group advised to take folic acid. [d] Total n / N estimated at 28,087 / 112,953.

3.8.2 Cohort studies

Summary: Cohort studies on the association between multiple micronutrient supplementation during pregnancy and the risk of a low birth weight infant.

Aspect	Explanation
Selected studies	One systematic review of two cohort studies.[57]
Heterogeneity	Not applicable.
Strength of the association	No summarised risk estimate.
Study population	North America and Europe.

Conclusion (cohort studies):

There is too little research to draw a conclusion on the association between multiple micronutrient supplementation during the periconceptional period and the risk of a low birth weight infant.

Explanation

Wolf et al. (2017) is the only systematic review summarising cohort studies on the risk of low birth weight infants.[57] They included two prospective cohort studies in their meta-analysis. However, since the number of studies in the meta-analysis is low and the individual studies reported risk estimates in different directions, the committee described the cohort studies separately (Table 23).

Scholl et al. (1997) describes whether the periconceptional use of multivitamins versus no vitamins is associated with the risk of low birth weight of the infant in an American cohort of women who want to become pregnant.[92] The risk of bias in this study was low as assessed with the Newcastle-Ottawa Scale. They found a statistically significant reduction in the risk of having a child with a low birth weight. They controlled their analysis for multiple confounders.

Czeizel et al. (2004) compared multivitamin use with no vitamin use and its association with low birth weight in a Hungarian cohort of women who want to become pregnant.[87] This study also had a low risk of bias on the

Newcastle-Ottawa Scale. The authors found no significant association between periconceptional multivitamin use and the risk of low birth weight.

In view of the fact that there are only two studies available, the committee concludes that there is too little research to draw a conclusion on the association between periconceptional multiple micronutrient supplementation and the risk of a low birth weight infant.

Table 23. Results of the cohort studies included in the systematic review of Wolf et al. (2017) on the association between multiple micronutrient supplementation (three or more vitamins or minerals in a tablet) during the periconceptional period versus no vitamin use and the risk of a low birth weight infant.

Cohort name	n / N exposure	n / N control	RR estimate (95%CI)
Camden Study[92]	112 / 1,148	47 / 282	0.59 (0.43-0.80)
Cohort from Hungarian Periconceptional Service and standard regional antenatal care clinics[87]	150 / 3,029	143 / 3,039	1.05 (0.84-1.32)

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

3.9 Large for gestational age

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of a large-for-gestational-age infants.

Aspect	Explanation
Selected studies	Two meta-analyses of 12 RCTs[64] and 13 RCTs.[61]
Heterogeneity	No
Strength of the effect	RR = 1.13 (95%CI 1.00-1.28)[64] RR = 1.04 (95%CI 0.92-1.18)[61]
Study population	Healthy pregnant women from low and middle-income countries (Asia, Africa), some at increased risk of pregnancy complications.

Conclusion:

Based on RCTs, multiple micronutrient supplementation starting between the first and third trimester increases the risk of a large-for-gestational-age infant in low and middle-income countries.

Level of evidence: Limited.

Explanation

Fall et al. (2009) and Smith et al. (2017) reported on the risk of a large-for-gestational-age infant.[61,64] As the systematic reviews overlapped by nine studies and both provided additional trials, results from both systematic reviews are described by the committee (Table 24).

Fall et al. (2009) defined large for gestational age as birth weight above the within-each-study-population 90th percentile, and all 12 included studies were conducted in low-income countries. In the analysis on study level data, they found a statistically significant increased risk of delivering a large-for-gestational-age infant in women who took multiple micronutrient supplementation during pregnancy compared with women who only took folic acid and iron supplementation during pregnancy. There was no heterogeneity.

In their main analysis, Smith et al. (2017) defined large for gestational age as the > 90th percentile of birth weight (based on reference values from American data). They found no statistically significant increased risk summarising individual patient data of 13 trials. They did not report a measure of heterogeneity.

The committee restricts the conclusion to low and middle-income countries because there is too little research from high-income countries. In view of the large number of studies and the statistically significant association in one meta-analysis, the committee concludes that multiple micronutrient supplementation during pregnancy increases the risk of a large-for-gestational-age infant in low and middle-income countries. Since, the other meta-analysis showed an overall risk estimate close to one, the committee judges the level of evidence as limited.

Table 24. Results from the meta-analyses of Fall et al. (2009) and Smith et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation versus iron and folic acid during pregnancy on the risk of a large-for-gestational-age infant.

First author	N RCTs	Start intervention	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Fall[64]	12	Mean start moment between > 9 weeks and < 30 weeks of gestation	n.r. / 27,428	n.r. / 27,576	1.13 (1.00-1.28)	26%
Smith[61]	13	Before third trimester	n.r.[a]	n.r.[a]	1.04 (0.92-1.18)	n.r.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a]Total n / N estimated at: 4,605 / 108,472 (number of cases in Zagre et al. (2007)[90] not reported, thus total n must be interpreted as 'at least 4,605 cases').

3.10 Other birth measures of growth

Fall et al. (2009) describe other birth measures of growth: i.e. birth length (12 RCTs), head circumference (ten RCTs) and mid-upper-arm circumference (three RCTs).[64] In a meta-regression of all the included, no statistically significant overall effects were found. However, all the overall effects were in the direction of a larger growth measure.

3.11 Caesarean section

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of a caesarean section.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs.[67]
Heterogeneity	No
Strength of the effect	RR = 1.04 (95%CI 0.74-1.46)
Study population	Pregnant women mainly from low and middle-income countries.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of multiple micronutrient supplementation during pregnancy on the risk of a caesarean section.

Explanation

The committee found one systematic review on the outcome caesarean section: the review of Haider et al. (2017) (Table 25).[67]

Summarising the results on study level data of four RCTs, they found no overall effect of maternal multiple micronutrient supplementation on the risk of a caesarean section. There was no heterogeneity.

The overall risk estimate is close to one (with a rather wide confidence interval), which with four studies leads to the conclusion that there is too little research to draw a conclusion on the effect of maternal multiple micronutrient supplementation on the risk of caesarean section.

Table 25. Results from the meta-analysis of Haider et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation versus iron and folic acid during pregnancy (start before 37 weeks of gestation) on the risk of caesarean section.

N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
4	n.r. / 3,299	n.r. / 3,374	1.04 (0.74-1.46)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

3.12 Maternal mortality

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of maternal mortality.

Aspect	Explanation
Selected studies	One systematic review of three RCTs.[67]
Heterogeneity	No
Strength of the effect	RR = 0.97 (95%CI 0.63-1.48)
Study population	Pregnant women, from low or middle-income countries.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of maternal multiple micronutrient supplementation and the risk of maternal mortality.

Explanation

The review of Haider et al. (2017) is the only review which reported on the outcome maternal mortality (Table 26).[67]

They found no overall effect when summarising the results of study level data from three RCTs. The Indonesian RCT accounted for almost 80% of the weight of the overall effect, making the findings less reliable.

In view of the relatively low number of studies and the fact that the combined effect estimate is close to one, the committee concludes that there is too little research to draw a conclusion on the effect of maternal multiple micronutrient supplementation on the risk of maternal mortality.

Table 26. Results from the meta-analysis of Haider et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation versus iron and folic acid during pregnancy (start before 37 weeks) on the risk of maternal mortality.

N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
3	n.r. / 19,089	n.r. / 17,971	0.97 (0.63-1.48)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

3.13 Pre-eclampsia

Summary: Cohort studies on the association between multiple micronutrient supplementation before and during pregnancy and the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	One systematic review of four cohort studies.[79]
Heterogeneity	Not applicable.
Strength of the association	No summarised risk estimate available, but adjusted RR range between 0.33 and 0.88.
Study population	Pregnant women or women who want to become pregnant with or without overweight / obesity in North America, Europe, and Australia.

Conclusion:
Periconceptional multivitamin use is associated with a lower risk of pre-eclampsia in cohort studies.
Level of evidence: Limited.

Explanation
Shim et al. (2016), Ramakrishnan et al. (2012), Dean et al. (2014), and Liu et al. (2018) systematically searched the literature for cohort studies reporting on the association between multiple micronutrient use during pregnancy and the risk of pre-eclampsia.[35,58,65,79]

Liu et al. (2018) is the most complete and recent review.[79] However, the combined risk estimate they present in their meta-analysis is not useful for the committee for three reasons: i) they included a Canadian cohort twice (results from 2002-2005 and results from a longer follow-up period 2002-2008), ii) they included a retrospective cohort study, and iii) they included a Dutch study on the generation R cohort[93] which focused on folic acid alone rather than multivitamin use (i.e. only 15% of study population took multivitamins). Therefore, the results of the relevant individual cohort studies included by Liu et al. (2018) are discussed below (Table 27).

Bodnar et al. (2006) describe results from the Pregnancy Exposures and Pre-eclampsia Prevention study from the USA. They explored the association between maternal multivitamin use during the periconceptional

period or before 16 weeks of gestation (yes / no) and the risk of pre-eclampsia. They found a statistically significant association with a reduced risk of pre-eclampsia after adjustments for confounders. They do not comment on the use of folic acid or whether or not the multivitamin supplements contain folic acid. An indication was found that lean women (prepregnancy BMI < 25 kg / m^2) may benefit more from multivitamin supplementation (adjusted OR 0.29; 95%CI 0.12-0.65) than women with a prepregnancy BMI ≥ 25 kg / m^2 (adjusted OR 1.08; 95%CI 0.52-2.25)[94], but the committee notes that the confidence intervals overlap.

The study of Catov et al. (2011) was included in the review of Liu et al. (2018).[95] However, no risk estimates for pre-eclampsia are presented in that paper. The Catov et al. (2009) paper on the same cohort did report on pre-eclampsia.[96] Therefore, the committee describes the results of Catov et al. (2009). In the Danish National Birth Cohort, multivitamin use in the periconceptional period (4 weeks prior to 8 weeks after the last menstrual period) showed no statistically significant association with the risk of pre-eclampsia in the crude analysis nor in the adjusted analysis. However, the hazard ratio was in favour of the participants using multivitamins. In the group who only took folic acid, a slightly higher HR was found than for the multivitamin group (adjusted HR multivitamin = 0.88, 95%CI 0.70-1.10 versus adjusted HR folic acid only = 0.98; 95%CI 0.50-1.92).

In the Australian cohort Environments for Healthy Living Project, Vanderlelie et al. (2016) found an association between multivitamin use in the first trimester of pregnancy and a reduced risk of pre-eclampsia.[97] This study found an association with a somewhat greater reduction in the risk of pre-eclampsia in women with a prepregnancy BMI ≥ 25 kg / m^2 (adjusted OR 0.48; 95%CI 0.27-0.86) than in women with a prepregnancy BMI of < 25 kg / m^2 (adjusted OR 0.60; 95%CI 0.39-1.36). Slightly higher odds ratios, but in the same direction and with the same level of statistical significance, were found for the group using folic acid alone (adjusted OR multivitamin = 0.33, 95%CI 0.14-0.75 and adjusted OR folic acid alone = 0.42, 95%CI 0.13-0.98).

Wen et al. (2016) presented results of the Canadian OaK Birth Cohort.[33] They found no statistically significant association between folic acid supplementation (mostly taken via multivitamin tablets) starting before 20 weeks of gestation and the risk of pre-eclampsia. However, the direction of the association was in favour of the folic acid (i.e. multivitamin) group. Furthermore, almost 95% of the study population took some sort of folic acid supplementation (either folic acid alone, or via multivitamins), so the comparison group was very small. As a sensitivity analysis, they explored the supplementation of folic acid alone (i.e. not in a multivitamin supplement) and found similar results. The authors found that women with a high risk of pre-eclampsia might benefit more from supplementation than women at low risk of pre-eclampsia.

In the light of the consistent direction of the reported associations that were not close to zero, the committee concludes that there is limited evidence that periconceptional multivitamin use is associated with a reduced risk of pre-eclampsia. However, the findings of the available cohort studies do not provide information on whether the association is stronger for multivitamins than for folic acid alone.

Table 27. Results from the four cohort studies included in Liu et al. (2018) on the association between multiple micronutrient supplementation during pregnancy and the risk of pre-eclampsia.

Cohort name	Exposure	Timing exposure	n / N exposure	n / N control	RR estimate (95%CI)
Pregnancy Exposures and Pre-eclampsia Prevention study[94]	Multivitamin use (yes / no)	Preconceptional or before 16 weeks of gestation	3.8%	4.4%	0.55 (0.32-0.95)
Danish National Birth Cohort[96]	Multivitamin use (yes / no)[a]	Periconceptional (4 weeks prior to 8 weeks after the last menstrual period)	n.r. / 18,551	n.r. / 7,582	0.88 (0.70-1.10)
Environments for Healthy Living Project[97]	Multivitamin use (yes / no)[a]	First trimester	0.97% (total N 719)	2.9% (total N 1,066)	0.33 (0.14-0.75)
OaK Birth Cohort[33]	Folic acid supplementation mostly by taking multivitamins (yes / no)[b]	Before 20 weeks of gestation	228 / 7,265	17 / 404	0.58 (0.33-1.02)

CI: confidence interval; n / N: number of cases / total number of participants; n.r.: not reported; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] The 'no' group reported no use of multivitamin nor of folic acid [b] 95% took folic acid via a multivitamin supplement.

3.14 Maternal anaemia

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of maternal anaemia.

Aspect	Explanation
Selected studies	One systematic review of five RCTs with a meta-analysis of four RCTs.[67]
Heterogeneity	Yes, in size and direction of the effect.
Strength of the effect	RR = 1.03 (95%CI 0.85-1.24) (meta-analysis)[67]
Study population	Pregnant women mainly from low and middle-income countries.

Conclusion:

Study findings from RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of maternal anaemia are contradictory.

Explanation

The committee identified one systematic review on the outcome maternal anaemia; the review of Haider et al. (2017).[67] The authors found five RCTs, of which four were summarised in a meta-analysis of study level data (Table 28).

The four RCTs in the meta-analysis compared multiple micronutrient supplementation with iron and folic acid with a control group who received iron with / without folic acid. The fifth RCT uses a placebo group as control (i.e. not receiving iron or folic acid as part of the trial). The combined result of the meta-analysis showed no overall effect of multiple micronutrient

supplementation on the risk of maternal anaemia. Unexplained heterogeneity was substantial and present in size as well as direction of the effect. The RCT using a placebo in the control group showed a significant reduction in the risk of maternal anaemia in the multiple micronutrient group. Possibly, this is due to the fact that the control group received a placebo (neither iron nor folic acid).
Based on the meta-analysis of RCTs with control groups using iron and folic acid supplements, and in view of the fact that the risk estimates in the original studies ranged from nearly statistically significant above one and nearly significant below one in combination with significant heterogeneity in the direction of the effect, the committee concludes that study findings on the effect of multiple micronutrient supplementation during pregnancy on the risk of maternal anaemia are contradictory.

Table 28. Results from the meta-analysis of Haider et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation during pregnancy on the risk of maternal anaemia.

N RCTs	Control	Start intervention	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
4	Iron with or without folic acid[b]	Before 37 weeks of gestation	n.r. / 3,984	n.r. / 3,907	1.03 (0.85-1.24)	54%
1	Placebo[a]	Before 13 weeks of gestation	n.r. / 207	n.r. / 195	0.46 (0.29-0.73)	n.a.

CI: confidence interval; N: number; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Control group advised to take folic acid [b] One out of four studies had an iron-only control group, all other studies compared the intervention-supplement with a supplement containing both iron and folic acid. [b] Control group advised to take folic acid.

3.15 Offspring mortality

In this paragraph, the outcome offspring mortality is discussed by the committee. Studies on three measures were found: neonatal mortality (birth to < 28 days), infant death (birth to < 365 days), or child death. Hence, some of the outcome measures overlap.

The committee found seven systematic reviews on the effect of multiple micronutrient supplementation during pregnancy on the risk of offspring mortality.[58,60-63,67,68] The committee selected three systematic reviews that were the most complete and comprised one or more unique trials or cohort studies compared with the other systematic reviews.[61,67,68]

Devakumar et al. (2016)[68] and Haider et al. (2017)[67] performed meta-analyses of RCTs on study level data. Smith et al. (2017)[61] performed individual patient data (IPD) meta-analyses of RCTs.

There were no relevant RCTs or cohort studies published on this topic after the appearance of the included systematic reviews. In the next subparagraphs, the results will be discussed per outcome.

3.15.1 Neonatal mortality

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of neonatal mortality.

Aspect	Explanation
Selected studies	Two meta-analyses of 11[67] and 12[61] RCTs.
Heterogeneity	No
Strength of the effect	RR = 0.99 (95%CI 0.89-1.09)[61] and RR = 1.06 (95%CI 0.92-1.22)[67]
Study population	Pregnant women predominantly from low and middle-income countries. Some at increased risk of pregnancy complications.

Conclusion:

Study findings from RCTs on the effect of multiple micronutrient supplementation during pregnancy on neonatal death are inconclusive.

Explanation

Of the included systematic reviews, two reported on multiple micronutrient supplementation during pregnancy and the risk of neonatal mortality: Haider et al. (2017) and Smith et al. (2017).[61,67] Haider et al. (2017) summarised 11 trials on study level data. Smith et al. (2017) included individual patient data of 12 trials. Nine studies were incorporated in both reviews. Since the overlap is only partial, both will be discussed by the committee (Table 29).

The two reviews found no statistically significant effect of multiple micronutrient supplementation during pregnancy on the risk of neonatal mortality. Haider et al. (2017) classify the quality of their results as 'high' according to GRADE criteria, meaning that further research is very unlikely to change the authors' confidence in the effect estimate. Heterogeneity was moderate in Haider et al. (2017) and not explained. Visual inspection of the forest plot showed heterogeneity in the direction and size of the effect. Smith et al. (2017) did not report a measure of heterogeneity for the random-effects model.

In view of the large number of studies and the effect estimates from the two meta-analyses that are not in line with each other but not statistically significant either, the committee concludes that study findings on the effect of multiple micronutrient supplementation on the risk of neonatal mortality are inconclusive.

Table 29. Results from the meta-analyses of Haider et al. (2017) and Smith et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation versus iron and folic acid during pregnancy on the risk of neonatal mortality.

First author	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
Haider[67]	Before 37 weeks of gestation	11	n.r.[a]	n.r.[a]	1.06 (0.92-1.22)	31%
Smith[61]	Before third trimester	12	n.r.[b]	n.r.[b]	0.99 (0.89-1.09)	n.r.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).[a] Total N: 106,306. [b] Total n / N estimated at 3,433 / 106,234.

3.15.2 Infant mortality

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of infant mortality.

Aspect	Explanation
Selected studies	One systematic review with two meta-analyses of eight RCTs (mortality in first year) and nine RCTs (mortality in the first 6 months).[61]
Heterogeneity	Not reported.
Strength of the effect	Mortality < 6 months: RR = 0.93 (95%CI 0.86-1.00) Mortality < 12 months: RR = 0.97 (95%CI 0.88-1.06)
Study population	Pregnant women predominantly from low and middle-income countries (Asia, Africa), some at increased risk of pregnancy complications.

Conclusion:

Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of mortality in the first 6 months of life in low and middle-income countries.

Level of evidence: Limited.

Explanation

Smith et al. (2017) is the most complete and recent review on the effect of multiple micronutrient supplementation during pregnancy on infant mortality (Table 30).[61]

They performed individual patient data meta-analysis and found a reduced, but statistically non-significant, risk of multiple micronutrient supplementation during pregnancy on infant mortality in the first 6 months of life (nine RCTs) and an effect in the same direction for infant mortality in the first year of life (eight RCTs) (same results in the fixed effects and random-effects model). Of note is that almost 85% of infant mortality occurred in the first 6 months of life. Heterogeneity for the random-effects models was not reported, but visual inspection of the forest plot showed half of the risk estimates of the individual RCTs had values below one, and the other half above one. In their abstract, Smith et al. (2017) reported that anaemic women had a greater risk reduction in 6-month infant mortality as compared with non-anaemic women. However, this difference was only present in the fixed-effects model (anaemic women RR = 0.71, 95%CI 0.60-0.86; non-anaemic women RR = 0.93, 95%CI 0.78-1.11) and not in the random-effects model (anaemic women RR = 0.85, 95%CI 0.61-1.18; non-anaemic women RR = 0.93, 95%CI 0.87-1.11). The iron status is expected to improve (or at least be maintained) in both the intervention and the control group, because both received iron and folic acid. Smith et al. (2017) provided no rationale for the difference of the effect on infant mortality between anaemic and non-anaemic women, and therefore, the committee does not take the reported difference into account in the conclusion.

The committee restricts the conclusion to low and middle-income countries because there is too little research from high-income countries. The committee concludes that multiple micronutrient supplementation during pregnancy reduces the risk of infant mortality in the first 6 months of life in low and middle-income countries. In view of the fact that the confidence

interval included one and the forest plot showed effects under as well as above one, the committee judges the level of evidence as limited.

Table 30. Results from the meta-analysis of Smith et al. (2017) on the effect of multiple micronutrient with iron and folic acid supplementation versus iron and folic acid during pregnancy (start before the third trimester) on the risk of infant mortality.

Outcome	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
Infant mortality < 6 months	9	n.r.[a]	n.r.[a]	0.93 (0.86-1.00)	n.r.
Infant mortality < 12 months	8	n.r.[b]	n.r.[b]	0.97 (0.88-1.06)	n.r.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).[a] Total n / N estimated at 4,100 / 93,288. [b] Total n / N estimated at 3,415 / 61,998.

3.15.3 Childhood death

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on the risk of childhood death.

Aspect	Explanation
Selected studies	One meta-analysis of nine RCTs.[68]
Heterogeneity	No
Strength of the effect	Mortality difference per 1000 livebirths = -0.05 (95%CI -5.25 to +5.15)
Study population	Pregnant women predominantly from low and middle-income countries.

Conclusion:

Study findings from RCTs on the effect of multiple micronutrient supplementation on the risk of childhood death are inconclusive.

Explanation

Devakumar et al. (2016) performed a meta-analysis of study level data on the outcome childhood death (i.e. mortality up to 8 years of age) (Table 31).[68]

In a meta-regression of nine follow-up reports of RCTs, they found no mortality difference per 100,000 livebirths. There was no statistically significant heterogeneity, but the confidence interval was wide. Furthermore, the weight of the study of West et al. (2014).[91] was substantial (50%). The large impact of one RCT is a limitation of the meta-analysis, especially since that RCT used a control group which received a lower iron dose compared with most other RCTs in the meta-analysis (30 milligram per day versus 60 milligram per day). A subgroup analysis of the meta-analysis suggested less childhood death with the higher iron dose (effect sizes were, respectively, +4.51; 95%CI -2.91 to +11.94 with 0% heterogeneity for RCTs with supplements containing 60 milligram iron per day, and +0.41; 95%CI -14.76 to 15.57; I^2 62% with supplements containing 30 milligram iron per day).

The number of cases was substantial, and the difference in childhood mortality was close to the no effect level (0.00). However, the confidence interval is too wide to conclude that an effect is unlikely. Therefore, the committee concludes that study findings on the effect of multiple micronutrient supplementation on the risk of childhood death are inconclusive.

Table 31. Results of the meta-analysis of Devakumar et al. (2016) on the effect of multiple micronutrient supplementation versus iron and folic acid during pregnancy (starting from 9 to 22 weeks of gestation) on the risk of childhood death.

N RCTs	n / N intervention	n / N control	Difference in rates per 1000 live births (95%CI)	Heterogeneity I^2
9	1,513 / 33,884	1,578 / 33,266	-0.05 (-5.25 to +5.15)	8%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial.

3.16 Cognitive functioning of the offspring

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on cognitive functioning.

Aspect	Explanation
Selected studies	One systematic review of four RCTs.[68]
Heterogeneity	Not reported.
Strength of the effect	No summarised effect size.
Study population	Pregnant women, from South-Asia.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of maternal multiple micronutrient supplementation on cognitive functioning in the offspring.

Explanation

Both Haider et al. (2017) and Devakumar et al. (2016) included cognitive outcomes in their review.[67,68] Haider et al. (2017) based its findings on one study which is also incorporated in Devakumar et al. (2016). As the review of Devakumar et al. (2016) is the most complete, their results are discussed below.

They included four RCTs on this topic, one from Bangladesh (MINIMat), one from China, one form Indonesia and one from Nepal (Sariahi). The trials presented results on various cognitive tests and at different ages. No meta-analysis was performed by Devakumar et al. (2016).[68]

The Nepal trial found a slightly lower mean cognitive score at the age of 7 to 9 years in the offspring of women who took multiple micronutrient supplements during pregnancy compared with offspring of women who only took iron, folic acid and vitamin A (Universal Nonverbal Intelligence Test score: -2.4 95%CI -4.6;-0.2). Mixed results were found for motor and executive function tests.[98]

The trials from Bangladesh and China found no difference in motor or psychomotor ability in children of 7 months up to 1 year of age between the intervention (multiple micronutrient supplementation) and the control group (iron and folic acid). The trial from Bangladesh found no difference in problem solving nor in behaviour.[99] For mental development, the Chinese trial found a beneficial effect of maternal multiple micronutrient supplementation in the age-adjusted scores at 1 year of age (1.20 points; 95%CI 0.32-2.08) but not at 3 months and 6 months of age. At the age of

9 years, no differences were observed in cognitive scores compared with the folic acid or the iron and folic acid groups.[100]

The Indonesian trial found an increase in motor ability (fraction of the variation of the score: 0.19; 95%CI 0.02-0.37) at the age of 3.5 years in offspring of mothers who received multiple micronutrient supplementation during pregnancy compared with iron and folic acid alone. However, no differences in visual attention, executive functioning, language ability or socioemotional development were found.[101]

In the trials from Bangladesh and Indonesia, indications were found that maternal micronutrient supplementation improved cognitive outcomes in the offspring of mothers who had a poorer nutritional status. In Bangladesh, they found an increase in psychomotor development in children whose mothers had a BMI < 18.5 kg / m^2, and in Indonesia, they found that multiple micronutrient supplementation had a beneficial effect on motor ability and visual attention / spatial ability in children of undernourished mothers.

In view of the number of studies, the inconsistency of findings and the diverse outcome measures, the committee concludes that there is too little research to draw a conclusion on the effect of maternal micronutrient supplementation on cognitive functioning in the offspring.

3.17 Autism spectrum disorder in the offspring

Summary: Cohort studies on the association of multiple micronutrient supplementation during pregnancy and the risk of autism spectrum disorders in the offspring.

Aspect	Explanation
Selected studies	One meta-analysis of four cohort studies.[81]
Heterogeneity	Yes, in the size of the association.
Strength of the association	RR = 0.59 (95%CI 0.42-0.83)
Study population	Women before conception or pregnant women from Europe, North America, and Asia.

Conclusion:

Based on cohort studies, multiple micronutrient supplementation use before conception and/or use during pregnancy is associated with a lower risk of autism spectrum disorders in the offspring.
Level of evidence: Limited.

Explanation

There is one meta-analysis on the association between the intake of multiple micronutrient supplements during pregnancy and the risk of autism spectrum disorders in the offspring (Table 32).[81] The committee did not find additional cohort studies published after the final search date of the meta-analysis.

Guo et al. (2019) authors included four prospective cohort studies and found a statistically significant lower risk of autism spectrum disorders in

the offspring in mothers who took multiple micronutrient supplements during pregnancy compared with mothers who did not. Heterogeneity was high but only present in the size of the association, not in the direction. Heterogeneity was not explained by period of supplementation, geographical area, study quality, or study type. There was no publication bias detected.

Guo et al. (2019) included separate risk estimates from the original publications for multiple micronutrient intake before conception and during different trimesters of pregnancy into the meta-analysis. For example, the study of Levine et al. (2018) performed an analysis of before-conception supplementation and of during-pregnancy supplementation. Both estimates were included in the meta-analysis. By including separate risk estimates for different timings of supplementation, participants might be included multiple times in the meta-analysis, limiting the interpretation of the findings. However, subgroup analysis of supplementation during pregnancy (three studies; five risk estimates) revealed similar results as the analysis of supplementation before conception (two studies; two risk estimates) (RR = 0.57, 95%CI 0.36-0.91; I^2 94% and RR = 0.40, 95%CI 0.24-0.66; I^2 17% respectively). Moreover, heterogeneity was not present in the direction of the associations. Thus, the results appear robust.

In view of the number of studies, the fact that the risk estimate was not close to one and heterogeneity was only present in the size of the association, the committee concludes that multiple micronutrient supplementation use before conception and/or use during pregnancy is associated with a lower risk of autism spectrum disorders in the offspring.

Table 32. Results of the meta-analysis by Guo et al. (2019) on the association between multiple micronutrient supplementation versus no such supplementation before conception and/or during pregnancy and the risk of autism spectrum disorders in the offspring.

N cohorts	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
4	n.r.[a]	n.r.[a]	0.59 (0.42-0.83)	92%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Total n / N in all included cohort studies 4,252 / 230,847.

3.18 Childhood growth measures in the offspring

The committee found two systematic reviews on maternal multiple micronutrient supplementation and its effect on childhood growth.[68,80] Since the review of Lu et al. (2014) reported on older findings and also incorporated RCTs which essentially explored the effect of one micronutrient, the committee does not describe this review. The review of Devakumar et al. (2016) is described below. For weight for age, height for age and head circumference, effect estimates from meta-regression analyses were available. These measures are further discussed in the subparagraphs. The authors also described stunting, the effect of the use of multiple micronutrient supplements during pregnancy on underweight, wasting, BMI and body composition, without meta-analyses. They found

no significant beneficial nor detrimental effects of maternal multiple micronutrient supplementation on these outcomes in childhood.

3.18.1 Childhood weight for age

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on childhood weight for age z-score.

Aspect	Explanation
Selected studies	One meta-analysis of six RCTs.[68]
Heterogeneity	No
Strength of the effect	Weight for age z-score +0.02 (95%CI -0.03 to +0.07)
Study population	Pregnant women, predominantly from low and middle-income countries.

Conclusion:

Based on RCTs, an effect of maternal multiple micronutrient supplementation on weight for age in the offspring between 2 and 8 years of age is unlikely.

Explanation

Devakumar et al. (2016) included follow-up data on study level from six RCTs and found no overall effect of maternal micronutrient supplementation on weight for age in the offspring (Table 33). There was no heterogeneity. The authors describe that two of the included trials indicated a greater mean weight for age at a younger age, which disappeared at a later age.[102,103] The studies included in the meta-analysis were predominantly from low and middle-income countries.

In view of the effect estimate close to zero, the sufficient number of studies, lack of heterogeneity and small confidence interval, the committee concludes that an effect of maternal micronutrient supplementation on weight for age in the offspring between 2 and 8 years of age is unlikely.

Table 33. Results of the meta-analysis of Devakumar et al. (2016) on the effect of multiple micronutrient supplementation (at least three micronutrients) versus iron with or without folic acid during pregnancy (start between week 9 and week 18 of gestation) on infant weight for age z-score.

N RCTs	n / N intervention	n / N control	Effect size (95%CI)	Heterogeneity I^2
6	n.r.[a]	n.r.[a]	+0.02 (-0.03 to +0.07)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Total N: 10,795.

3.18.2 Childhood height for age

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on childhood height for age z-score.

Aspect	Explanation
Selected studies	One meta-analysis of six RCTs.[68]
Heterogeneity	No
Strength of the effect	Effect size +0.01 (95%CI -0.04 to +0.06)
Study population	Pregnant women from low and middle-income countries.

Conclusion:

Based on RCTs, an effect of maternal multiple micronutrient supplementation on height for age in the offspring between 2 and 8 years of age is unlikely.

Explanation

Devakumar et al. (2016) included follow-up data on study level from six RCTs and found no overall effect of maternal micronutrient supplementation during pregnancy on height for age in the offspring (Table 34).[68] There was no heterogeneity. The authors describe that one of the included trials indicated greater mean length for age at a younger age, which disappeared at a later age.[103] The studies included in the meta-analysis were predominantly from low and middle-income countries.

In view of the effect estimate close to zero, the sufficient number of studies, lack of heterogeneity and small confidence interval, the committee concludes that an effect of maternal micronutrient supplementation during pregnancy on height for age in the offspring between 2 and 8 years of age is unlikely.

Table 34. Results of the meta-analysis of Devakumar et al. (2016) on the effect of multiple micronutrient supplementation (at least three micronutrients) versus iron with or without folic acid during pregnancy (start between week 9 and week 18 of gestation) on infant height for age z-score.

N RCTs	n / N intervention	n / N control	Effect size (95%CI)	Heterogeneity I^2
6	n.r.[a]	n.r.[a]	+0.01 (-0.04 to +0.06)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Total N: 10,795

3.19 Blood pressure in the offspring

Summary: RCTs on the effect of multiple micronutrient supplementation during pregnancy on infant blood pressure.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[68]
Heterogeneity	No
Strength of the effect	+0.11 mmHg (95%CI -0.41 to +0.62) for systolic blood pressure +0.47 mmHg (95%CI -0.01 to +0.95) for diastolic blood pressure
Study population	Pregnant women from South-Asia.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of maternal multiple micronutrient supplementation on systolic and diastolic blood pressure of the offspring during childhood (age 4 to 8 years).

Explanation

Devakumar et al. (2016) is the only systematic review reporting on the outcome blood pressure in the offspring at the age of 4 to 8 years (Table 35).[68]

They included follow-up data at study level from three RCTs and reported no significant effect of maternal micronutrient supplementation on systolic and diastolic blood pressure in the offspring. There was no heterogeneity. One study found a significant reduction in mean systolic blood pressure at the age of 2 years, but not at the age of 8 years.[102,104]

In view of the number of studies and the effect estimates that are close zero but not statistically significant either, the committee concludes that there is too little research to draw a conclusion on the effect of maternal micronutrient supplementation on systolic and diastolic blood pressure in the offspring.

Table 35. Results of the meta-analysis of Devakumar et al. (2016) on the effect of multiple micronutrient supplementation (at least three micronutrients) versus iron with folic acid during pregnancy (start between week 11 and week 16 of gestation) on infant blood pressure.

Outcome	Start intervention	N RCTs	n / N intervention	n / N control	Effect size (95%CI)	Hetero-geneity I^2
Systolic blood pressure	Mean start between 11 and 16 weeks of gestation	3	n.r.[a]	n.r.[a]	+0.11 (-0.41 to +0.62)	0%
Diastolic blood pressure	Mean start between 11 and 16 weeks of gestation	3	n.r.[a]	n.r.[a]	+0.47 (-0.01 tot +0.95)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Total N: 4,685

3.20 Summary of findings on multiple micronutrients

The committee eventually found 24 outcomes for which at least two RCTs or cohort studies were summarised in a systematic review or meta-analysis. Seven systematic reviews provided data for this chapter.[12,57,61,64,67,68,81]

In the available meta-analyses, multiple micronutrient supplementation is generally defined as supplements combining at least three micronutrients. The composition of these supplements differed between studies, was sometimes unknown, and therefore, could not be specified in the conclusions. Often, a combination of B-vitamins (including folic acid), vitamin C, vitamin D, and some minerals like iron and calcium were studied. In a fair number of studies, the United Nations International Multiple Micronutrient Preparation (UNIMMAP) was studied versus a combination of folic acid and iron. The UNIMMAP supplement contains one recommended daily allowance of vitamin A, vitamin B_1, vitamin B_2, vitamin B_{12}, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium, iodine with 30 milligram of iron, and 15 milligram of zinc.

Of note is that almost all control conditions included iron supplementation (30 milligram or 60 milligram) with folic acid. A single study only supplemented iron in the control condition.

Some subgroups appear to benefit more from supplementation for certain outcome measures than others: mothers who started supplementation ≥ 20 weeks of gestation (perinatal mortality), mothers with a prepregnancy BMI < 20 kg / m^2 (preterm birth), mothers with a prepregnancy BMI ≥ 20 kg / m^2 and mothers with a height of ≥ 154.9 cm (small for gestational age). The committee notes that the findings vary substantially between outcomes and do not show a consistent pattern. The subgroup analyses of Smith et al. 2017 suggest that further subgroup differences cannot be ruled out. Again, findings vary substantially between outcomes. Smith

reported that infant sex (protective direction for female foetuses), start moment of supplementation (protective direction for both < 20 weeks of gestation and ≥ 20 weeks of gestation, depending on the outcome), maternal adherence to the supplementation (protective direction for ≥ 95% adherence), maternal underweight at baseline (protective direction for both BMI < 18.5 kg / m^2 and BMI ≥ 18.5 kg / m^2, depending on the outcome), maternal stature (protective direction for height ≥ 150 cm), maternal haemoglobin at baseline (protective direction for both anaemic and non-anaemic, depending on the outcome), and maternal education (protective direction for ≥ one year of formal education) were effect modifiers for at least one of the outcomes under study in their meta-analyses of individual patient data: i.e. stillbirth, neonatal mortality, infant mortality, low birth weight, preterm birth, small for gestational age, and large for gestational age.

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

Committee's conclusion	Outcome
Strong evidence	• Preterm birth < 37 weeks: Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of preterm birth in low and middle-income countries in women with a low prepregnancy BMI with 15% (-20% to -10%). • Early preterm birth < 34 weeks: Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of early preterm birth in low and middle-income countries by 13% (95%CI 5%-21%). • Small for gestational age: Based on RCTs, supplementation with multiple micronutrients containing iron and folic acid starting during pregnancy reduces the risk of a small-for-gestational-age infant with 6% (95% CI 2%-10%) in low and middle-income countries. • Low birth weight: Based on RCTs, supplementation with multiple micronutrient supplementation containing iron and folic acid during pregnancy reduces the risk of low birth weight in low and middle-income countries.
Limited evidence	• Preterm birth < 37 weeks: Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of preterm birth in low and middle-income countries. • Small for gestational age: Based on cohort studies, multiple micronutrient supplementation during the periconceptional period is associated with a lower risk of a small-for-gestational-age infant. • Large for gestational age: Based on RCTs, multiple micronutrient supplementation starting between the first and third trimester increases the risk of a large-for-gestational-age infant in low and middle-income countries. • Pre-eclampsia: Based on cohort studies, periconceptional multivitamin use is associated with a lower risk of pre-eclampsia in cohort studies. • Infant mortality: Based on RCTs, multiple micronutrient supplementation during pregnancy reduces the risk of mortality in the first six months of life in low and middle-income countries. • Autism spectrum disorders in the offspring: Based on cohort studies, multiple micronutrient supplementation during pregnancy is associated with a lower risk of autism spectrum disorders in the offspring.
Unlikely	• Stillbirth: Based on RCTs, the effect of multiple micronutrient supplementation during pregnancy on the risk of stillbirth is unlikely. • Childhood weight for age: Based on RCTs, an effect of maternal multiple micronutrient supplementation on weight for age in the offspring between 2 and 8 years of age is unlikely. • Childhood height for age: Based on RCTs, an effect of maternal multiple micronutrient supplementation on height for age in the offspring between 2 and 8 years of age is unlikely.

Committee's conclusion	Outcome
Contradictory	• Perinatal mortality (RCTs); • Maternal anaemia (RCTs).
Too little research	• Stillbirth (cohort studies); • Recurrent neural tube defects (RCTs); • Cleft lip with or without cleft palate and recurrent clefts (cohort studies); • Preterm birth < 37 weeks (cohort studies); • Low birth weight (cohort studies); • Caesarean section (RCTs); • Maternal mortality (RCTs); • Cognitive functioning in the offspring (RCTs); • Blood pressure in the offspring (RCTs).
Inconclusive	• Miscarriage (RCTs); • Neonatal mortality (RCTs); • Childhood mortality (RCTs).

3.21 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 strong evidence level.

Strong evidence from RCTs was found for a lower risk of preterm birth (< 34 weeks of gestation and < 37 weeks), small for gestational age and low birth weight. However, as almost all included trials were from low or middle-income countries, the committee considered that these findings have little relevance for the Dutch situation. Therefore, these conclusions are not mentioned in the advisory report.

The same applies to the findings, based on RCTs, with limited evidence for a lower risk of infant mortality and a higher risk of an infant that is large for gestational age.

Limited evidence based on cohort studies was found for an association with a lower risk of small for gestational age, pre-eclampsia, and autism spectrum disorders in the offspring. Although these findings were more generalisable to the Dutch situation, as they were based on data from Western countries, the committee considers the evidence not sufficient for the formulation of recommendations.

04
vitamin D

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of vitamin D supplementation (alone) during pregnancy on the risk of stillbirth, perinatal mortality, preterm birth, an infant that is small for gestational age, gestational diabetes, gestational hypertension, pre-eclampsia, allergy and atopic diseases in the offspring, respiratory tract infections in the offspring, and bone mineral density in the offspring. For these outcomes, at least two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two intervention studies.

Update July 2018 - July 2019

In the update, one umbrella review was found.[105] All reviews included by Pilz et al. (2018) had already been included in the evaluation of the committee. Therefore, this publication was not further discussed by the committee.

4.1 Stillbirth

Summary: Vitamin D supplementation and the risk of stillbirth.

Aspect	Explanation
Selected studies	One meta-analysis 16 RCTs.[106]
Heterogeneity	No
Strength of the effect	RR = 0.75 (95%CI 0.50-1.12); low number of cases
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 vitamin D supplementation during pregnancy on the risk of stillbirth.

Explanation

There are four systematic reviews of the effect of vitamin D supplementation on the risk of stillbirth.[106-109] In their review of systematic reviews, Autier et al. (2017) summarise the results of the meta-analysis by De Regil et al. (2017), in which three RCTs are summarised.[108,109]
In addition to these three RCTs, Autier et al. (2017) describe three more recently published RCTs (six in total). The six RCTs are included in the meta-analysis by Roth et al. (2017) in combination with ten other RCTs.[106] Therefore, the results from the meta-analysis of Roth et al. (2017) are described below (Table 36).

Roth et al. (2017) find no significant effect of vitamin D supplementation on the risk of stillbirth. The number of cases in the meta-analysis, however, was small, limiting the interpretation of this finding.[106] Heterogeneity was low.

As the relative risk estimate was far from one and in view of the small number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of stillbirth.

Table 36. Results from the meta-analysis of Roth et al. (2017) on the effect of vitamin D supplementation during pregnancy on the risk of stillbirth.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
10-410 microgram / day vitamin D[a] versus placebo, no or up to 10 microgram / day vitamin D	12 to 28 weeks gestation	16	42 / 2,458	49 / 2,148	0.75 (0.50-1.12)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Three RCTs provided a bolus of 1,250 microgram vitamin D twice, 5,000 microgram vitamin D once, or twice in combination with six times 1,250 microgram vitamin D.

4.2 Perinatal mortality

Summary: Vitamin D supplementation and the risk of perinatal mortality.

Aspect	Explanation
Selected studies	One meta-analysis of 12 RCTs.[107]
Heterogeneity	No
Strength of the effect	RR = 0.73 (95%CI 0.49-1.10); low number of cases
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 vitamin D-supplementation during pregnancy on the risk of perinatal mortality.

Explanation

There is one systematic review of the effect of vitamin D supplementation during pregnancy on the risk of perinatal mortality in terms of foetal or neonatal mortality (Table 37).[107]

Bi et al. (2018) find no significant effect of vitamin D-supplementation on the risk of perinatal mortality. The number of cases was low, however.

The committee, therefore, concludes that there is too little evidence to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of perinatal mortality.

Table 37. Results from the meta-analysis of Bi et al. (2018) on the effect of vitamin D supplementation during pregnancy on the risk of perinatal mortality.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (%)	Hetero-geneity I^2
20-125 microgram / day vitamin D[a] versus placebo, no or up to 10 microgram / day vitamin D	10 weeks gestation to third trimester	11	37 / 2,036	48 / 1,888	0.73 (0.49-1.10)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Three RCTs provided a bolus of 875 or 1,250 microgram vitamin D per week or 5,000 microgram vitamin D once.

4.3 Preterm birth

Summary: Vitamin D supplementation and the risk of preterm birth.

Aspect	Explanation
Selected studies	Two meta-analyses of 13[106] and 11 RCTs.[107]
Heterogeneity	No
Strength of the effect	RR = 1.00 (95%CI 0.77-1.33)[106] and RR = 0.98 (95%CI 0.77-1.26)[107]
Study population	Healthy pregnant women and pregnant women with gestational diabetes.

Conclusion:

Based on RCTs, an effect of vitamin D supplementation during pregnancy on the risk of preterm birth is unlikely.

Explanation

There are seven meta-analyses of vitamin D supplementation and the risk of preterm birth (37 weeks). In the review of Autier et al. (2017), the results of four previous systematic reviews of Thorne-Lyman et al. (2012), Perez-Lopez et al. (2015), De-Regil et al. (2016) and Zhou et al. (2017) are summarised.[108-112] The RCTs in these meta-analyses are also summarised in two more recent systematic reviews by Roth et al. (2017) and Bi et al. (2018), except for one trial in which the control group received no treatment.[106,107] Therefore, the committee focused on the findings of the latter two systematic reviews (Table 38). Bi et al. (2018) focuses on healthy pregnant women and Roth et al. (2017) focused both on healthy pregnant women and women with gestational diabetes.

Roth et al. (2017) summarise 13 RCTs and Bi et al. (2018) summarise 11 RCTs. Eight RCTs are summarised in both reviews. Roth et al. (2017) and Bi et al. (2018) find no significant association between vitamin D-supplementation and the risk of preterm birth. The relative risk was (close to) one, the number of cases was considerable and heterogeneity was low or moderate.[106,107]

In conclusion, an effect of vitamin D-supplementation during pregnancy on the risk of preterm birth is unlikely.

Table 38. Results of the meta-analyses of Roth et al. (2017) and Bi et al. (2018) on the effect of vitamin D supplementation during pregnancy on the risk of preterm birth.

First author	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Roth[106]	25-410 microgram / day[a] vitamin D versus placebo, no or up to 10 microgram / day vitamin D	12 to 28 weeks gestation	13	110 / 1,996	102 / 1,795	1.00 (0.77-1.30)	0%
Bi[107]	25-125 microgram / day[a] vitamin D versus placebo or low dose vitamin D	10 to 30 weeks gestation	11	n.r.[b]	n.r.	0.98 (0.77-1.26)	33%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One RCT provided a bolus of 5,000 microgram vitamin D twice in combination with six times 1,250 microgram vitamin D. [b] 3,822 participants in total.

4.4 Small for gestational age

Summary: Vitamin D supplementation and the risk of small-for-gestational-age infants.

Aspect	Explanation
Selected studies	One meta-analysis of six RCTs.[107]
Heterogeneity	No
Strength of the effect	RR = 0.71 (95%CI 0.52-0.98)
Study population	Healthy pregnant women from Asia, Europe, and North America.

Conclusion:
Based on RCTs, vitamin D supplementation during pregnancy reduces the risk of small-for-gestational-age infants.
Level of evidence: Limited.

Explanation
There are six systematic reviews on vitamin D supplementation and the risk of small-for-gestational-age infants.[106-108,110,112,113] Small for gestational age was defined as an infant birth weight less than the 10th percentile for gestational age. Autier et al. (2017) review the findings from the systematic reviews of Thorne-Lyman (2012) and Perez-Lopez (2015).[108,110,112]
The RCTs in these systematic reviews and in the systematic reviews of Harvey et al. (2014) and Roth et al. (2017) are all summarised by Bi et al. (2018).[106,107,113] Therefore, the committee focuses on the review of Bi et al. (2018) of the six RCTs (seven interventions) (Table 39).[107] For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix C.1.

Bi et al. (2018) show that vitamin D supplementation during pregnancy lowers the risk of small-for-gestational-age infants. There was little heterogeneity. In addition, funnel plots showed no publication bias.
The upper level of the confidence interval was close to one (0.98) and the number of cases was small in each study (the number per treatment group was 19 or less). In a subgroup analysis, the effect seemed somewhat stronger in the two RCTs providing a bolus vitamin D (RR = 0.58; 0.43-1.04) than in the five RCTs providing vitamin D daily or weekly (RR = 0.79; 0.55-1.15). The number of studies in other subgroup analyses was too small to draw a conclusion on the effect of the initiation of vitamin D supplement use (before or after 20 weeks) and the dose of vitamin D (less or more than 50 microgram / d).

In conclusion, vitamin D supplementation during pregnancy reduces the risk of small-for-gestational-age infants. In view of the number of cases that was too small for strong evidence (i.e. < 100), the committee judges the level of evidence as limited.

Table 39. Results of the meta-analysis of Bi et al. (2018) on the effect of vitamin D supplementation during pregnancy on the risk of small-for-gestational-age infants. For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix C.1.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
25-178 microgram / day[a] vitamin D versus placebo or low dose vitamin D	12-28 weeks gestation	6	59 / 512	67 / 410	0.71 (0.52-0.98)	12%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One RCT provided a bolus of vitamin D of 1,500 microgram once or 3,000 microgram twice or four times, depending on baseline vitamin D status; in one other RCT one of the treatment arms received of a bolus of 5,000 microgram vitamin D.

Update July 2018 - July 2019

The committee found one new meta-analysis that was published between July 2018 and July 2019.[114] The meta-analysis of Maugeri et al. (2019) included one extra RCT compared with Bi et al. (2018). The additional RCT added 8 cases to the total intervention group (reaching 59+8=67 cases) and 13 cases to the overall control group (reaching 67+13=80 cases). As neither the intervention nor the control group reaches the cut-off of 100 cases (necessary for strong evidence), the new meta-analysis did not result in a change of the initial conclusion.

4.5 Gestational diabetes

Summary: Vitamin D supplementation and the risk of gestational diabetes.

Aspect	Explanation
Selected studies	One meta-analysis of 12 RCTs (14 comparisons), five RCTs had good quality case definitions and methods of assessment.[106]
Heterogeneity	No
Strength of the effect	RR = 0.61 (95%CI 0.45-0.83) (all studies) RR = 0.65 (95%CI 0.39-1.08) (good quality)
Study population	Healthy pregnant women from North America, Asia, Europe, and Australia

Conclusion:

Based on RCTs, vitamin D supplementation during pregnancy reduces the risk of gestational diabetes.

Level of evidence: Limited.

Explanation

There are five systematic reviews of vitamin D supplementation and the risk of gestational diabetes.[106,109,110,115,116] Joergensen et al. (2014) describe one publication in which the results of two RCTs are pooled. In the publication, however, the control group in one of the RCTs is also used as the reference group for the other RCT. Therefore, the committee does not include this pooled analysis in its review.[116] Roth et al. (2017) summarise 14 RCTs.[106] Among those 14 are the two RCTs summarised by De-Regil et al. (2016), the three RCTs summarised by Perez-Lopez et al. (2015) and the four RCTs summarised by Zhang et al. (2018).[109,110,115] Therefore, the committee focuses below on the findings by Roth et al. (2017) (Table 40).[106] For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix C.2.

Five out of 14 RCTs fulfilled the criteria for case definitions and methods of assessment the authors specified in advance. Using all trials irrespective of these criteria, the relative risk of gestational diabetes was 0.61 (0.45-0.83). None of the 14 trials had a low risk of bias. In addition, six out of the 14 RCTs included a very low number of cases (1 to 7) and three other RCTs included 5 to 9 cases. Nevertheless, heterogeneity was low.

Using the five RCTs fulfilling the predefined criteria, the relative risk did not materially change, but was no longer significant (RR = 0.65; 0.39-1.08). Again, four of the five RCTs encompassed a small number of cases (5 to

15 per group). Heterogeneity was moderate and had to do with both the size and direction of the effect.[106]

In conclusion, vitamin D supplementation during pregnancy lowers the risk of gestational diabetes. In view of the moderate to high risk of bias in all RCTs, the small number of cases in the RCTs with a good quality of case definitions and methods of assessment and the fact that the effect was no longer significant in these studies, the committee judges the level of evidence as limited.

Table 40. Results from the meta-analysis of Roth et al. (2017) on the effect of 10-410 microgram / day[a] vitamin D versus placebo, no or up to 10 microgram / day vitamin D supplementation starting from 12 to 28 weeks of gestation on the risk of gestational diabetes. For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix C.2.

Meta-analysis	N RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2
All studies	14	68 / 1,438	101 / 1,205	0.61	0.45-0.83	0
Good quality studies	5	44 / 502	74 / 528	0.65	0.39-1.08	44%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a]One RCT provided a bolus of vitamin D of 1,500 microgram once or 3,000 microgram twice or four times, depending on baseline vitamin D status.

4.6 Gestational hypertension

Summary: Vitamin D supplementation and the risk of gestational hypertension.

Aspect	Explanation
Selected studies	One meta-analysis of eight RCTs, two of which have good quality case definitions and methods of assessment.[106]
Heterogeneity	No
Strength of the effect	RR = 0.83 (95%CI 0.53-1.30) (all studies); low number of cases. RR = 1.69 (95%CI 0.73-3.92) (good quality); low number of cases.
Study population	Healthy pregnant women.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of gestational hypertension.

Explanation

There is one systematic review of vitamin D supplementation during pregnancy and the risk of gestational hypertension (Table 41).[106]

Roth et al. (2017) found eight RCTs, two of which fulfilled the criteria for case definitions and methods of assessment the authors specified in advance. Using all trials irrespective of these criteria, the relative risk of gestational hypertension was 0.83 (0.53-1.30; 2,430 participants). In the two RCTs fulfilling the criteria, relative risks were 1.63 (0.66-4.00) and 2.18 (0.20-23.87) respectively.[106] The confidence intervals in the two RCTs

is very broad due to the small number of cases. This limits the interpretation of the findings.

In conclusion, there is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of gestational hypertension.

Table 41. Results from the meta-analysis of Roth et al. (2017) on the effect of 25-410 microgram / day vitamin D versus placebo, no or up to 10 microgram / day vitamin D supplementation starting from 12 to 28 weeks of gestation on the risk of gestational hypertension.

Meta-analysis	N RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2
All studies	8	37 / 1,290	38 / 1,140	0.83	0.53-1.30	0%
Good quality studies	2	13 / 272	8 / 292	1.69	0.73-3.92	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a]One RCT provided a bolus of vitamin D of 1,500 microgram once or 3,000 microgram twice or four times, depending on baseline vitamin D status.

4.7 Pre-eclampsia

Summary: Vitamin D supplementation and the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	One meta-analysis of 14 RCTs, three of which have good quality case definitions and methods of assessment[106] and one additional RCT.[117]
Heterogeneity	No
Strength of the effect	RR = 0.82 (95%CI 0.63-1.07) (all studies) RR = 1.09 (95%CI 0.43-2.76) (good quality)
Study population	Pregnant women: healthy, with gestational diabetes or at increased risk of pre-eclampsia.

Conclusion:

Study findings from RCTs on the effect of vitamin D supplementation during pregnancy on the risk of pre-eclampsia are inconclusive.

Explanation

There are ten systematic reviews of the effect of vitamin D supplementation during pregnancy on the risk of pre-eclampsia.[106,108-110,113,118-122] Two publications describe the findings of the same Cochrane review (2016).[109,121] Two other publications (2017 / 2018)[108,120] are umbrella reviews and describe the outcomes of other systematic reviews published between 2014 and 2016.[109,110,113,119]

In some of the systematic reviews, studies on vitamin D are combined with studies of vitamin D in combination with calcium or other micronutrients.[110,113,118,119] It is not possible to draw a conclusion on the independent effect of vitamin D on the basis of these analyses.

Roth et al. (2017) summarise all RCTs on vitamin D that are included in other systematic reviews, except for one RCT by Qian et al. (2015) from the systematic review by Fu et al.[117,118] Therefore, the committee focuses below on the findings by Roth et al. (2017) and describes the RCT by Qian et al. (2015) separately (Table 42a and 42b).[106,117]

Roth et al. (2017) found 14 RCTs (16 comparisons), three of which fulfilled the criteria for case definitions and methods of assessment the authors specified in advance. Using all trials irrespective of these criteria, the relative risk of pre-eclampsia was 0.82 (0.63-1.07). Heterogeneity was low. The number of cases in the individual studies was below 20 in 13 of the 16 comparisons. Using the three RCTs fulfilling the predefined criteria, the relative risk was 1.09 (0.43 to 2.76). Due to the small number of cases, the confidence interval was wide. In addition, heterogeneity was considerable among these three trials.[106]

In the RCT by Qian et al. (2015), women at risk of pre-eclampsia received 50 microgram vitamin D per day or placebo between gestational weeks 20 to 32 for 12 weeks. Vitamin D supplementation reduced the risk of pre-eclampsia by more than 50%, although the effect was not statistically significant.[117]

In conclusion, due to the large number of studies and due to the fact that the relative risk estimate is not close to one, the committee concludes that study findings on the effect of vitamin D supplementation during pregnancy on the risk of pre-eclampsia are inconclusive.

Table 42a. Results from the meta-analysis of Roth et al. (2017) on the effect of 10-410 microgram / day[a] vitamin D versus placebo, no or up to 10 microgram / day vitamin D supplementation starting from 12 to 28 weeks of gestation on the risk of pre-eclampsia.

Meta-analysis	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
All studies	14	98 / 1,782	113 / 1,616	0.82 (0.63-1.07)	0%
Good quality studies	3	28 / 342	32 / 364	1.09 (0.43-2.76)	67%

CI: confidence interval; N: number; n.a.: not applicable; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a]One RCT provided a bolus of vitamin D of 1,500 microgram twice, one RCT provided a bolus of vitamin D of 1,500 microgram once or 3,000 microgram twice or four times, depending on baseline vitamin D status; One RCT provided a bolus of 5,000 microgram vitamin D twice in combination with six times 1,250 microgram vitamin D.

Table 42b. Results from the additional RCT of Qian et al. (2015) in women at risk of pre-eclampsia on the effect of vitamin D supplementation during pregnancy on the risk of pre-eclampsia.

Intervention versus control	Start of intervention	n / N intervention	n / N control	RR estimate (95%CI)
50 microgram vitamin D / day versus placebo	20-32 weeks gestation	6 / 30	13 / 30	0.46 (0.20-1.05)[a]

CI: confidence interval; n.a.: not applicable; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a]RR and CI derived from the meta-analysis by Fu et al. (2018).[118]

4.8 Allergy in the offspring

4.8.1 Skin prick test

Summary: Vitamin D supplementation and the risk of a positive allergy skin prick test.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[107]
Heterogeneity	Yes
Strength of the effect	RR = 0.88 (95%CI 0.52-1.49)
Study population	Pregnant women with or without atopic disease.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of a positive allergy skin prick test in children at 3 years of age.

Explanation

There is one systematic review of three RCTs on the effect of vitamin D supplementation on the risk of a positive allergy skin prick test (Table 43).[107] Bi et al. (2018) find no significant effect of vitamin D on the risk of a positive allergy skin prick test. The relative risk estimate was not close to one and there was considerable heterogeneity in the direction of the effect. However, the individual studies in the meta-analysis showed non-significant effect estimates above one and below one.

Therefore, the committee concluded that there is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy and the risk of a positive allergy skin prick test in children at 3 years of age.

Table 43. Results from the meta-analysis of Bi et al. (2018) on the effect of vitamin D supplementation on the risk of a positive allergy skin prick test.

Intervention versus control	Start intervention, follow-up	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
25-110 microgram / day vitamin D versus placebo or low dose vitamin D	10-27 weeks gestation, 3 years	3	n.r.[a]	n.r.	0.88 (0.52-1.49)	60%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a]1,304 participants.

4.8.2 Allergen-specific IgE

Summary: Vitamin D supplementation and the risk of the presence of allergen-specific IgE.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[107]
Heterogeneity	Yes
Strength of the effect	RR = 0.80 (95%CI 0.39-1.67)
Study population	Pregnant women with or without atopic disease.

Conclusion:

Study findings from RCTs on the effect of vitamin D supplementation during pregnancy on the risk the presence of allergen-specific IgE in children at three years of age are contradictory.

Explanation

There are three systematic reviews of the effect of vitamin D supplementation and the risk of the presence of allergy-specific immunoglobulin E (IgE).[107,123,124]. As Bi et al. (2018) summarised the one RCT from the systematic review of Hall et al. (2017) and the two RCTs from the systematic reviews by Wolsk et al. (2017), the committee focuses on the former (Table 44).[107]

Bi et al. (2018) find no significant effect of vitamin D supplementation on the risk of the presence of allergen-specific IgE. The relative risk estimate was not close to one and there was considerable heterogeneity in the direction of the effect. One of the included individual studies showed a risk estimate that was statistically significantly in favour of the intervention group. However, the study that favours the control group was not statistically significant.

Therefore, the committee concluded that study findings on the effect of vitamin D supplementation during pregnancy and the risk of the presence of allergen-specific IgE are contradictory in children at 3 years of age.

Table 44. Results from the meta-analysis of Bi et al. (2018) on the effect of vitamin D supplementation on the risk of the presence of allergen-specific IgE.

Intervention versus control	Start intervention, follow up	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
25-110 microgram / day vitamin D versus placebo or low dose vitamin D	10-27 weeks gestation, 3 years	3	n.r.[a]	n.r.	0.80 (0.39-1.67)	78%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a]1,298 participants.

4.9 Asthma-like symptoms or wheezing in the offspring

Summary: Vitamin D supplementation and the risk of wheeze or asthma-like symptoms.

Aspect	Explanation
Selected studies	One meta-analysis of five RCTs, two of which have good quality case definitions and methods of assessment.[106]
Heterogeneity	No
Strength of the effect	RR = 0.80 (95%CI 0.67-0.96) all studies and RR = 0.81 (95%CI 0.67-0.98) (good quality studies)
Study population	Pregnant women with or without atopic disease from Asia, Europe, North America, and Australia.

Conclusion on RCTs:

Vitamin D supplementation during pregnancy reduces the risk of wheeze or asthma-like symptoms in children at 3 years of age.

Level of evidence: Limited.

Explanation

There are seven systematic reviews on the effect of vitamin D supplementation during pregnancy on the risk of wheezing and asthma-like symptoms in children at 3 years of age. Roth et al. (2017) summarise five RCTs, two of which fulfilled the criteria for case definitions and methods of assessment the authors specified in advance.[106] Four of the five RCTs have also been summarised in other systematic reviews.[107,108,124-127] Therefore, the committee focuses below on the findings by Roth et al. (2017) (Table 45). For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix C.3.

Roth et al. (2017) show both in the analysis of the two RCTs that fulfil the criteria for case definitions and methods of assessment and in the five RCTs that did not necessarily fulfil these criteria that vitamin D supplementation during pregnancy reduces the risk of wheezing and asthma by 3 years. Heterogeneity was low.[106]

In conclusion, vitamin D supplementation during pregnancy reduces the risk of wheeze or asthma-like symptoms in children at 3 years of age. In view of the fact that the authors combined wheezing and asthma-like symptoms, and that only two RCTs fulfilled the criteria for case definitions and methods of assessment, the committee judges the level of evidence as limited.

Table 45. Results from the meta-analysis of Roth et al. (2017) on the effect of 20-110 microgram / day[a] vitamin D versus placebo, no or up to 10 microgram / day vitamin D supplementation starting from 10-27 weeks of gestation on the risk of wheeze or asthma-like symptoms after 3 years follow-up.

Meta-analysis	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
All studies	5	167 / 1,000	194 / 833	0.80 (0.67-0.96)	0%
Good quality studies	2	145 / 700	177 / 687	0.81 (0.67-0.98)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one RCT, one of the treatment arms consisted of a bolus of 5,000 microgram vitamin D.

Update July 2018 - July 2019

In the update, the committee found one new meta-analysis on the effect of vitamin D supplementation on the risk of wheeze in the offspring.[128] This meta-analysis by Li et al. (2018) included both RCTs and cohort studies. Two out of three RCTs overlapped with Roth et al. (2017) and showed a combined effect estimate that was in line with Roth et al. (2017) (RR = 0.75, 95%CI 0.59-0.95, based on three RCTs).

Please note that this publication also includes a meta-analysis of cohort studies on the association of vitamin D intake with wheezing in the offspring, showing a statistically significant association: RR = 0.58, 95%CI 0.38-0.88 for the upper versus lowest quartiles or quintiles of intake in multivariate analyses from four cohorts. There is limited evidence for an association between vitamin D intake during pregnancy and a lower risk of

asthma-like symptoms or wheezing in the offspring. This conclusion, based on cohort studies, is not further considered, because the topic of this background document is vitamin D intake from supplements, not total vitamin D intake.

4.10 Eczema in the offspring

Summary: Vitamin D supplementation and the risk of eczema.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[107]
Heterogeneity	No
Strength of the effect	RR = 0.92 (95%CI 0.77-1.11)
Study population	Pregnant women with or without atopic disease.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of eczema in children at 3 years of age.

Explanation

There are four systematic reviews of vitamin D supplementation and the risk of eczema or atopic dermatitis in children at 3 years of age. Bi et al. (2018) summarise three RCTs that have also been summarised in part or narratively in the other systematic reviews.[107,108,124,127] Autier et al. (2017) describe one additional trial. However, as it was carried out in lactating women rather than pregnant women, the committee does not include it in its analyses.[108]

Bi et al. (2018) find no significant effect of vitamin D supplementation on the risk of eczema. The relative risk was not close to one and heterogeneity was low (Table 46).[107]

In conclusion, there is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of eczema in children at 3 years of age.

Table 46. Results from the meta-analysis of Bi et al. (2018) on the effect of vitamin D supplementation during pregnancy on the risk of eczema in the offspring.

Intervention versus control	Start intervention, follow up	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
20-110 microgram / day vitamin D versus placebo or low dose vitamin D	10-27 weeks gestation, 3 years	3	n.r.[a]	n.r.[a]	0.92 (0.77-1.11)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] 1,538 participants.

4.11 Upper respiratory tract infection in the offspring

Summary: Vitamin D supplementation and the risk of upper respiratory tract infection.

Aspect	Explanation
Selected studies	Two RCTs.[129,130]
Heterogeneity	Not applicable.
Strength of the effect	IRR = 0.99 (95%CI 0.90-1.09)[129] and RR = 1.60 (95%CI 0.67-3.85)[130]
Study population	Pregnant women without chronic disease.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of upper respiratory tract infection in children at 3 years of age.

Explanation

There are three systematic reviews of vitamin D supplementation and the risk of upper respiratory tract infection in children up to 3 years of age.[106,107,126] Each of the systematic reviews summarised two RCTs, which amounted to three independent RCTs in total. However, in one of the RCTs, vitamin D was not only supplemented during pregnancy, but also to the infant in the first 6 months after birth.[131] The committee, therefore, does not include this RCT in its analyses, and focuses on the other two (Table 47).

The two remaining RCTs did not find a significant effect of vitamin D supplementation during pregnancy on the risk of upper respiratory tract infections in children up to the age of 3, either in terms of the number of infections per year or in terms of incidence of at least four infections per year. In the larger of the two studies, the incidence risk ratio (IRR) was close to one, and in the other, the confidence interval was wide due to the small number of cases suffering from at least four infections per year.[129,130]

In view of the small number of studies, the committee concludes that there is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of upper respiratory tract infection in children at 3 years of age.

Table 47. Results from the RCTs of Chawes et al. (2016) and Goldring et al. (2013) on the effect of vitamin D supplementation during pregnancy on the risk of upper respiratory tract infection in the offspring at 3 years follow-up.

RCT name or first author	Intervention versus control	Start intervention	Outcome	n / N intervention	n / N control	IRR or RR estimate (95%CI)
COPSAC$_{2000}$[129]	70 microgram / day vitamin D versus 10 microgram / day vitamin D	From 24 weeks gestation onwards until 1 week post-partum	Number of infections at 3 years of age	5.2	5.3	0.99 (0.90-1.09)
Goldring[130]	20 microgram / day vitamin D or 5.000 microgram vitamin D as bolus versus no treatment	From 27 weeks gestation onwards or at 27 weeks gestation	At least four infections per year	20 / 103	7 / 50	1.60 (0.67-3.85)

CI: confidence interval; IRR, incidence risk ratio; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

4.12 Lower respiratory tract infection in the offspring

Summary: Vitamin D supplementation and the risk of lower respiratory tract infection.

Aspect	Explanation
Selected studies	One meta-analyses of four RCTs.[106]
Heterogeneity	No
Strength of the effect	RR = 0.97 (95%CI 0.84-1.12)
Study population	Pregnant women.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of lower respiratory tract infection in children at 3 years of age.

Explanation

There are four systematic reviews of vitamin D supplementation and the risk of lower respiratory tract infection.[106,107,124,126] The two RCTs pooled by Wolsk et al. (2017) are summarised by Christensen et al. (2017) in a narrative review together with two other RCTs.[124,126] Both Bi et al. (2018) and Roth et al. (2017) summarised the four RCTs from the narrative review by meta-analysis. The committee describes the findings of Roth et al. (2017), as the authors provide information on the number of cases and participants (Table 48).[106]

Roth et al. (2017) find no significant association between the use of vitamin D supplements and the risk of lower respiratory tract infection up to the age of 3. Heterogeneity was low. The outcome of the meta-analysis is largely determined by two large RCTs, together contributing for 85% of the weight. In the other studies, the number of cases was relatively small.

In view of the fact that there are only two large RCTs on vitamin D supplementation and the risk of lower respiratory tract infection, the committee concludes that there is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on the risk of lower respiratory tract infection in children at 3 years of age.

Table 48. Results from the meta-analysis of Roth et al. (2017) on the effect of vitamin D supplementation during pregnancy on the risk of lower respiratory tract infection in the offspring.

Intervention versus control	Start intervention, follow-up	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
25-110 microgram / day[a] vitamin D versus placebo or 10 microgram / day vitamin D	10-27 weeks gestation, 3 years	4	291 / 954	262 / 815	0.97 (0.84-1.12)	0

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one RCT, one of the treatment arms consisted of a bolus of 5,000 microgram / day vitamin D.

4.13 Bone mineral density in the offspring

Summary: Vitamin D supplementation and bone mineral density in infants.

Aspect	Explanation
Selected studies	One systematic review of two RCTs[106] and one additional RCT.[132]
Heterogeneity	Not applicable.
Strength of the effect	0.00 g / cm^2 (two RCTs)[133,134] and -0.04 (significant) and -0.05 (not significant) g / cm^2 (one RCT)[132]
Study population	Pregnant women without chronic disease.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on bone mineral density in infants.

Explanation

There is one systematic review of two RCTs on the effect of vitamin D supplementation on bone mineral density in infants.[106] As there are only two trials included which used different doses and timing of supplementation, the committee describes the trials separately (Table 49).

Both trials do not find a significant effect of respectively 25 or 50 microgram vitamin D per day supplementation during pregnancy on bone mineral density in up to 1-month-old infants.[133,134]

There is one more recent RCT, carried out in India.[132] The women received 1,500 microgram vitamin D either every four weeks (28 microgram / day) or every eight weeks (14 microgram / day) or placebo from 14 to 20 weeks gestation onwards. Bone mineral density in 12 to 16-month-old infants was significantly lower in children of women who received the highest dose of vitamin D as compared with the other two groups. The doses in this study were smaller than in the other two RCTs when expressed per day.

In view of the small number of studies and small number of participants in two of the three studies, the committee concludes that there is too little research to draw a conclusion on the effect of vitamin D supplementation during pregnancy on bone mineral density in infants.

Table 49. Results from the RCTs summarised by Roth et al. (2017) and the additional trial of Sahoo et al. (2017) on the effect of vitamin D supplementation versus placebo on bone mineral density in the offspring.

Trial name or first author	Intervention versus control	Start intervention, follow up	N intervention	N control	Difference in gram / cm^2 (95%CI)
MAVIDOS[133]	25 microgram / day	14 weeks gestation, within 2 weeks after birth	338	327	0.00 (-0.00 to +0.00)
Vaziri[134]	50 microgram / day	26-28 weeks gestation, on average 23 days after birth	13	12	0.00 (-0.03 to +0.03)
Sahoo[132]	28 microgram / day	14-20 weeks gestation, 12-16 months after birth	23	16	-0.04 (significant)
Sahoo[132]	14microgram / day	14-20 weeks gestation, 12-16 months after birth	13	16	-0.05 (n.s.)

CI: confidence interval; N: number of participants; n.s.: not significant.

4.14 Summary of findings on vitamin D

In conclusion, this chapter is based on two systematic reviews of intervention studies[106,107] and three additional RCTs.[117,129,130] Limited evidence was found for the effect of vitamin D supplementation on the risk of a small-for-gestational-age infant, gestational diabetes, and asthma-like symptoms or wheezing in the offspring. It was unlikely that vitamin D supplementation had an effect on the risk of preterm birth.

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

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence.
Limited evidence	• Small for gestational age: Based on RCTs, vitamin D supplementation during pregnancy reduces the risk of small-for-gestational-age infants. • Gestational diabetes: Based on RCTs, vitamin D supplementation during pregnancy reduces the risk of gestational diabetes. • Asthma-like symptoms or wheezing in the offspring: Based on RCTs, vitamin D supplementation during pregnancy reduces the risk of wheeze or asthma-like symptoms in children at 3 years of age.
Unlikely	• Preterm birth: Based on RCTs, an effect of vitamin D-supplementation during pregnancy on the risk of preterm birth is unlikely.
Contradictory	• Allergen-specific IgE (RCTs)
Too little research	• Stillbirth (RCTs); • Perinatal mortality (RCTs); • Gestational hypertension (RCTs); • Skin prick test (RCTs); • Eczema in the offspring (RCTs); • Respiratory tract infections in the offspring (RCTs); • Bone mineral density in the offspring (RCTs).
Inconclusive	• Pre-eclampsia (RCTs)

4.15 Findings cited in the advisory report

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

In this chapter on vitamin D supplementation, conclusions with strong evidence level were not available. However, there are three conclusions with limited evidence level based on RCTs pointing in the direction of a beneficial effect of vitamin D supplementation in pregnancy. It concerns the outcomes: small for gestational age, gestational diabetes, and asthma-like symptoms or wheezing in the offspring. As there were three conclusions with limited evidence level, all based on RCTs, consistently pointing in the direction of a beneficial effect, the committee considers it sufficient to recommend the use of vitamin D supplements to pregnant women. Therefore, these conclusions are mentioned in the advisory report.

05
calcium

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of calcium supplementation (alone) during pregnancy and the risk of perinatal mortality, preterm birth, intrauterine growth retardation, an infant that is small for gestational age, maternal mortality, gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome, and blood pressure in the offspring. For these outcomes, at least two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two intervention studies.

There are 45 systematic reviews or meta-analyses reporting on calcium supplementation during pregnancy in relation to pregnancy outcomes.[66,69,70,73,75,122,135-173]

Seven of these represent the most recent and complete reviews.[122,135-140] Therefore, results described in this chapter are based on these seven reviews.

5.1 Perinatal mortality

Summary: Calcium supplementation during pregnancy and the risk of perinatal mortality.

Aspect	Explanation
Selected studies	Perinatal mortality: three meta-analyses of eight[135] and 11 RCTs[136,139] and one more RCT on low-calcium dose from the meta-analysis of Hofmeyr et al. (2014).[174] Stillbirth or foetal death: one meta-analysis of six RCTs.[135]
Heterogeneity	No
Strength of the effect	Perinatal mortality: RR = 0.90 (95%CI 0.74-1.09)[136,139] and RR = 0.87 (95%CI 0.72-1.06)[135] Stillbirth or foetal death: RR = 0.91 (95%CI 0.72-1.14)[135]
Study population	Women with normal and high-risk pregnancies, and women with mild pre-eclampsia.

Conclusion:

Study findings based on RCTs on the effect of calcium supplementation during pregnancy on the risk of perinatal mortality, or stillbirth or foetal death are inconclusive.

Explanation

There are four meta-analyses on calcium supplementation during pregnancy and the risk of perinatal mortality (combining stillbirth and neonatal death or stillbirth and foetal death after 20 weeks of gestation or during labour).[135-137,139] The review of An et al. (2015) included one RCT on the effect of calcium supplementation on neonatal death.[137,175] This RCT was also included in the other three meta-analyses. The committee describes the results of Imdad et al. (2012) and Hofmeyr et al. (2014). Both included the same 11 RCTs for their analysis and retrieve the same

results.[136,139] Additionally, the results of the review by Buppasiri et al. (2015) are described.[135] They included eight RCTs, five of which overlap with the analysis of Hofmeyr et al. (2014) and Imdad et al. (2012). Only the review of Buppasiri et al. (2015) reports on the outcome stillbirth or foetal death. For this analysis, they included six RCTs (Table 50a).

Hofmeyr et al. (2014) present separate results for high (≥ 1000 milligram per day) and low-dose (< 1000 milligram per day[a]) calcium supplementation.[136] They included 11 RCTs in their analysis for high-dose calcium, six of which contributed to the total number of cases. Imdad et al. (2012) include the same 11 RCTs.[139] Both meta-analyses retrieve the same results and find no significant effect of calcium supplementation on the risk of perinatal mortality (stillbirth or death before hospital discharge). The number of cases was substantial, but they largely originated from one trial.[175] This trial had a strong influence on the results of the meta-analysis: contributing more than 80% of the weight of the risk estimate. There was no heterogeneity. For low-dose calcium, supplementation Hofmeyr et al. (2014) included only one trial (Table 50b).[174] As there occurred only 2 cases in the trial, the committee did not further include the trial in its considerations.

Buppasiri et al. (2015) included eight RCTs in their analysis, seven of which contributed to the total number of cases.[135] They found no statistical significant effect of calcium supplementation during pregnancy on the risk of perinatal mortality (stillbirth or neonatal death). There was a considerable amount of cases; however, they largely came from one trial.[175] This trial contributed for more than 80% to the weight of the risk estimate. There was no heterogeneity.

In an additional analysis of six RCTs, Buppasiri et al. (2015) did not find a statistically significant effect of calcium supplementation during pregnancy and the risk of stillbirth or foetal death (> 20 weeks of gestation or during labour) either. Although the number of cases was substantial, they largely originated from one study[175], making the results les robust.

There was a large number of studies and cases; the cases originate largely from one study, but there was no heterogeneity. In view of the effect estimates that were not close to one, but with a rather wide confidence interval that included one, the committee concludes that study findings on the effect of calcium supplementation during pregnancy on the effect of perinatal mortality, or stillbirth or foetal death are inconclusive.

[a] In one RCT 600 milligram / day was supplemented from week 22-32 followed by 1200 milligram / day from week 32 until birth.[176] This study was categorised as ‘low calcium supplementation’ by Hofmeyr et al. (2014).

Table 50a. Results from the meta-analyses of Imdad et al. (2012), Hofmeyr et al. (2014), and Buppasiri et al. (2015) on the effect of calcium supplementation during pregnancy on the risk of perinatal mortality and stillbirth or foetal death.

First author	Outcome	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
Imdad, Hofmeyr[136,139]	Perinatal mortality	1500 to 2000 milligram / day calcium versus placebo[a, b]	Before 26 weeks of gestation	11 (6 with cases)	183 / 7,821	205 / 7,844	0.90 (0.74-1.09)	0%
Buppasiri[135]	Perinatal mortality	500 to 2000 milligram / day calcium versus Placebo or no treatment[a, b, c]	Before 24 weeks of gestation[d]	8 (7 with cases)	179 / 7,870	206 / 7,915	0.87 (0.72-1.06)	0%
Buppasiri[135]	Stillbirth or foetal death	500 to 2000 milligram / day calcium versus placebo or no treatment[a, c]	Before 25 weeks of gestation	6	137 / 7,636	151 / 7,633	0.91 (0.72-1.14)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177] [b] In another study, all women received prenatal vitamin tablets containing 200 milligram calcium per day.[178] [c] In one study, the intervention group received 500 milligram calcium in combination with 5 milligram vitamin D[179] [d] One study did not report the starting moment of the intervention.[180]

Table 50b. Results from the RCT of Bassaw et al. (1998) included in the systematic review of Hofmeyr et al. (2014) on the effect of calcium supplementation during pregnancy on the risk of perinatal mortality.

Intervention versus control	Start of intervention	n / N intervention	n / N control	RR estimate (95%CI)
1200 milligram / day calcium versus control	Before 20 weeks of gestation	1 / 84	1 / 87	1.04 (0.07-16.29)

CI: confidence interval; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

One additional meta-analysis was identified on the effect of calcium supplementation and the risk of perinatal mortality: Hofmeyr et al. (2018).[181] Hofmeyr et al. (2018) is an update of Hofmeyr et al. (2014). In the 2018 version, no changes relative to the 2014 version were found for the outcome perinatal mortality. Therefore, results from this publication did not lead to changes in the committee's conclusion.

5.2 Preterm birth

Summary: Calcium supplementation during pregnancy and the risk of preterm birth < 37 weeks.

Aspect	Explanation
Selected studies	Two meta-analyses of 11[136] and 12 RCTs[135] about high-dose calcium and one more RCT on low-dose calcium included in Hofmeyr et al. (2014).[182]
Heterogeneity	Yes, in the size of the effect.
Strength of the effect	RR = 0.76 (95%CI 0.60-0.97)[136] and RR = 0.81 (95%CI 0.66-0.99)[135]
Study population	Women with normal and high-risk pregnancies, and women with mild pre-eclampsia, from Asia, South America, North America, Africa, and Australia.

Conclusion:

Calcium supplementation during pregnancy reduces the risk of preterm birth < 37 weeks in RCTs.

Level of evidence: Strong.

Explanation

There are five meta-analyses of the effect of maternal calcium supplementation on the risk of preterm birth (< 37 weeks of gestation).[135-139] Bucher et al. (1996)[138] included five RCTs and Imdad et al. (2012)[139] included 11 RCTs which were all included in the review of Hofmeyr et al. (2014)[136] as well. An et al. (2015)[137] included four multicentre RCTs, which were all included in the reviews of Hofmeyr et al. (2014)[136] and Buppasiri et al. (2015).[135] Together, Hofmeyr et al. (2014) and Buppasiri et al. (2015) identified 16 RCTs, eight of which are described in both reviews. Since the reviews overlap only partially, the results of Hofmeyr et al. (2014) and Buppasiri et al. (2015) are described below (Table 51a). For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix D.1.

Hofmeyr et al. (2014) presented separate results for high (≥ 1000 milligram per day) and low-dose (< 1000 milligram per day[a]) calcium supplementation.[136] They included 11 RCTs in the analysis for high-dose calcium, of which nine studies contributed to the number of cases. They find a significant reduction in the risk of preterm birth (< 37 weeks of gestation) in the supplement group compared with the control group. The number of cases is considerable and largely originates from the two largest trials.[175,177] Together contributing to approximately 50% of the weight of the effect estimate. There was heterogeneity, but mainly in the size of the effect. Maternal risk of hypertension at trial entry and trial size were factors that appeared to account for the heterogeneity. High maternal risk of hypertension (RR = 0.45; 95%CI 0.24-0.83 versus low risk RR = 0.84; 95%CI 0.67-1.05) and small study size (RR = 0.43; 95%CI 0.24-0.76 versus large study size RR = 0.86; 95%CI 0.69-1.07) were associated with a larger effect. Asymmetric funnel plots for the analysis suggest that the effect may be overestimated due to small-study effects. Of note is that all studies included in the analysis for the subgroup with a high maternal risk of hypertension were small studies. For low-dose calcium supplementation, only one trial was available (Table 51b). Results were in the same direction as the results of the meta-analysis of high-dose calcium supplementation.[182]

Buppasiri et al. (2015) included 12 RCTs (11 with low risk of bias for concealment allocation) and reported a statistically significant effect of calcium supplementation during pregnancy on the risk of preterm birth (< 37 weeks of gestation).[135] There was a considerable amount of cases, mainly from two large trials.[175,177] These two studies contribute to almost

[a] In one RCT 600 milligram / day was supplemented from week 22-32 followed by 1200 milligram / day from week 32 until birth.[176] This study was categorised as 'low calcium supplementation' by Hofmeyr et al. (2014).

50% of the weight of the effect estimate. Heterogeneity was substantial and mostly present in the size of the effect. Buppasiri et al. (2015) conclude that there was no strong evidence of publication bias for this outcome. They provided a subgroup analysis on the start moment of supplementation (< 20 weeks of gestation vs. ≥ 20 weeks of gestation). This analysis did not show differences in effect. Other meta-analyses do not report on a subgroup analysis by start moment. However, the committee itself notes that almost all RCTs commenced their intervention ≥ 20 weeks of gestation (Appendix D.1).

Both meta-analyses suggest that calcium supplementation during pregnancy reduces the risk of preterm birth. However, in one of the meta-analyses (Hofmeyr et al. (2014)), there were signs of publication bias, in the other there were not. Furthermore, there was substantial heterogeneity in both meta-analyses, but mainly in the size of the effect. As the results from the two meta-analyses go in the same direction, and the effect estimates were not close to one with sufficient studies and cases, the committee concludes that there is strong evidence that calcium supplementation during pregnancy decreases the risk of preterm birth < 37 weeks. As there were signs of publication bias and substantial heterogeneity, the committee does not quantify the effect.

As 73% of the individual RCTs started at or after 20 weeks of gestation, the committee considers that the evidence for the effect on preterm birth relates especially to the use of calcium supplements from 20 weeks onwards (see appendix D.1).

Table 51a. Results of the meta-analyses of Hofmeyr et al. (2014) and Buppasiri et al. (2015) on the effect of calcium supplementation during pregnancy on the risk of preterm birth < 37 weeks. For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix D.1.

First author	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Hofmeyr[136]	1,500 to 2,000 milligram / day calcium versus placebo[a, b]	At or before 32 weeks gestation	11, 9 with cases	722 / 7,620	795 / 7,655	0.76 (0.60-0.97)	60%
Buppasiri[135]	1,500 to 2,000 milligram / day calcium versus placebo or no treatment[a, b]	At or before 31 weeks gestation[c]	12, 11 with cases	744 / 7,744	817 / 7,735	0.81 (0.66-0.99)	51%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177] [b] In another study, all women received prenatal vitamin tablets containing 200 milligram calcium per day.[178] [c] One study did not report the start moment of the intervention.[180]

Table 51b. Results of the RCT of Almirante et al. (1998) included in the systematic review of Hofmeyr et al. (2014) on the effect of low-dose calcium supplementation during pregnancy on the risk of preterm birth < 37 weeks.

Intervention versus control	Start of intervention	n / N intervention	n / N control	RR estimate (95%CI)
500 milligram / day calcium versus no treatment	16-20 weeks of gestation	12 / 212	30 / 210	0.40 (0.21-0.75)

CI: confidence interval; n / N: number of cases / total number of participants; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

One additional meta-analysis was identified on the effect of calcium supplementation on the risk of preterm birth: Hofmeyr et al. (2018).[181] Hofmeyr et al. (2018) is an update of Hofmeyr et al. (2014). In the 2018 version, no changes relative to the 2014 version were found for the outcome preterm birth. Therefore, results from this publication did not lead to changes in the committee's conclusion.

5.3 Intrauterine growth retardation

Summary: Calcium supplementation during pregnancy and the risk of intrauterine growth retardation.

Aspect	Explanation
Selected studies	One meta-analysis of six RCTs.[135]
Heterogeneity	No
Strength of the effect	RR = 0.83 (95%CI 0.61-1.13)
Study population	Women with normal and high-risk pregnancies, and women with mild pre-eclampsia.

Conclusion:

Study findings from RCTs on the effect of calcium supplementation during pregnancy on the risk of intrauterine growth retardation are inconclusive.

Explanation

Buppasiri et al. (2015) is the only meta-analysis reporting on the effect of calcium supplementation during pregnancy on the risk of intrauterine growth retardation (Table 52).[135] The results of the review are described below.

The review of Buppasiri et al. (2015) includes six RCTs and finds no significant effect of calcium supplementation on the risk of intrauterine growth retardation. There are no signs of heterogeneity. Around 50% of the cases came from one study.[179] That study, by Taherian et al. (2002), combined calcium supplementation with 5 milligram vitamin D supplementation per day. This combined supplementation is the topic of Chapter 6, and outside of the scope of the chapter on calcium. However, no analysis was available without this study. As the risk estimate of Taherian et al. (2002) was in line with the risk estimates of the included studies on calcium supplementation only, the committee decided to present the risk estimate from the meta-analysis.

In view of the number of studies and the risk estimate that is not close to one, but not statistically significant either because of a wide confidence interval, the committee concludes that study findings on the effect of calcium supplementation during pregnancy on the risk of intrauterine growth retardation are inconclusive.

Table 52. Results from the meta-analysis of Buppasiri et al. (2015) on the effect of calcium supplementation during pregnancy on the risk of intrauterine growth retardation.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
500 to 2000 milligram / day calcium versus placebo or no treatment[a,b]	Before 25 weeks of gestation[c]	6	69 / 859	82 / 842	0.83 (0.61-1.13)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).[a] In one study, all women received prenatal vitamin tablets containing 200 milligram calcium per day.[178] [b] In one study, the intervention group received 500 milligram calcium in combination with 5 milligram vitamin D.[179] [c] One study did not report the start moment of the intervention.[180]

5.4 Small for gestational age

Summary: Calcium supplementation during pregnancy and the risk of small-for-gestational-age infants.

Aspect	Explanation
Selected studies	One meta-analysis of seven RCTs.[139]
Heterogeneity	No
Strength of the effect	RR = 1.01 (95%CI 0.84-1.12)
Study population	Women with normal and high-risk pregnancies.

Conclusion:

Based on RCTs, an effect of calcium supplementation on the risk of small-for gestational-age infants is unlikely.

Explanation

There are two systematic reviews on the effect of calcium supplementation during pregnancy and the risk of small-for-gestational-age infants.[136,139] Hofmeyr et al. (2014)[136] include four RCTs which are all included in the analysis of Imdad et al. (2012)[139] as well. Since Imdad et al. (2012) included three more RCTs, the result of their meta-analysis is described below (Table 53).

Imdad et al. (2012) included seven RCTs and found no significant effect of calcium supplementation on the risk of small-for-gestational-age infants. The number of cases is substantial, but approximately half of the weight of the effect estimate came from one large study.[177] This particular study showed a risk ratio above one, while the other six studies showed a risk ratio below one. Heterogeneity was nevertheless low.

As the effect estimate is close to one, the committee concludes that an effect of calcium supplementation on the risk of small-for-gestational-age infants is unlikely.

Table 53. Results from the meta-analysis of Imdad et al. (2012) on the effect of calcium supplementation during pregnancy on the risk of small-for-gestational-age infants.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
500 to 2000 milligram / day calcium versus placebo[a]	At or before 25 weeks gestation	7 RCTs	218 / 7,225	215 / 7,213	1.01 (0.84-1.21)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177]

Update July 2018 - July 2019

One additional meta-analysis was identified on the effect of calcium supplementation on the risk of an infant that is small for gestational age: Hofmeyr et al. (2018).[181] Hofmeyr et al. (2018) is an update of Hofmeyr et al. (2014). In the 2018 version, no changes relative to the 2014 version were found for the outcome small for gestational age. Therefore, results from this publication did not lead to changes in the committee's conclusions.

5.5 Maternal mortality

Summary: Calcium supplementation during pregnancy and the risk of maternal death.

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs.[135]
Heterogeneity	No
Strength of the effect	RR = 0.29 (95%CI 0.06-1.38)
Study population	Healthy pregnant women.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of calcium supplementation during pregnancy on the risk of maternal mortality.

Explanation

There is one meta-analysis on the effect on calcium supplementation on the risk of maternal death (Table 54).[135]

They find no significant effect of calcium supplementation on the risk of maternal death. The number of cases is very low.

The committee, therefore, concludes that there is too little research to draw a conclusion on the effect of calcium supplementation on the risk of maternal death.

Table 54. Results from the meta-analysis of Buppasiri et al. (2015) on the effect of calcium supplementation during pregnancy on the risk of maternal death.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
1500 to 2000 milligram / day calcium versus placebo	20 weeks of gestation	2	2 / 4,481	7 / 4,493	0.29 (0.06-1.38)	4%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

5.6 Gestational hypertension

5.6.1 Gestational hypertension overall

Summary: Calcium supplementation during pregnancy and the risk of gestational hypertension.

Aspect	Explanation
Selected studies	Two meta-analyses of 14[122] and 12 RCTs[136]
Heterogeneity	Yes, in size of the effect, explained by dietary calcium, maternal risk of hypertension and trial size.
Strength of the effect	RR overall = 0.65 (95%CI 0.53-0.81) (for low mean dietary calcium RR = 0.44 (95%CI 0.28-0.70); for adequate mean dietary calcium RR = 0.90 (95%CI 0.81-0.99))[136] RR = 0.77 (95%CI 0.65-0.92)[122]
Study population	Low and high-risk women from Europe, South America, North America, Asia, and Australia.

Conclusion:

Based on RCTs, supplementation with 120 to 2,000 milligram calcium per day during pregnancy decreases the risk of gestational hypertension by at least 10%, especially when dietary calcium intake is low.
Level of evidence: Strong.

Explanation

There are three reviews on the effect of calcium supplementation during pregnancy on the risk of gestational hypertension.[122,136,137] An et al. (2015)[137] included four RCTs which were also included by Khaing et al. (2017).[122] The review of Hofmeyr et al. (2014)[136] contains 15 RCTs of which 13 are also included in the review by Khaing et al. (2017). Since the overlap is partial, the results of both reviews are described below (Table 55a).

For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix D.2.

Khaing et al. (2017) included 14 RCTs on the effect of calcium supplementation during pregnancy on the risk of gestational hypertension (defined as gestational hypertension or pregnancy induced hypertension).[122] They find a significantly reduced risk of gestational hypertension in the calcium group compared with the placebo group. Heterogeneity was substantial, but mainly present in the size of the effect. Thirteen of the 14 RCTs showed results that favours the calcium group; one small RCT (N = 30) showed a risk estimate that favours the placebo group. The number of cases was considerable. Three studies contributed most to that number.[175,177,183]

Hofmeyr et al. (2014) included 12 RCTs on the effect of high-dose calcium supplementation during pregnancy on the risk of gestational hypertension (defined as high blood pressure with or without proteinuria) and three RCTs on the effect of low-dose calcium supplementation.[136] They found a significantly reduced risk of high-dose calcium supplementation on the risk of gestational hypertension. There was substantial heterogeneity in the size of the effect, but not in the direction. According to the authors, factors that accounted for the heterogeneity appeared to be maternal risk at trial entry, dietary calcium intake, and trial size. They found that the effect of calcium supplementation is more marked in studies with a population with

a low dietary calcium intake versus an adequate intake: meta-analysis of studies with low mean calcium intakes: RR = 0.44, 95%CI 0.28-0.70; meta-analysis of studies with adequate mean calcium intakes: RR = 0.90, 95%CI 0.81-0.99 respectively), and in women at high risk of hypertension versus women at low risk (RR = 0.47, 95%CI 0.22-0.97 versus RR = 0.71, 95%CI 0.57-0.89 respectively) (Table 55b). Of note is that all studies among high risk women were small studies. The authors suggest that based on the asymmetric funnel plots, the treatment effect may be overestimated due to small-study effects. For low-dose calcium supplementation, Hofmeyr et al. (2014) included three trials and found a significant reduced risk of calcium supplementation on the risk of gestational hypertension. The number of cases was low and there were no signs of heterogeneity.

In view of the high number of studies and number of cases, the committee concludes that there is strong evidence that supplementation with 120 to 2,000 milligram calcium per day during pregnancy reduces the risk of gestational hypertension by at least 10%. The effect is stronger in women with a low dietary calcium intake and in women at high risk of gestational hypertension. The committee considers that the statistically significant finding in populations with a generally adequate intake of dietary calcium may well be caused by the pregnant women with low dietary calcium intakes in these populations because the mean intakes in these populations are not far above 900 mg/day and the ranges of calcium intakes are very broad (Appendix D.2a). Therefore, populations with a mean intake of at least 900 mg/day will comprise a substantial number of individual participants with intakes lower than 900 mg/day (it may even be possible that a majority of the participants have intakes lower than 900 mg/day). A meta-analysis with Individual Participant Data (IPD) is required to elucidate whether it is beneficial for women with adequate calcium intake to take calcium supplementation during pregnancy. However, such IPD analyses are currently not available. Based on the current state of knowledge, the committee judges that the evidence is most robust for the subgroup with a low dietary intake of calcium. Therefore, it specifies the conclusion mainly on this subgroup. Since there is substantial heterogeneity in the size of the effect and a possibility of publication bias, the committee quantifies the effect by the upper limit of the range of reported effect estimates in the meta-analyses: RR = 0.90.

As 75% of the individual RCTs started at or after 20 weeks of gestation, the committee considers that the evidence for the effect on gestational hypertension relates especially to the use of calcium supplements from 20 weeks onwards (see appendix D.2).

Table 55a. Results of the overall meta-analyses of high and low-dose calcium supplementation of Khaing et al. (2017) and Hofmeyr et al. (2014) on the effect of calcium supplementation on the risk of gestational hypertension. For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix D.2.

First author	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Khaing[122]	600 to 2000 milligram / day calcium versus placebo or no treatment[a, b, c]	Before 32 weeks of gestation	14	1,623 / 12,394	1,877 / 12,519	0.77 (0.65-0.92)	65%
Hofmeyr[136]	High dose calcium: 1500 to 2000 milligram / day calcium versus placebo [b, c]	12 to 32 weeks of gestation	12	1,260 / 7,726	1,472 / 7,744	0.65 (0.53-0.81)	74%
Hofmeyr[136]	Low-dose calcium: 120 to 1200 milligram / day calcium versus no treatment[a]	Before 20 weeks of gestation[d]	3	45 / 340	47 / 218	0.57 (0.39-0.82)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one RCT 600 milligram / day was supplemented from week 22-32 followed by 1200 milligram / day from week 32 until birth.[176] [b] In one study, all women received 50 milligram calcium per day as normal supplementation.[177] [c] In another study, all women received prenatal vitamin tablets containing 200 milligram calcium per day.[178] [d] In one study, it is not clear when the intervention started.[184]

Table 55b. Results of the subgroup meta-analyses of Hofmeyr et al. (2014) of high-dose calcium supplementation (1500 to 2000 milligram / day) versus placebo on the effect of calcium supplementation on the risk of gestational hypertension.

Subgroup analysis	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
Adequate dietary calcium intake	13 to 26 weeks of gestation	4	547 / 2,505	614 / 2,517	0.90 (0.81-0.99)	0%
Low dietary calcium intake	12 to 32 weeks of gestation	7	703 / 5,206	847 / 5,212	0.44 (0.28-0.70)	85%
Low risk of hypertension	13 to 26 weeks of gestation	8	1,235 / 7,570	1,407 / 7,573	0.71 (0.57-0.89)	76%
High risk of hypertension	20 to 30 weeks of gestation	4	25 / 156	65 / 171	0.47 (0.22-0.97)	73%

CI: confidence interval; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

Two additional meta-analyses were identified on the effect of calcium supplementation and the risk of gestational hypertension: Sun et al. (2019) and Hofmeyr et al. (2018).[181,185] Results from these new publications did not lead to changes in the committee's conclusions.

Sun et al. (2019) included 19 RCTs and found that calcium supplementation reduced the risk of gestational hypertension compared with the control group (RR = 0.70; 95%CI 0.60-0.82; I^2 = 65%). There was statistically significant heterogeneity; however, it was only present in the size of the effect. Subgroup analyses showed a stronger effect in populations with a high risk of gestational hypertension (six trials; RR = 0.38; 95%CI 0.19-0.77; I^2 = 72%) than in populations with a low risk (13

trials; RR = 0.79; 95%CI 0.69-0.90; I^2 = 59%). Both risk estimates were highly significant, indicating that the substantial heterogeneity was related to the size of the effect. Sun et al. (2019) did not perform subgroup analyses based on dietary calcium intake. However, they did compare results from developed and developing countries and mentioned that baseline calcium intake is commonly sufficient in developed countries and that this may explain why the effect was statistically not significant for developed countries (four trials: RR = 0.82; 95%CI 0.64-1.04; I^2 = 33%) but highly significant for developing countries (15 trials; RR = 0.61; 95%CI 0.49-0.76; I^2 = 70%). The committee notes that the number of trials in developed versus developing countries was substantially smaller, which may have contributed to the wider confidence interval. Sun et al. (2019) could not establish an optimal dose of calcium supplementation in the prevention of gestational hypertension; the committee notes that only one trial with a calcium dose below 0.6 gram/day was included, showing a similar risk estimate as moderate-dose and high-dose subgroups, but the effect estimates were statistically significant only for the moderate and high doses.[185]

Hofmeyr et al. (2018) is an update of Hofmeyr et al. (2014). In the 2018 version, no changes relative to the 2014 version were found for the outcome gestational hypertension.

5.6.2 Severe gestational hypertension

Summary: Calcium supplementation during pregnancy and the risk of severe gestational hypertension.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[137]
Heterogeneity	No
Strength of the effect	RR = 0.81 (95%CI 0.60-1.09)
Study population	Low and high-risk women.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of calcium supplementation during pregnancy and the risk of severe gestational hypertension.

Explanation

An et al. (2015) is the only meta-analysis that reported on severe gestational hypertension (Table 56).[137]

They included three RCTs on this outcome and found no significant effect of calcium supplementation on the risk of severe gestational hypertension. The number of cases is considerable and there is no heterogeneity. One trial contributed almost 65% of the weight of the effect estimate.[175]

The committee concludes that there is too little research to draw a conclusion on the effect of calcium supplementation on severe gestational hypertension, since the cases largely originate from one study.

Table 56. Results of the meta-analysis of An et al. (2015) on the effect of calcium supplementation on the risk of severe gestational hypertension.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
1000 to 2000 milligram / day calcium[a]	11 to 20 weeks of gestation	3	74 / 6,673	92 / 6,684	0.81 (0.60-1.09)	0

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177]

5.7 Pre-eclampsia

5.7.1 Pre-eclampsia

Summary: Calcium supplementation during pregnancy and the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	Four meta-analyses of nine[138], 15[139], 16[122] and 17 RCTs.[136]
Heterogeneity	Yes, in the size of the effect.
Strength of the effect	High dose: RR = 0.54 (95%CI 0.41-0.70)[122]; RR = 0.48 (95%CI 0.34-0.67)[139]; RR = 0.38 (95%CI 0.22-0.65)[138]; RR = 0.45 (95%CI 0.31-0.65)[136]; Low dose: RR = 0.36 (95%CI 0.23-0.57)[136]
Study population	Women with high and low risk pregnancies, from Europe, South America, North America, Asia, Australia, and Africa.

Conclusion:

Based on RCTs, Supplementation with 120 to 2,000 milligram calcium per day during pregnancy starting any time before 32 weeks of gestation reduces the risk of pre-eclampsia, especially when dietary calcium intake is low.

Level of evidence: Strong.

Explanation

There are five meta-analyses reporting on the effect of calcium supplementation on the risk of pre-eclampsia. An et al. (2015)[137] included four RCTs which were all included in at least three of the other four reviews. A total of 23 trials are identified by all reviews together. Khaing et al. (2017)[122] performed the most recent meta-analysis and included 16 RCTs. Thirteen of these trials are also included by Hofmeyr et al. (2014).[136] Imdad et al. (2012)[139] and Khaing et al. (2017) overlap by 12 trials and Khaing et al. (2017) and Bucher et al. (1996)[138] overlap by five trials. Since all four reviews overlap only partially, the results of all these reviews are described below (Table 57). For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix D.2.

Khaing et al. (2017) find a significant reduction in the risk of pre-eclampsia in the calcium group compared with the placebo group.[122] There was substantial heterogeneity, but visual inspection of the forest plot revealed that the heterogeneity was mostly present in the size of the effect.

One study reported an effect in favour of the placebo group, all other included RCTs found effect estimates that favour the calcium group. The authors report that the heterogeneity could partly be explained by type of pregnancy (low versus high-risk pregnancies) and duration of calcium supplementation (> 18 weeks versus ≤ 18 weeks). The protective effect of calcium supplementation appeared greater in high-risk pregnancies than in low-risk pregnancies (RR = 0.42, 95%CI 0.53-0.62 versus RR = 0.69, 95%CI 0.52-0.91), and for supplementation duration of 18 weeks or shorter versus longer than 18 weeks (RR = 0.36, 95%CI 0.23-0.54 versus RR = 0.69, 95%CI 0.53-0.91). Studies from developing and developed countries showed a similar decrease in risk (RR = 0.50, 95%CI 0.35-0.70 and RR = 0.52, 95%CI 0.26-1.07, respectively).

Hofmeyr et al. (2014) summarised 13 RCTs with high-dose calcium supplementation and found a significant reduction in the risk of pre-eclampsia in the calcium group compared with the placebo group.[136] Heterogeneity was substantial but only present in the effect size, not the direction of the effect. All of the included RCTs showed effect estimates that favoured the calcium group. According to the authors, heterogeneity could be attributed to maternal risk at trial entry, dietary calcium intake (cut-off value not quantified but roughly around 900 mg/day), and trial size.

The reduction in the risk of pre-eclampsia was statistically significant for the subgroup of studies with low mean baseline dietary calcium intakes (RR = 0.36, 95%CI 0.20-0.65), but not significant for the studies with adequate mean dietary calcium intakes (RR = 0.62, 95%CI 0.32-1.20). Reduction in the risk of pre-eclampsia seemed greatest for women at high risk of pre-eclampsia (RR = 0.22, 95%CI 0.12-0.42) versus women with low risk (RR = 0.59, 95%CI 0.41-0.83). Asymmetric funnel plots suggest that the treatment effect may be overestimated due to small-study effects. A subgroup analysis showed that the effect of the intervention was stronger in small studies than in larger studies (RR = 0.21, 95%CI 0.12-0.36 versus RR = 0.71, 95%CI 0.52-0.97). Of note is that all studies among high risk women were small studies. Additionally, the reviewers summarised four studies with low-dose calcium supplementation and found a significant reduction in the risk of pre-eclampsia as well. Heterogeneity in this analysis was low.

Just as Khaing et al. (2017) and Hofmeyr et al. (2014), Imdad et al. (2012) find a significantly reduced risk of pre-eclampsia in the calcium group. Heterogeneity was again substantial, but mostly present in the size of the effect. The authors report that the reduction of the risk was substantial and statistically significant in populations with low mean calcium intake (RR = 0.42, 95%CI 0.26-0.69), but not statistically significant in populations with adequate mean calcium intake (RR = 0.62, 95%CI 0.32-1.20).[139]

Lastly, Bucher et al. (1996) also find a significant reduction in the risk of pre-eclampsia in the intervention group.[138] They report no significant heterogeneity for this analysis (p = 0.23). In addition, visual inspection of the forest plot does not point out heterogeneity in the direction of the effect. One RCT included in this review is not about calcium supplementation alone, but compared calcium plus vitamin D with placebo, and is, therefore, less relevant for our own analysis.[186] However, no pooled data was available in this review by Bucher et al. (1996) without this particular study. In view of the consistent significant findings of the reduced risk of pre-eclampsia in a large number of studies with a considerable number of cases, the committee concludes that there is strong evidence that supplementation with 120 to 2,000 milligram calcium per day during pregnancy reduces the risk of pre-eclampsia, especially in populations with low dietary calcium intake. Because there is heterogeneity in the size of the effect and signs of possible publication bias, the committee does not quantify the effect.

As 89% of the individual RCTs started at or after 18 weeks of gestation (66% started at or after 20 weeks of gestation), the committee considers that the evidence for the effect on pre-eclampsia relates especially to the use of calcium supplements from 18 or 20 weeks onwards (see appendix D.2).

Table 56. Results from the meta-analyses of Khaing et al. (2017), Hofmeyr et al. (2014), Imdad et al. (2012) and Bucher et al. (1996) of high and low-dose calcium supplementation during pregnancy on the risk of pre-eclampsia. For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix D.2.

First author	Intervention versus control	Start intervention	N RCTs	n / N inter-vention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Khaing[122]	500 to 2000 milligram / day calcium versus placebo[a, b]	Before 32 weeks of gestation	16	772 / 12,876	931 / 13,060	0.54 (0.41-0.70)	73%
Hofmeyr[136]	High dose: 1500 to 2000 milligram / day calcium versus placebo[a, b]	Before 32 weeks of gestation	13	379 / 7,851	510 / 7,879	0.45 (0.31-0.65)	70%
Hofmeyr[136]	Low dose: 120 to 1200 milligram / day calcium versus placebo or no treatment [c]	At or before 22 weeks of gestation[d]	4	24 / 552	57 / 428	0.36 (0.23-0.57)	0%
Imdad[139]	500 to 2000 milligram / day calcium versus placebo[a, b]	Before 32 weeks of gestation	15	398 / 8,231	543 / 8,259	0.48 (0.34-0.67)	70%
Bucher[138]	120 to 2000 milligram / day calcium versus placebo or no treatment[b, e]	20 to 32 weeks of gestation[d]	9	n.r.	n.r.	0.38 (0.22-0.65)	n.s.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; n.s.: not significant; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177] [b] In another study, all women received prenatal vitamin tablets containing 200 milligram calcium per day.[178] [c] In one RCT, 600 milligram / day was supplemented from week 22-32 followed by 1200 milligram / day from week 32 until birth.[176] [d] In one study, it is not clear when the intervention started.[184] [e] In one study, calcium + vitamin D supplements were the intervention.[186]

Update July 2018 - July 2019

Two additional meta-analyses were identified on the effect of calcium supplementation on the risk of pre-eclampsia: Sun et al. (2019) and Hofmeyr et al. (2018).[181,185] Results from these new publications did not lead to changes in the committee's conclusions.

Sun et al. (2019) included 25 studies in their meta-analysis and found a statistically significantly reduced risk of pre-eclampsia in the intervention group compared with the control group (RR = 0.51; 95%CI 0.40-0.64; I^2 = 65%). There was significant heterogeneity, but that was mainly present in the size of the effect rather than the direction.

Subgroup analyses showed a stronger effect in populations with a high risk of hypertension pre-eclampsia (12 trials; RR = 0.32; 95%CI 0.23-0.44; I^2 = 0%) than in populations with a low risk (13 trials; RR = 0.70; 95%CI 0.56-0.87; I^2 = 60%). Both risk estimates were highly significant, indicating that the substantial heterogeneity in the low-risk population was related to the size of the effect.

Sun et al. (2019) did not perform subgroup analyses based on dietary calcium intake. However, they did compare results from developed and developing countries and mentioned that baseline calcium intake is commonly sufficient in developed countries and that this may (partly) explain why the effect was statistically not significant for developed countries (four trials: RR = 0.77; 95%CI 0.56-1.07; I^2 = 66%) but strongly significant for developing countries (21 trials; RR = 0.41; 95%CI 0.29-0.58; I^2 = 65%). The committee notes that the number of trials in developed versus developing countries was substantially smaller, which may have contributed to the wider confidence interval.

Furthermore, subgroup analyses for trials using a low, moderate or high dose of calcium all showed highly significant effects. Sun et al. (2019) found no evidence for publication bias.[185]

Hofmeyr et al. (2018) is an update of Hofmeyr et al. (2014). In the 2018 version, no changes relative to the 2014 version were found for the outcome pre-eclampsia.

5.7.2 Severe pre-eclampsia

Summary: Calcium supplementation during pregnancy and the risk of severe pre-eclampsia.

Aspect	Explanation
Selected studies	Two meta-analyses of three[137] and five RCTs.[139]
Heterogeneity	No
Strength of the effect	RR = 0.80 (95%CI 0.60-1.09)[137]; RR = 0.75 (95%CI 0.57-0.98)[139]
Study population	Women with high and low risk pregnancies.

Conclusion (RCTs):

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

Explanation

Three reviews report on the risk of severe pre-eclampsia.[136,137,139]. Hofmeyr et al. (2014)[136] include only one RCT, which was also included by An et al. (2015)[137] and Imdad et al. (2012).[139] Since An et al. (2015) and Imdad et al. (2012) overlap by two studies, the results of both reviews are described for this outcome (Table 58).

The estimate is not close to one and is based on three RCTs, two of which contributed to almost 95% of the weight of the risk estimate.[175,177] There were no signs of heterogeneity and the number of cases was considerable. Imdad et al. (2012) reported that calcium supplementation during pregnancy significantly reduced the risk of severe pre-eclampsia.[139] No signs of heterogeneity were reported and the number of cases was considerable. However, again almost 90% of the weight of the estimate came from two large studies.[175,177] Furthermore, both meta-analyses used a fixed effect model which results in more narrow confidence intervals and thus a higher chance of a significant effect. Therefore, the results are less robust and the committee relies more on the meta-analysis by An et al. (2015) when formulating the conclusions.

The effect estimate is not close to one and one of the meta-analyses included five RCTs, but the results of both meta-analyses rely largely on two studies. Therefore, the committee concludes that there is too little research to draw a conclusion on the effect of calcium supplementation during pregnancy on the risk of severe pre-eclampsia.

Table 58. Results of the meta-analyses of An et al. (2015) and Imdad et al. (2012) on the effect of calcium supplementation during pregnancy on the risk of severe pre-eclampsia.

First author	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
An[137]	1500 to 2000 milligram / day calcium versus placebo[a]	13 to 20 weeks	3	89 / 6,673	112 / 6,684	0.80 (0.60-1.05)	0%
Imdad[139]	500 to 2000 milligram / day calcium versus placebo[a]	13 to 24 weeks of gestation	5	89 / 6,855	120 / 6,869	0.75 (0.57-0.98)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177]

5.8 Eclampsia

Summary: Calcium supplementation during pregnancy and the risk of eclampsia.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs.[136]
Heterogeneity	No
Strength of the effect	High dose : RR = 0.73 (95%CI 0.41-1.27); Low dose : RR = 0.17 (95%CI 0.01-4.06)
Study population	Healthy pregnant women.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of calcium supplementation during pregnancy on the risk of eclampsia.

Explanation

There is one meta-analysis on the effect of calcium supplementation on the risk of eclampsia (Table 59).[136]

Hofmeyr et al. (2014) include three RCTs with high-dose calcium supplementation and one RCT with low-dose calcium supplementation. They performed only separate analyses for these subgroups. They found no significant effect of high-dose calcium supplementation on the risk of eclampsia. The number of cases was low, and only two trials contributed to the number of cases.[175,177] The study with low-dose calcium supplementation included only 1 case, which does not enable any conclusion.[184]

Due to the low number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of calcium supplementation on the risk of eclampsia.

Table 59. Results of the meta-analysis of Hofmeyr et al. (2014) on the of high and low-dose calcium supplementation during pregnancy on the risk of eclampsia.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
High dose: 1500 to 2000 milligram / day calcium versus placebo[a]	13 to 25 weeks of gestation	3	21 / 6,719	29 / 6,706	0.73 (0.41-1.27)	0%
Low dose: 120 to 240 milligram / day calcium versus no treatment	n.r.	1	0 / 112	1 / 56	0.17 (0.01-4.06)	n.a.

CI: confidence interval; N: number; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177]

Update July 2018 - July 2019

One additional meta-analysis was identified on the effect of calcium supplementation and the risk of eclampsia: Hofmeyr et al. (2018).[181] Hofmeyr et al. (2018) is an update of Hofmeyr et al. (2014). In the 2018 version, no changes relative to the 2014 version were found for the outcome eclampsia. Therefore, results from this publication did not lead to changes in the committee's conclusions.

5.9 HELLP syndrome

Summary: Calcium supplementation during pregnancy and the risk of HELLP syndrome.

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs.[136]
Heterogeneity	No
Strength of the effect	RR = 2.67 (95%CI 1.05-6.82)
Study population	Healthy pregnant women.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of calcium supplementation during pregnancy on the risk of HELLP syndrome.

Explanation

There is one meta-analysis on the effect on calcium supplementation on the risk of HELLP syndrome – a hypertensive pregnancy complication in which haemolysis, thrombocytopenia, and high liver enzymes play a role (Table 60).[136]

They find a significant increased risk of HELLP syndrome in the calcium group. However, there are only two studies summarised in the meta-analysis and the number of cases is very low.

The committee, therefore, concludes that there is too little research to draw a conclusion on the effect of calcium supplementation on the risk of HELLP syndrome.

Table 60. Results from the meta-analysis of Hofmeyr et al. (2014) on the effect of calcium supplementation during pregnancy on the risk of HELLP syndrome.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
1500 to 2000 milligram / day calcium versus placebo[a]	13-20 weeks of gestation	2	16 / 6,446	6 / 6,455	2.67 (1.05-6.82)	0

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received 50 milligram calcium per day as normal supplementation.[177]

Update July 2018 - July 2019

One additional meta-analysis was identified on the effect of calcium supplementation and the risk of HELLP syndrome: Hofmeyr et al. (2018).[181] Hofmeyr et al. (2018) is an update of Hofmeyr et al. (2014). In the 2018 version, no changes relative to the 2014 version were found for the outcome HELLP syndrome. Therefore, results from this publication did not lead to changes in the committee's conclusions.

5.10 Blood pressure in the offspring

Summary: Calcium supplementation during pregnancy and the influence on offspring's blood pressure.

Aspect	Explanation
Selected studies	One systematic review (without meta-analysis) of four RCTs and three cohort studies.[140]
Heterogeneity	Not applicable.
Strength of the effect	No summarised risk estimate.
Study population	Women with normal and high-risk pregnancies.

Conclusion on cohort studies:

There is too little research to draw a conclusion on the association between calcium supplementation and blood pressure of the offspring.

Conclusion on RCTs:

There is too little research to draw a conclusion on the effect of calcium supplementation during pregnancy on blood pressure of the offspring.

There are two systematic reviews on the influence of calcium supplementation during pregnancy on blood pressure of the offspring.[136,140] The review of Hofmeyr et al. (2014)[136] includes only one RCT that is also included by Jamshidi et al. (2015).[140] The latter describes the results of four RCTs and three cohort studies narratively.

Regarding the cohort studies

One of the three included cohort studies is not relevant for this background document since it is not about calcium supplementation, but about dietary calcium intake.[187] One cohort study shows an association between maternal calcium supplementation and a lower systolic blood pressure at the age of 6 months[188], whereas the other finds no association with blood pressure of the child at age 9.[189]

In view of the small number of studies, the committee concludes that there is too little research on the association between calcium supplementation during pregnancy and the blood pressure of the offspring.

Regarding the intervention studies

Two trials pointed in the direction of a blood-pressure lowering effect in the offspring, a third trial only found such an effect in infants from mothers with high blood pressure during pregnancy, and the fourth trial reported no significant effect (Table 61).

Belizan et al. (1997) reported a decreased risk (RR = 0.59, 95%CI 0.39-0.90) of high systolic blood pressure at age 7 in infants of mothers who took calcium supplements during pregnancy.[190]

Hatton et al. (2003) found that maternal calcium supplementation reduced systolic blood pressure at age 2 years by 4.8 mm Hg. However, loss to follow-up was 90% at the age of 2 years, which is a major limitation of the study.[191]

Hiller et al. (2007) found no statistically significant difference in blood pressure of the offspring at the age of 4 to 7 years. However, they showed that children of calcium-supplemented mothers with (severe) pregnancy-induced hypertension and pre-eclampsia tended to have lower blood pressure at 4 to 7 years. Although this trend was statistically significant, the number of participants in this analysis was very low (n = 12).[192]

Hawkesworth et al. (2010) did not find a significant effect of maternal calcium supplementation on blood pressure at age 5 to 10.[193]

Since the findings of the four trials are not consistent, the committee concludes that there is too little research to draw a conclusion on the effect of calcium supplementation during pregnancy on blood pressure of the offspring.

Table 61. Results of the RCTs included by Jamshidi et al. (2015) on the effect of calcium supplementation during pregnancy on blood pressure of the offspring.

First author	Outcome	Intervention versus control	Start intervention	n / N intervention	n / N control	Risk measure (95%CI)
Belizan[190]	Risk of high blood pressure at age 7 years	2 gram / day calcium supplementation versus placebo	20 weeks of gestation	n.r.[a] / 298	n.r.[b] / 293	RR = 0.59 (0.39-0.90)
Hiller[192]	Blood pressure at age 4 to 7 years	1.8 gram / day calcium supplementation versus placebo	Before 24 weeks of gestation	105	104	-0.1 mm Hg (2.4 to +2.3) mean difference in systolic blood pressure +0.5 mm Hg (1.6 to +2.6) mean difference in diastolic blood pressure
Hatton[191]	Blood pressure at age 2 years	2 gram / day calcium supplementation versus placebo	13 to 21 weeks of gestation	35	18	-4.8 mm Hg (significant) mean difference systolic blood pressure. -3 mm Hg (not significant) mean difference diastolic blood pressure
Hawkesworth[193]	Blood pressure at age 5 to 10 years	1.5 gram / day calcium supplementation versus placebo	20 weeks of gestation	193	196	-0.04 mm Hg (1.78 to +1.69) mean difference systolic blood pressure. +0.25 mm Hg (1.27 to +1.77) mean difference diastolic blood pressure.

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] 11.4%; [b] 19.3%.

5.11 Summary of findings on calcium

In conclusion, this chapter is based on seven systematic reviews of intervention studies.[122,135-140] The committee found strong evidence that calcium supplementation reduced the risk of preterm birth (<37 weeks), gestational hypertension, and the risk of pre-eclampsia. It was unlikely that calcium supplementation had an effect on the risk of a small-for-gestational-age infant.

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

Committee's conclusion	Outcome
Strong evidence	• Preterm birth: Based on RCTs, calcium supplementation during pregnancy reduces the risk of preterm birth < 37 weeks. • Gestational hypertension: Based on RCTs, supplementation with 120 to 2,000 milligram calcium per day during pregnancy reduces the risk of gestational hypertension by at least 10%, especially when dietary calcium intake is low. • Pre-eclampsia: Based on RCTs, Supplementation with 120 to 2,000 milligram calcium per day during pregnancy starting any time before 32 weeks of gestation reduces the risk of pre-eclampsia, especially when dietary calcium intake is low.
Limited evidence	No conclusions with limited evidence.
Unlikely	• Small for gestational age: Based on RCTs, the effect of calcium supplementation on the risk of small-for gestational-age infants is unlikely.
Contradictory	No conclusions with contradictory evidence.
Too little research	• Maternal mortality (RCTs); • Severe gestational hypertension (RCTs); • Severe pre-eclampsia (RCTs); • Eclampsia (RCTs); • HELLP syndrome (RCTs); • Blood pressure in the offspring (RCTs and cohort studies).
Inconclusive	• Perinatal mortality, stillbirth or foetal death (RCTs); • Intrauterine growth retardation (RCTs).

5.12 Findings cited in the advisory report

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

Strong evidence from RCTs was found for a lower risk of preterm birth, gestational hypertension and pre-eclampsia. The conclusions on gestational hypertension and pre-eclampsia were especially related to populations with low calcium intakes.

As a large majority of the individual RCTs on all of these three outcomes started at, or after 20 weeks of gestation, the committee considers that the evidence for the effects on preterm birth, gestational hypertension and pre-eclampsia relate to the use of calcium supplements from 20 weeks onwards.

The committee notes here that there was too little research to draw a conclusion on the effect of calcium supplementation on HELLP syndrome, because the total number of studies and cases was too small. Nevertheless, this conclusion is mentioned in the advisory report as the effect was statistically significant and points in the opposite direction compared with the outcomes with a strong evidence level. The committee notes that the finding on HELLP syndrome is based on RCTs using supplements with 1,500 to 2,000 milligram calcium per day, which is a

higher dose than recommended in the advisory report for women who cannot achieve an adequate calcium intake through dietary changes. Furthermore, the three outcomes with strong evidence outweigh the finding on HELPP syndrome based on both the evidence levels and prevalence of the outcomes.

The committee further notes another outcome that was statistically significant but with too little research to draw a conclusion. This finding – a lowering of the risk of severe pre-eclampsia – points in the same direction as the three conclusions with strong evidence level and was not mentioned in the advisory report.

In the background document *Health effects of food consumption and dietary patterns during pregnancy*, an association of a higher dairy intake with a lower risk of wheeze in the offspring was found.[194] A higher dietary intake of calcium may be achieved by a higher dairy intake. This is relevant, as effects from calcium supplementation are more pronounced in populations with low dietary calcium intake. The conclusion on dairy is, however, not put forward in the advisory report, as the conclusion was based on limited evidence, but the committee notes that the finding does comply with the recommendation on calcium-rich foods in the advisory report.

06 combination of calcium and vitamin D

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of combined calcium and vitamin D supplementation during pregnancy and the risk of preterm birth, and pre-eclampsia. For these outcomes, at least two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two intervention studies.

In total, six systematic reviews of RCTs were identified (published before July 2018), covering the topic of calcium supplementation in combination with vitamin D supplementation during pregnancy in relation to pregnancy outcomes, maternal health and child health. Two systematic reviews were excluded because they were outdated and more recent reviews / versions were available.[151,195] One review was excluded because only one RCT on the outcome was described.[66] Hence, three systematic reviews were considered for inclusion in this chapter.[109,121,122]

The identified systematic reviews described these outcomes: pre-eclampsia, gestational diabetes, preterm birth, gestational hypertension, and neonatal death. Only pre-eclampsia and preterm birth are described in this background document since for these outcomes at least two RCTs were summarised in a meta-analysis or systematic review.

6.1 Preterm birth (< 37 weeks)

Summary: RCTs on the effect of calcium in combination with vitamin D supplementation during pregnancy on the risk of preterm birth (< 37 weeks of gestation).

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[109] (one RCT had no cases)
Heterogeneity	No
Strength of the effect	RR = 1.57 (95%CI 1.02-2.43)[109]
Study population	Healthy pregnant women and women at risk of pre-eclampsia from the Middle East and South America.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of combined supplementation of calcium and vitamin D during pregnancy on the risk of preterm birth.

Explanation

There is one systematic review with meta-analysis on combined supplementation of calcium and vitamin D during pregnancy on the risk of preterm birth (Table 62).[109]

De-Regil et al. (2016) included three RCTs in their meta-analysis. Two RCTs contributed to the number of cases (one large trial n = 660 and one small trial n = 54), the third RCT reported no cases. The large trial contributed to 98% of the weight of the meta-analysis, which hampers

interpretation. No additional RCTs were published after the search date of the systematic review.

The meta-analysis reported a significant increase of the risk of preterm birth with the intervention of using calcium and vitamin D supplements during pregnancy compared with the control group.

However, since one study was responsible for 98% of the weight of the effect estimate and the total number of cases was low, the committee concludes that there is too little research to draw a conclusion on the effect of combined supplementation of calcium and vitamin D during pregnancy on the risk of preterm birth.

Table 62. Results from the meta-analysis of De-Regil et al. (2016) on the effect of combined supplementation of calcium and vitamin D during pregnancy on the risk of preterm birth.

Intervention	Control	Start intervention	N RCTs	n / N inter-vention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Combined supplementation of 500 to 600 milligram calcium (as calcium carbonate) and 200IU (i.e. 5 microgram) vitamin D	Placebo (no vitamins or minerals) or no treatment	At or after 20 weeks of gestation	3	46 / 400	29 / 398	1.57 (1.02-2.43)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

One additional meta-analysis was identified in the update: Hofmeyr et al. (2018).[181] Results from this meta-analysis did not change the conclusion of the committee. Hofmeyr et al. (2018) based their conclusions on three RCTs, two of which were already included in the meta-analysis of De-Regil et al. (2016). The additional RCT was performed by Asemi et al. (2016).[196] This study provided one extra case. Hence, this does not change the conclusions.

6.2 Pre-eclampsia

Summary: RCTs on the effect of calcium in combination with vitamin D supplementation during pregnancy on the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs.[122]
Heterogeneity	No
Strength of the effect	RR = 0.50 (95%CI 0.32-0.78)
Study population	Healthy pregnant women and women at risk of pre-eclampsia from the Middle-East and Asia.

Conclusion:

Based on RCTs, combined supplementation of calcium and vitamin D during pregnancy reduces the risk of pre-eclampsia in the Middle-East and Asian countries.

Level of evidence: Limited.

Explanation

There were three systematic reviews with meta-analysis on combined supplementation of calcium and vitamin D during pregnancy on the risk of pre-eclampsia.[109,121,122] As Khaing et al. (2017) is the most recent and largest of these three, the committee only describes the results of this meta-analysis (Table 63).[122] No additional RCTs were published after the search date of the systematic review.

They included four RCTs (two larger trials: n = 400 and n = 660 among women with low risk pregnancies; and two small trials: n = 49 and n = 60 among women with high-risk pregnancies). The meta-analysis reported a significant reduction of the risk of pre-eclampsia with the intervention of using calcium and vitamin D supplements during pregnancy compared with the control group.

Table 63. Results from the meta-analysis of Khaing et al. (2017) on the effect of combined supplementation of calcium and vitamin D during pregnancy on the risk of pre-eclampsia.

Intervention	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
375-1000 milligram calcium per day + 200-1200IU (5-30 microgram) vitamin D per day OR 375-1000 milligram calcium per day + 50,000 IU (1.25 milligram) per 2 weeks	Placebo or no treatment	At or after 20 weeks of gestation	4	27 / 584	55 / 585	0.50 (0.32-0.78)	0

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial RR: relative risk estimate (can also be an odds ratio or hazard ratio).

The committee restricts the conclusion to the Middle-East and Asian countries, because the four trials were carried out in Pakistan, India, and two in Iran, and there were no trials from western countries. The total number of cases was slightly below 60 in the control group (55 cases). However, the risk estimate, as well as the full 95% confidence interval differed substantially from one and there was no statistical heterogeneity. Therefore, the committee concludes that combined supplementation of calcium and vitamin D during pregnancy reduces the risk of pre-eclampsia in the Middle-East and Asian countries; the evidence level is limited.

Update July 2018 - July 2019

One additional meta-analysis was identified in the update: Hofmeyr et al. (2018).[181] Hofmeyr et al. (2018) based its conclusions on two RCTs that were already included by Khaing et al. (2017). Therefore, results from this meta-analysis did not change the conclusion of the committee.

6.3 Summary of findings on calcium and vitamin D

In the end, the conclusions in this chapter are based on two systematic reviews.[109,122] The committee concluded that there is limited evidence that supplementation with a combination of calcium and vitamin D reduces the risk of pre-eclampsia.

The following overview presents all the conclusions from this chapter:

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence.
Limited evidence	• Pre-eclampsia: Based on RCTs, combined supplementation of calcium and vitamin D during pregnancy reduces the risk of pre-eclampsia in the Middle-East and Asian countries.
Unlikely	No unlikely associations or effects.
Contradictory	No conclusions with contradictory evidence.
Too little research	• Preterm birth (RCTs)
Inconclusive	No inconclusive associations or effects.

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 strong evidence level.

In this chapter, conclusions with strong evidence level are not available. There is one conclusion with limited evidence pointing in the direction of a benefit of a combination of calcium and vitamin D supplementation in reducing the risk of pre-eclampsia. This finding is consistent with the recommendations on calcium-rich foods and vitamin D supplementation in the advisory report.

The finding on the effect of a combined calcium plus vitamin D supplement on the outcome preterm birth is based on too little research, because the total number of cases in the meta-analysis of three RCTs was too low. This finding is not taken into account in the advisory report. The committee notes here that this meta-analysis reported a statistically significant increased risk of preterm birth with the combination supplement compared with the placebo, which is not consistent with the conclusions on calcium supplements and vitamin D supplements, which are both based on strong evidence (see Appendix A). The committee considers in paragraph 5.2 that calcium supplements lower the risk of preterm birth, and in paragraph 4.3 that an effect of vitamin D supplements on the risk of preterm birth is unlikely.

07
iron

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of iron supplementation during pregnancy and the risk of neonatal death, preterm birth, an infant that is small for gestational age, admission to a special care unit, maternal blood transfusion, maternal death, gestational diabetes, pre-eclampsia, and neurodevelopment in the offspring. For these outcomes, at least two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two intervention studies.

7.1 Neonatal death

Summary: Iron supplementation and the risk of neonatal death.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs[197] and one systematic review of four RCTs.[198] (one RCT overlapped)
Heterogeneity	No
Strength of the effect	RR = 0.91 (95%CI 0.71-1.18) [197], no summarised effect estimate in Cantor et al. (2015).[198]
Study population	Pregnant women with or without anaemia.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iron supplementation during pregnancy on the risk of neonatal death.

Explanation

There are four systematic reviews of the effect of iron supplementation on the risk of neonatal death (within 28 days of delivery), infant mortality or perinatal mortality.[85,197-199] Iqbal et al. (2017) describe the meta-analysis of Pena-Rosas et al. (2015) in their umbrella review.[85,197] Imdad et al. (2012) summarise four RCTs.[199] The authors, however, did not describe which four RCTs were summarised. Cantor et al. (2015) summarise four RCTs narratively.[198] One of the RCTs (the largest) is also summarised by Pena-Rosas et al. (2015) in combination with three other RCTs by meta-analysis. The committee, therefore, describes below the findings by Cantor et al. (2015) and Pena-Rosas et al. (2015) (Table 64).[197,198]

Pena-Rosas et al. (2015) found no significant effect of iron supplementation on the risk of neonatal death. The effect was not close to one and there were more than 200 cases in the systematic review, most of which stemmed from three of the four RCTs. Heterogeneity was low.[197]

Cantor et al. (2015) describe four RCTs which anecdotally reported on infant mortality, with rates of 0% to 1.9 % in the intervention group and 0% to 1.7% in the placebo group. There was no clear effect according to the authors.[198]

In conclusion, in view of the fact that the number of RCTs is limited and the relative risk estimate is not close to one, the committee concludes that there is too little research to draw a conclusion on the effect of iron supplementation on the risk of neonatal death.

Table 64. Results of the meta-analysis of Pena-Rosas et al. (2015) on the effect of iron supplementation on the risk of neonatal death.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
50-60 milligram / day iron in any supplement versus the same supplement without iron or no iron / placebo	12 to 28 weeks gestation	4	107 / 8,261	122 / 8,342	0.91 (0.71-1.18)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

7.2 Preterm birth (< 37 weeks)

Summary: Iron supplementation and the risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of 13 RCTs[197] and one more recent large RCT.[200]
Heterogeneity	No
Strength of the effect	RR = 0.93 (95%CI 0.84-1.03)[197] and RR = 0.99 (95%CI 0.85-1.16)[200]
Study population	Pregnant women with or without anaemia.

Conclusion:

Based on RCTs, an effect of iron supplementation during pregnancy on the risk of preterm birth is unlikely.

Explanation

There are five systematic reviews of iron supplementation during pregnancy on the risk of preterm birth (< 37 weeks).[85,197-199,201,202] The publication of Cantor et al. (2015)[198] is a summary of the evidence report by McDonagh et al. (2015)[202]. In the rest of this chapter, the committee will only refer to Cantor et al. (2015).[198]

Iqbal et al. (2017) summarised in their umbrella review the findings of the other four systematic reviews.[85] Imdad et al. (2012) summarise eight RCTs on preterm birth. The authors, however, do not indicate which RCTs are included in their analysis.[199] Cantor et al. (2015) summarise two RCTs, which are also summarised by Pena-Rosas et al. (2015) and Haider et al. (2013).[197,201] Pena-Rosas et al. (2015) summarise 13 RCTs, 11 of which are also described by Haider et al. (2013) The committee, therefore, describes the findings of Pena-Rosas et al. (2015) below (Table 65).[197]

Pena-Rosas et al. (2015) found no significant effect of iron supplementation during pregnancy on the risk of preterm birth. Heterogeneity was low. The relative risk was not close to one. There were, however, indications of publication bias, with smaller studies tending to report more pronounced treatment effects, which does not support the existence of an effect.

There is one more recent RCT from China of the effect of iron supplementation on the risk of preterm birth.[200] Li et al. (2017) found no

significant effect of supplementation with iron and folic acid as compared with folic acid in Chinese women (RR = 0.99; 95%CI 0.85-1.16). The study comprised a large number of cases: about half of the number of cases in the meta-analysis by Pena Rosas et al. (2015).[197,200]

In conclusion, in view of the fact that the meta-analysis did not find any significant effect and found indications of publication bias and in view of the fact that one more recent RCT with a large number of cases found a relative risk close to one, the committee concludes that an effect of iron supplementation during pregnancy on the risk of preterm birth is unlikely.

Table 65. Results of the meta-analysis of Pena-Rosas et al. (2015) and the RCT of Li et al. (2016) on the effect of iron supplementation on the risk of preterm birth <37 weeks.

Study type	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Meta-analysis[197]	9.2-100 milligram / day iron in any supplement versus the same supplement without iron or no iron / placebo	Before 13 to 20 weeks gestation	13	651 / 9,698	698 / 9,588	0.93 (0.84-1.03)	0%
RCT[200]	30 milligram / day iron and 0.4 milligram / day folic acid versus 0.4 milligram / day folic acid	Before 20 weeks gestation	1	335 / 5,888	334 / 5,920	0.99 (0.85-1.16)	n.a.

CI: confidence interval; N: number; n.a.: not applicable; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

7.3 Preterm birth (< 34 weeks)

Summary: Iron supplementation and the risk of preterm birth (< 34 weeks).

Aspect	Explanation
Selected studies	One meta-analysis of five RCTs.[197]
Heterogeneity	No
Strength of the effect	RR = 0.51 (95%CI 0.29-0.91), number of cases below 60.
Study population	Pregnant women with or without anaemia.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iron supplementation on the risk of preterm birth < 34 weeks of gestation.

Explanation

There is one meta-analysis on the effect of iron supplementation on the risk of preterm birth (< 34 weeks of gestation) (Table 66).[197] There were no additional RCTs published after the search date of the meta-analysis.

Pena-Rosas et al. (2015) included five RCTs and found a statistically significantly reduced risk of iron supplementation on very preterm birth. There was no heterogeneity. However, the number of cases was very low.

In view of the low number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of iron supplementation on the risk of preterm birth < 34 weeks of gestation.

Table 66. Results of the meta-analysis of Pena-Rosas et al. (2015) on the effect of iron supplementation during pregnancy on the risk of preterm birth (< 34 weeks).

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
20-60 milligram / day iron versus placebo or no treatment	At or before 20 weeks gestation	5	17 / 1861	35 / 1882	0.51 (0.29-0.91)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

7.4 Small for gestational age

Summary: Iron supplementation and the risk of small-for-gestational-age infants.

Aspect	Explanation
Selected studies	One meta-analysis of seven RCTs.[201]
Heterogeneity	Yes
Strength of the effect	RR = 0.84 (95%CI 0.66-1.07)
Study population	Pregnant women with or without anaemia.

Conclusion:

Study findings from RCTs on the effect of iron supplementation during pregnancy on the risk of small-for-gestational-age infants are contradictory.

Explanation

There are four systematic reviews of the effect of iron supplementation during pregnancy on the risk of small-for-gestational-age infants.[85,198,199,201] Imdad et al. (2012) summarise four RCTs.[199] The authors, however, did not describe which four RCTs were summarised. Iqbal et al. (2017) summarise four meta-analyses in their umbrella review: the meta-analysis of Haider et al. (2013), two other meta-analyses focusing on the effect of multiple micronutrient supplementation in developing countries and one studying the effect of iron in combination with folic acid.[85] Haider et al. (2013) summarised seven RCTs. These seven RCTs also included the four that were summarised narratively by Cantor et al. (2015).[198,201] The committee, therefore, describes the findings by Haider et al. (2013) below (Table 67).

Haider et al. (2013) found no significant association between the use of iron supplements and the risk of small-for-gestational-age infants. Heterogeneity was considerable and present in the size and direction of the effect. One RCT largely influenced the results of the meta-analysis, contributing for more than 75% of the weight to the risk estimate.[201]

In view of the fact that the risk estimate is not close to one and heterogeneity was considerable, the committee concludes that study findings on the effect of iron supplementation during pregnancy on the risk of small-for-gestational-age infants are contradictory.

Table 67. Results of the meta-analysis of Haider et al. (2013) on the effect of iron supplementation on the risk of small-for-gestational-age infants.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
30-60 milligram / day iron versus placebo or no treatment	12 to 28 weeks gestation	7	n.r.	n.r.	0.84 (0.66-1.07)	65%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

7.5 Infant admission to special care unit, maternal blood transfusion and maternal death

Conclusion:

There is too little research to draw a conclusion on the effect of iron supplementation during pregnancy on the risk of infant admission to a special care unit, maternal blood transfusion or maternal death.

Explanation

There is one systematic review of the effect of iron supplementation during pregnancy and the risk of admission to a special care unit, blood transfusion and maternal death.[197] Pena-Rosas et al. (2015) summarise one RCT reporting on the risk of infant admission to a special care unit, two RCTs on the risk of maternal blood transfusion and two RCTs on the risk of maternal death. However, the number of cases varied in the RCTs from 0 to 1. In view of the small number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of iron supplementation during pregnancy on the risk of admission to a special care unit, blood transfusion or maternal death.

7.6 Maternal anaemia

Summary: Iron supplementation and the risk of maternal anaemia.

Aspect	Explanation
Selected studies	One meta-analysis of 16 RCTs[199], and two individual RCTs.[203,204]
Heterogeneity	Yes, in the size of the effect.
Strength of the effect	Meta-analysis: RR = 0.31 (95%CI 0.22-0.44)[199] RCT: RR adolescents = 0.34 (95%CI 0.13-0.89); RR adults = 0.32 (95%CI 0.13-0.78)[a203] RCT : RR = 1.11 (95%CI 0.71-1.71)[b204]
Study population	Pregnant women with and without anaemia.

[a] RR derived from Cantor et al. (2015).[198] [b] RR derived from Haider et al. (2013).[201]

Conclusion:

Based on RCTs, supplementation with 20 to 300 milligram iron per day during pregnancy reduces the risk of maternal anaemia at term.

Level of evidence: Strong.

Explanation

We found one umbrella review of meta-analyses, by Iqbal and Ekmekcioglu (2017), that summarised maternal outcomes related to iron supplementation.[85] They identified four meta-analyses on the outcome maternal anaemia: Cantor et al. (2015); Haider et al. (2013); Imdad and Butta (2012); and Pena-Rosas et al. (2015).[197-199,201] Cantor et al. (2015) summarised three RCTs, all conducted in high-income countries.[198]

Two of these were also summarised in the other three reviews. Haider et al. (2013),[201] Imdad and Butta (2012)[199], and Pena-Rosas et al. (2015)[197] summarised 19, 16, and 14 RCTs respectively on maternal anaemia. Twelve studies were summarised in all three reviews, ten of those were from high-income countries. All reviews showed similar overall results in their meta-analyses: ranging from RR = 0.30 to RR = 0.50 (all significant). As Imdad and Butta (2012) included the highest number of studies from high-income countries, the committee based its conclusions on their findings (Table 68a). Their results were supplemented with additional studies from high-income countries that were found in the other reviews but were not included in Imdad and Butta (2012); i.e. one study by Meier et al. (2003)[203], from the review of Cantor et al. (2015), and one study by Siega-Riz et al. (2006)[204], from the review of Haider et al. (2013) (Table 68b). Hence, results from 18 individual studies in total contributed to the conclusions of the committee. Fourteen of these were from high-income countries. No additional individual studies from high-income countries were found after the search date of the reviews. For information on the original studies (supplement doses, start moments, iron status at start), see Appendix E.

Imdad and Butta (2012) found a statistically significantly reduced risk of iron supplementation on maternal anaemia at term versus no iron supplementation. These results were supported with results from the RCT of Meier et al. (2003). They found a statistically significantly reduced risk of iron deficiency anaemia during pregnancy. Siega-Riz et al. (2006) found a non-significant effect of iron on anaemia in the third trimester. In the meta-analysis, there was substantial heterogeneity in the size of the effect, but not in the direction. Imdad and Butta (2012) did not perform subgroup analyses, but Haider et al. (2013) and Pena-Rosas et al. (2015) did. As the latter reviews included almost the same set of studies as Imdad and Butta (2012), the committee used their subgroup analyses to get an idea on how the heterogeneity could be explained. Only the dose of supplementations seemed to explain some part of the heterogeneity: a dose of 30 milligram/day or less appeared to have a less effect (RR = 0.49; 95%CI 0.24-1.03; three studies) compared with a dose of 60 milligram/day or more (RR = 0.25; 95%CI 0.14-0.45; ten studies). However, in these analyses too, heterogeneity was still 45% and 85% respectively. Heterogeneity could not be explained by start of supplementation, anaemic status at baseline, malarial setting, high vs. low or middle-income country. Both Pena-Rosas et al. (2015) and Haider et al. (2013) reported publication bias from small studies. The treatment effect appeared more pronounced in smaller studies. Furthermore, Pena-Rosas downgraded the level of evidence to ‘low quality’ because several studies had design limitations and one had serious design limitations. However, they did not specify which studies or which limitations they refer to.

The committee concludes that iron supplementation reduces the risk of maternal anaemia at term and judges the level of evidence as strong as

the direction of the effect was consistent, the number of included studies was high and there were sufficient cases. Because of the high heterogeneity in the size of the effect that could not be explained, the committee does not quantify the effect.

Table 68a. Results of the meta-analysis of Imdad and Butta (2012) on the effect of iron supplementation during pregnancy on the risk of maternal anaemia at term. For information on the original studies (supplement doses, start moments, iron status at start), see Appendix E.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
20 to 300 mg/ day iron versus no iron or placebo	At or before 28 weeks gestation	16	218 / 4,364	495 / 4,301	0.31 (0.22-0.44)	72%

CI: confidence interval; n.a.: not applicable; n / N: number of cases / total number of participants; RCT: randomized controlled trial.

Table 68b. Results of the two additional RCTs on the effect of iron supplementation during pregnancy on the risk of maternal anaemia during pregnancy.

First author RCT	Intervention versus control	Start intervention	n / N intervention	n / N control	P-value
Meier[203]	60 milligram / day iron versus placebo. Both plus 1 milligram folic acid/day	Median in first trimester (range 7 to 18 weeks of gestation)	Adolescents: 4 / 20 Adults: 5 / 38	Adolescents: 10 / 17 Adults: 15 / 36	Adolescents: 0.021 Adults: 0.0008
Siega-Riz[204]	30 milligram iron and multivitamin versus placebo and multivitamin	At or before 20 weeks of gestation	21%	19%	0.65

CI: confidence interval; n.a.: not applicable; n / N: number of cases / total number of participants; RCT: randomized controlled trial.

7.7 Gestational diabetes

Summary: Iron supplementation and the risk of gestational diabetes.

Aspect	Explanation
Selected studies	One systematic review of two RCTs.[205]
Heterogeneity	Not applicable.
Strength of the effect	No summarised effect measure, but not significant in the individual RCTs.[206,207]
Study population	Pregnant women without anaemia.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iron supplementation during pregnancy on the risk of gestational diabetes.

Explanation

There is one systematic review of the effect of iron supplementation during pregnancy and the risk of gestational diabetes (Table 69).[205]

Khambalia et al. (2016) summarise two RCTs, which both find no significant effect of iron supplementation early in pregnancy on the risk of gestational diabetes (only p-values presented).[206,207] According to Khambalia et al. (2016), only the RCTs of Chan et al. (2009) were of high quality. Data were not combined by the authors of the systematic review, as there were only two RCTs.

In conclusion, there is too little research to draw a conclusion on the effect of iron supplementation during pregnancy on the risk of gestational diabetes.

Table 69. Results of the RCTs from the systematic review of Khambalia et al. (2016) on the effect of iron supplementation during pregnancy on the risk of gestational diabetes.

First author RCT	Intervention versus control	Start intervention	n / N intervention	n / N control	P-value
Chan[206]	60 milligram / day iron versus placebo	At or before 16 weeks gestation	56 / 565	60 / 590	0.86
Ouladsahebmadarek[207]	30 milligram iron and multivitamin versus placebo and multivitamin	First trimester	2 / 480	3 / 480	0.67

CI: confidence interval; n.a.: not applicable; n / N: number of cases / total number of participants; RCT: randomized controlled trial.

7.8 Pre-eclampsia

Summary: Iron supplementation and the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs.[197]
Heterogeneity	No
Strength of the effect	RR = 1.63 (95%CI 0.87-3.07)
Study population	Pregnant women with or without anaemia.

Conclusion (RCTs):

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

Explanation

There are three systematic reviews of the effect of iron supplementation during pregnancy and the risk of pre-eclampsia.[85,197,199] Iqbal et al. (2017) summarise the systematic reviews of Imdad et al. (2012) and Pena-Rosas et al. (2015) in their umbrella review.[85] Imdad et al. (2012) summarise two RCTs.[199] The authors, however, did not describe which two RCTs were summarised. Pena-Rosas et al. (2015) summarise four RCTs.[197] Therefore, the committee describes the findings of the latter systematic review below (Table 70).

Pena-Rosas et al. (2015) found no significant effect of iron supplementation on the risk of pre-eclampsia. Due to the small number of cases, however, the confidence interval was wide. Heterogeneity was low.

In view of the small number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of iron supplementation on the risk of pre-eclampsia.

Table 70 Results from the meta-analysis of Pena-Posas et al. (2015) on the effect of iron supplementation during pregnancy on the risk of pre-eclampsia.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
9.2-60 milligram / day iron in any supplement versus the same supplement without iron or no iron / placebo	12 to 20 weeks gestation	4	27 / 874	15 / 830	1.63 (0.87-3.07)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

7.9 Neurodevelopment in the offspring

Summary: Iron supplementation and neurodevelopment in the offspring.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[208]
Heterogeneity	No
Strength of the effect	Mean difference +0.54 units on different mental development scales (95%CI -0.67 to +1.75).
Study population	Pregnant women.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iron supplementation during pregnancy on neurodevelopment in the offspring.

Explanation

There is one meta-analysis on the effect of iron supplementation during pregnancy on neurodevelopment in the offspring (Table 68).[208] They included six publications on four RCTs. One RCT was excluded from the meta-analysis as the control group, who received folic acid, was not included in the follow-up study.

The authors did not find a statistically significant effect of iron supplementation during pregnancy on neurodevelopment in the offspring. There was moderate heterogeneity, which was not explained. Different measurement scales were used to assess mental development in the offspring: Bayley's Scale of Infant Development, Stanford-Binet Intelligence Scale, Strengths and Difficulties Questionnaire, Wechsler Intelligence Scale for Children, Universal Nonverbal Intelligence Test and the Peabody Developmental Motor Scale. The tools assessed intelligence and cognitive function in children. The authors of the meta-analysis used units of the scores as outcome; however, it was not clearly stated how these units were defined. No additional publications were found that were published after the final search date of the meta-analysis.

In view of the limited number of studies (< 5) and the fact that the mean difference is relatively close to zero, the committee concludes that there is too little research to draw a conclusion on the effect of iron supplementation during pregnancy on neurodevelopment in the offspring.

Table 68. Results from the meta-analysis of Jayasinghe et al. (2018) on the effect of iron supplementation during pregnancy on neurodevelopment in the offspring.

Intervention versus control	Start intervention	N RCTs	N iron	N control	Mean difference (units)	95%CI	Hetero-geneity I^2
20 or 60 milligram iron with or without 400 microgram folic acid versus placebo with or without 400 microgram folic acid or folic acid alone.	At or before 28 weeks gestation	3	917	821	+0.54	-0.67 to +1.75	48%

CI: confidence interval; N: number; RCT: randomized controlled trial.

7.10 Summary of findings on iron

The conclusions in this chapter are based on five systematic reviews[197,198,201,205,208] and one additional RCT.[200] The committee concluded that is it unlikely that iron supplementation has an effect on preterm birth. For other outcomes, the effect of iron supplementation was either contradictory or there was too little research to draw a conclusion.

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

Committee's conclusion	Outcome
Strong evidence	• Maternal anaemia: Based on RCTs, supplementation with 20 to 300 milligram iron per day during pregnancy reduces the risk of maternal anaemia at term.
Limited evidence	No conclusions with limited evidence.
Unlikely	• Preterm birth (< 37 weeks): Based on RCTs, an effect of iron supplementation during pregnancy on the risk of preterm birth is unlikely.
Contradictory	• Small for gestational age (RCTs)
Too little research	• Neonatal death (RCTs); • Very preterm birth (< 34 weeks) (RCTs); • Infant admission to a special care unit (RCTs); • Maternal blood transfusion (RCTs); • Maternal death (RCTs); • Gestational diabetes (RCTs); • Pre-eclampsia (RCTs); • Neurodevelopment in the offspring (RCTs).
Inconclusive	No inconclusive associations or effects.

7.11 Findings cited in the advisory report

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

There is strong evidence that the use of iron supplements during pregnancy reduces the risk of maternal anaemia at term. The majority of these RCTs were carried out in high-income countries.

There was too little research (insufficient number of cases) to formulate a conclusion on the effect of iron supplements during pregnancy on the risk of preterm birth < 34 weeks. Therefore, the finding is not mentioned in the advisory report. The committee notes here that the meta-analysis of five RCTs on this outcome did report a statistically significant reduction of the risk (RR = 0.51; 95%CI 0.29-0.91).

08
iodine

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of iodine supplementation during pregnancy and the risk of miscarriage, perinatal mortality, preterm birth, birth growth measures, maternal goitre, neonatal thyroid outcomes, and child mental and motor development. For these outcomes, at least two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two intervention studies.

In total, seven systematic reviews of RCTs were identified by the committee (published before July 2018) covering the topic of iodine supplementation during pregnancy in relation to pregnancy outcomes, maternal health and child health.[58,209-214] Five systematic reviews were excluded because they were outdated and more recent reviews / versions were available or because only one RCT on an outcome was included.[58,210,212-214] Hence, two systematic reviews were considered for inclusion in this chapter.[209,211]

The identified systematic reviews described the following outcomes: maternal thyroid outcomes, preterm birth, perinatal mortality, growth measures, neonatal thyroid outcomes, miscarriage, and child mental and motor development. No additional RCTs on iodine supplementation were found that were published after the search date of the systematic reviews.

8.1 Miscarriage

Summary: RCTs on the effect of iodine supplementation during pregnancy on the risk of spontaneous miscarriage.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[211]
Heterogeneity	No
Strength of the effect	RR = 1.31 (95%CI 0.64-2.69)
Study population	Pregnant women with or without mild iodine deficiency.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of miscarriage.

Explanation

There is one meta-analysis reporting on the effect of iodine supplementation during pregnancy on the risk of a spontaneous miscarriage (Table 71).[211]

It included three trials and found no statistically significant effect of iodine supplementation during pregnancy. There was no heterogeneity, but the number of cases was low.

In view of the limited number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of miscarriage.

Table 71. Results from the meta-analysis of Harding et al. (2017) on the effect of iodine supplementation during pregnancy on the risk of spontaneous miscarriage.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
150 to 200 microgram / day iodine tablet with or without other vitamins / minerals versus placebo with or without other vitamins / minerals	Before 20 weeks of gestation	3	15 / 308	13 / 337	1.31 (0.64-2.69)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

8.2 Perinatal mortality

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of perinatal mortality.

Explanation

There was one meta-analysis reporting on the effect of iodine supplementation during pregnancy on the risk of perinatal mortality.[211] It included two RCTs on this outcome; however, one of these did not report any cases. Hence, the 'summarised' effect estimate was based on one RCT which found a non-significant reduced risk of perinatal mortality (RR 0.66 95%CI 0.42-1.03).

Because of the limited available RCTs, the committee concludes that there is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of perinatal mortality.

8.3 Preterm birth

Summary: RCTs on the effect of iodine supplementation during pregnancy on the risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs.[211]
Heterogeneity	No
Strength of the effect	RR = 0.71 (95%CI 0.30-1.66)
Study population	Pregnant women with or without mild iodine deficiency.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of preterm birth.

Explanation

There is one meta-analysis describing the effect of iodine supplementation during pregnancy on the risk of preterm birth (Table 72).[211]

Two RCTs were included. It was not specified by the authors of the meta-analysis how preterm birth was defined in the included RCTs. A lower, but statistically non-significant, risk of preterm birth was found for the group receiving iodine supplementation compared with the control group.

In view of the fact that only two RCTs were summarised in a meta-analysis on this outcome, the committee concludes that there is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of preterm birth.

Table 72. Results from the meta-analysis of Harding et al. (2017) on the effect of iodine supplementation during pregnancy on the risk of preterm birth.

Intervention versus control	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
150 to 200 microgram / day iodine tablets with or without other vitamins / minerals	placebo with or without other vitamins / minerals	Before 20 weeks of gestation	2	13 / 177	22 / 199	0.71 (0.30-1.66)	32%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

8.4 Birth growth measures

8.4.1 Small for gestational age

Summary: RCTs on the effect of iodine supplementation during pregnancy on the risk of a small-for-gestational-age infant.

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs.[211]
Heterogeneity	No
Strength of the effect	RR = 1.26 (95%CI 0.77-2.05)
Study population	Pregnant women with mild iodine deficiency.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of a small-for-gestational-age infant.

Explanation

There is one meta-analysis on the effect of iodine supplementation during pregnancy on the risk of a small-for-gestational-age infant (Table 73).[211]

Harding et al. (2017) included two RCTs from Australia and Asia. The risk estimate for the effect of iodine supplementation during pregnancy on the risk of a small-for-gestational-age infant was not statistically significant. There was no heterogeneity. One of the studies had a high risk of attrition bias due to a high percentage loss to follow-up (i.e. > 20%).

In view of the fact that there are no more than two RCTs summarised in a systematic review, the committee concludes that there is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of a small-for-gestational-age infant.

Table 73. Results from the meta-analysis of Harding et al. (2017) on the effect of iodine supplementation during pregnancy on the risk of a small-for-gestational-age infant.

Intervention versus control	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
150 to 200 microgram / day iodine with or without other vitamins / minerals	placebo with or without other vitamins / minerals	Before 20 weeks of gestation	2	29 / 178	26 / 199	1.26 (0.77-2.05)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

8.4.2 Other birth growth measures

Farebrother et al. (2018), and Harding et al. (2017) reported on other birth measures of growth: head circumference (two RCTs), birth weight (four RCTs), and birth length (three RCTs).[209,211] No statistically significant effects were found of iodine supplementation during pregnancy on head circumference, birth length and birth weight.

8.5 Maternal goitre

Summary: RCTs on the effect of iodine supplementation during pregnancy on the risk of maternal goitre.

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs.[211]
Heterogeneity	Yes, in direction of effect.
Strength of the effect	RR = 1.00 (95%CI 0.33-3.06)
Study population	Pregnant women with mild iodine deficiency.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of maternal goitre.

Explanation

There is one meta-analysis reporting on the effect of iodine supplementation during pregnancy on the risk of maternal goitre.[211] For information on the original studies (supplement doses, start moments, iodine status at start), see Appendix F.1. The meta-analysis included two trials which showed effects in opposite directions (Table 74).[211] Hence, heterogeneity was substantial, but statistically not significant. The summarised effect estimate was one. In the general population, iodine deficiency eventually causes goitre. The authors of the meta-analysis do not elaborate on possible explanations why one of the included trials (Gowachirapant et al. (2014)) showed a non-significant effect in favour of the control group. The committee argues that this is possibly because almost 90% of the participants from Gowachirapant et al. (2014) used iodized salt, while in the study of Glinoer et al. (1993), which showed an effect estimate in favour of the iodine group, no fortification appeared present.

In view of the fact that only two trials with very few cases were summarised in the meta-analysis, the committee concludes that there is too little

research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of maternal goitre.

Table 74. Results from the meta-analysis of Harding et al. (2017) on the effect of iodine during pregnancy on the risk of maternal goitre. For information on the original studies (supplement doses, start moments, iodine status at start), see Appendix F.1.

Intervention	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
100 to 200 microgram / day oral iodine with or without other vitamins minerals	Placebo with or without other vitamins / minerals	Before 16 weeks of gestation	2	13 / 236	14 / 250	1.00 (0.33-3.06)	53%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

8.6 Neonatal hypothyroidism or elevated thyroid-stimulating hormone

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of neonatal hypothyroidism or elevated thyroid-stimulating hormone.

Explanation

There was one meta-analysis reporting on the effect of iodine supplementation during pregnancy on the risk of neonatal hypothyroidism or elevated thyroid stimulation hormone (TSH).[211] They included two RCTs on this outcome, however, one of them did not report any cases. The 'summarised' effect estimate showed a reduced risk of neonatal hypothyroidism or elevated thyroid-stimulating hormone, but was not statistically significant (RR = 0.58 95%CI 0.11-3.12) and was based on one RCT.

In view of the limited number of studies, the committee concludes that there is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of neonatal hypothyroidism or elevated TSH.

8.7 Neonatal thyroid volume

Summary: RCTs on the effect of iodine supplementation during pregnancy on neonatal thyroid volume.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[211]
Heterogeneity	Yes, mainly in the size of the effect.
Strength of the effect	Mean difference = -0.34 mL (95%CI -0.58 to -0.11)
Study population	Pregnant women with mild to moderate iodine deficiency, in Europe and Asia.

Conclusion:

Based on RCTs, in pregnant women with iodine deficiency, iodine supplementation lowers the neonatal thyroid volume.

Level of evidence: Limited.

Explanation

The committee found one meta-analysis which reported on the effect of iodine supplementation during pregnancy on neonatal thyroid volume (Table 75).[211] For information on the original studies (supplement doses, start moments, iodine status at start), see Appendix F.2.

They included three RCTs and showed a statistically significantly lower thyroid volume in infants of mothers who received iodine supplementation during pregnancy when compared with infants of mothers who received a placebo or no intervention. There was high statistical heterogeneity, but that was mainly present in the size of the effect and not in the direction of the effect. Possibly, the presence of iodine fortification programs is a source of effect modification according to the committee. Studies performed in countries without fortification at the time of study showed a greater reduction in neonatal thyroid volume as compared with the study that was performed in a setting with fortification.

In view of the number of included RCTs, the number of participants and the observation that the heterogeneity did not apply to the direction of the effect the committee concludes that iodine supplementation during pregnancy lowers the neonatal thyroid volume when compared with placebo or no intervention. The level of evidence was considered limited.

Table 75. Results from the meta-analysis of Harding et al. (2017) on the effect of iodine supplementation during pregnancy on neonatal thyroid volume. For information on the original studies (supplement doses, start moments, iodine status at start), see Appendix F.2.

Intervention versus control	Control	Start intervention	N RCTs	N iodine	N control	Mean difference in milliliter (95%CI)	Hetero-geneity I^2
100 to 300 microgram / day oral iodine with or without other vitamins / minerals	Placebo with or without other vitamins / minerals or no intervention	Before 16 weeks of gestation	3	162	197	-0.34 (-0.58 to -0.11)	93%

CI: confidence interval; N: number; RCT: randomized controlled trial.

8.8 Neonatal goitre

Summary: RCTs on the effect of iodine supplementation during pregnancy on the risk of neonatal goiter.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[211]
Heterogeneity	No
Strength of the effect	RR = 0.11 (95%CI 0.02-0.56)
Study population	Pregnant women with sufficient iodine status or mild to moderate iodine deficiency.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on the risk of neonatal goitre.

Explanation

There is one meta-analysis reporting on the effect of iodine supplementation during pregnancy on the risk of neonatal goitre (Table 76).[211]

Three RCTs were included. The largest RCT was carried out in a population which – on average – was iodine sufficient at baseline (i.e. iodine status of 170 microgram / L). All women of childbearing age received an iodine injection; hence the women received the supplement either preconceptional or during pregnancy, which is broader than the scope of the committee. This large trial (n = 456) was conducted in the 1960s in Peru. No cases of neonatal goitre occurred during follow-up (neither in the intervention group, nor in the control group). According to the committee, a possible explanation for this finding is the iodine sufficiency at baseline.[215]

Both other trials were carried out during pregnancy in women with mild or moderate iodine deficiency: a Belgian trial among 120 pregnant women with mild iodine deficiency[216,217] and a German trial among 108 pregnant women with moderate iodine deficiency.[218] Both found a lower risk of neonatal goitre in infants of mothers in the iodine supplementation group compared with the control group, albeit not statistically significant in the Belgium study (respectively RR = 0.08 95%CI 0.00-1.34 and RR = 0.13 95%CI 0.02-0.96).

The meta-analysis over these three trials indicates that iodine supplementation significantly reduces the risk of neonatal goitre. The statistically significant effect estimate was far below one with a relatively narrow confidence interval and there was no statistical heterogeneity. This finding appears to be consistent with the fact that goitre is caused by iodine deficiency, especially because the trial in women with a sufficient iodine status showed no effect, whereas both trials in women with mild or moderate iodine deficiency reported very low risk estimates. The committee notes that these two trials were carried out in our neighbouring countries (Belgium and Germany). However, the total number of cases in the three trials was far too low (< 60 cases in both arms). Therefore, the committee concludes that there is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy and the risk of neonatal goitre.

Table 76. Results of the meta-analysis of Harding et al. (2017) on the effect of iodine supplementation during pregnancy on the risk of neonatal goitre.

Intervention	Control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
100 to 300 microgram / day oral iodine OR two injections of 950 milligram containing iodized oil (3y interval)	Placebo or no iodine or injection with non-iodized poppy-seed oil (3y interval)	Before 16 weeks of gestation[a]	3	1 / 352	20 / 332	0.11 (0.02-0.56)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] One study injected women of childbearing age regardless of pregnancy.[215]

8.9 Child mental or motor development

Summary: RCTs on the effect of iodine supplementation during pregnancy on child mental or motor development.

Aspect	Explanation
Selected studies	One systematic review of two RCTs[211] and one additional RCT.[219]
Heterogeneity	Not applicable.
Strength of the effect	See Explanation.
Study population	Pregnant women with mild to severe iodine deficiency

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on mental or motor development of the child.

Explanation

The committee found one systematic review, without meta-analysis, on the effect of iodine supplementation during pregnancy on child mental or motor development (Table 77).[211] The committee found one additional RCT.[219]

Harding et al. (2017) included two RCTs which reported on IQ points, cognitive score, language score, motor score, social-emotional score and adaptive behaviour score. The RCT of Zhou et al. (2015)[220] found no significant difference between the intervention and control group for cognitive score, language score, motor score, social-emotional score and adaptive behaviour score at the age of 18 months. The other included RCT of Thilly et al. (1978)[221], found a significantly higher IQ in the children aged 4 to 23 months in the intervention group (their mothers received a single iodine injection during pregnancy) versus the control group. The prevalence of goitre in the research population (the pregnant women) was 70% indicating deficiency in the participants.

The RCT of Gowachirapant et al. (2017) was conducted in Thailand and India. They found no statistically significant differences between the intervention and control group on verbal and performance IQ and overall executive functioning at the age of 5 to 6 years. Women were mildly iodine-deficient at study entry. [219]

In view of the fact that there were only three RCTs available and no consistent results were found, the committee concludes that there is too little research to draw a conclusion on the effect of iodine supplementation during pregnancy on child mental and motor development.

Table 77. Results from the RCTs of Zhou et al. (2015) and Thilly et al. (1978) on the effect of iodine supplementation during pregnancy on various child mental or motor development measures.

RCT	Intervention versus control	Outcome	Start intervention	N iodine	N control	Mean difference (points)	95%CI
Zhou[220]	150 microgram / day iodine tablets versus placebo	Cognitive score	Before 20 weeks of gestation	27	26	-2.30	-7.88 to +3.28
Zhou[220]	150 microgram / day iodine tablets versus placebo	Language score	Before 20 weeks of gestation	27	26	-0.70	-7.08 to +5.68
Zhou[220]	150 microgram / day iodine tablets versus placebo	Motor score	Before 20 weeks of gestation	27	26	+1.50	-4.02 to +7.02
Zhou[220]	150 microgram / day iodine tablets versus placebo	Social-emotional score	Before 20 weeks of gestation	27	26	+0.40	-8.25 to +9.05
Zhou[220]	150 microgram / day iodine tablets versus placebo	Adaptive behaviour score	Before 20 weeks of gestation	27	26	+1.70	-6.40 to +9.80
Thilly[221]	Single injection with iodized oil, 475 milligram iodine	IQ points	Mean 28 weeks of gestation	66	72	+11.00	+7.58 to +14.42
Gowachirapant[219]	200 microgram / day iodine tablets versus placebo	IQ overall	Before 14 weeks of gestation	159	154	-1.20	-3.50 to +1.10
Gowachirapant[219]	200 microgram / day iodine tablets versus placebo	Overall executive functioning	Before 14 weeks of gestation	159	154	-0.90	-6.80 to +5.00

CI: confidence interval; N, total number of participants; RCT: randomized controlled trial.

8.10 Summary of findings on iodine

The conclusions in this chapter are based on two systematic reviews.[209,211]

The committee found that iodine supplementation reduces the neonatal thyroid volume (level of evidence: limited).

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

Committee's conclusion	Outcome
Strong evidence	No conclusions with strong evidence.
Limited evidence	• Neonatal thyroid volume: Based on RCTs, in pregnant women with iodine deficiency, iodine supplementation lowers the neonatal thyroid volume.
Unlikely	No unlikely associations or effects.
Contradictory	No conclusions with contradictory evidence.
Too little research	• Miscarriage (RCTs); • Perinatal mortality (RCTs); • Preterm birth (RCTs); • Small for gestational age (RCTs); • Maternal goitre (RCTs); • Neonatal hypothyroidism or elevated thyroid-stimulating hormone (RCTs); • Neonatal goitre (RCTs); • Child mental or motor development (RCTs).
Inconclusive	No inconclusive associations or effects.

8.11 Findings cited in the advisory report

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

In this chapter on iodine supplementation, conclusions with strong evidence level were not available. However, there is limited evidence based on RCTs that the use of iodine supplements during pregnancy lowers neonatal thyroid volume. The RCTs were conducted in populations with low iodine intakes (see Appendix F.2). However, based on the dietary reference intake, the importance of iodine in pregnancy, and the lack of sufficient knowledge of iodine intakes of pregnant women in the Netherlands, the committee does formulate a recommendation on the consumption of iodine-rich foods.

There was too little research (insufficient number of cases) to formulate a conclusion on the effect of iodine supplements during pregnancy on the occurrence of neonatal goitre. Therefore, the finding is not mentioned in the advisory report. The committee notes here that the meta-analysis of three RCTs on this outcome did report a statistically significant reduction of the risk (RR = 0.11; 95%CI 0.02-0.56).

09 magnesium

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of magnesium supplementation during pregnancy on the risk of miscarriage, perinatal mortality, preterm birth, an infant that is small for gestational age, gestational hypertension, and pre-eclampsia. For these outcomes, at least two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two intervention studies.

There are nine systematic reviews or meta-analyses reporting on magnesium supplementation during pregnancy in relation to pregnancy outcomes.[69,70,73,75,171,222-225] The review of Makrides et al. (2014) includes ten trials and is the most recent and complete review on the effect of magnesium supplementation on pregnancy outcomes. Makrides et al. (2014) is an update of Makrides et al. (2001)[225], which in turn is an update of Makrides et al. (2000).[224] Villar et al. (2004) (on the risk of pre-eclampsia)[171], Villar et al. (2003) (on the risk of pre-eclampsia and preterm delivery)[69], Merialdi et al. (2003) (on the risk of small for gestational age)[73] and Villar et al. (1998)[70] (on the risk of preterm birth) based their results on Makrides et al. (2000)[224] or Makrides et al. (2001)[225], and do not include additional trials. Kulier et al. (1998) (on the risk of pre-eclampsia)[75] included four RCTs on effects of magnesium supplementation, which were all included in the review of Makrides et al. (2014).[223] The two RCTs included by the review of De Onis et al. (1998) (on the risk of intra uterine growth retardation)[222] were also included in the review of Makrides et al. (2014).[223] Therefore, the results from the meta-analysis of Makrides et al. (2014)[223] are described below. They included nine RCTs[226-235] and one quasi-RCT[236] and based their results on both study types. Since no sensitivity analysis was available for RCTs only, risk estimates presented in our overview are also based on both study types. One RCT has a cluster design; the authors of this trial do not correct for the cluster design.[230,231] Since Makrides et al. (2014) do not present a sensitivity analysis without this cluster-RCT, risk estimates presented in our overview also include this study. The authors of the review judge the risk of bias in general as moderate.

One additional relevant RCT[237] was identified by the committee that was published after the search period of Makrides et al. (2014). The researchers compare three groups: those with ≥ 1.9 mg / dl serum magnesium level receiving a multiple mineral tablet once a day (group A); those with < 1.9 mg / dl serum magnesium level receiving a multiple mineral tablet once a day (group B); and those with < 1.9 mg / dl serum magnesium level receiving a multiple mineral tablet and a 200 milligram magnesium tablet daily (group C). Only the comparison between group B and C is of interest for the committee, since these groups only differ in magnesium supplementation, whereas group A also differs in magnesium serum level. Furthermore, the study does not add a lot of cases and does not present risk estimates. However, for the sake of completeness, the results of this RCT are incorporated in the results of this document.

9.1 Miscarriage

Summary: Magnesium supplementation during pregnancy and the risk of miscarriage.

Aspect	Explanation
Selected studies	One meta-analysis of five RCTs and one quasi-RCT.[223]
Heterogeneity	No
Strength of the effect	RR = 0.85 (95%CI 0.49-1.49)
Study population	Women with normal and high-risk pregnancies.

Conclusion:

Study findings from RCTs on the effect of magnesium supplementation during pregnancy on miscarriage are inconclusive.

Explanation

Makrides et al. (2014) included five RCTs and one quasi-randomized trial in their meta-analysis (Table 78).

They found no significant effect of magnesium supplementation during pregnancy on the risk of miscarriage (< 20 weeks of gestation).
The relative risk is not close to one, the number of cases is considerable, but mainly from one study, and there is moderate heterogeneity in the size and direction of the effect. The reviewers suggest that the heterogeneity is possibly explained by the different types of magnesium supplement and the different regimens for administration used across the six trials.
However, they did not carry out additional subgroup analyses.
The relative risk was not close to one, but not statistically significant either. There were more than five studies, but the number of cases per arm was less than 100 (and more than 60) in both arms of the meta-analysis. In view of the wide confidence interval, the committee concludes that study findings on the effect of magnesium supplementation during pregnancy on the risk of miscarriage are inconclusive.

Table 78. Results from the meta-analysis of Makrides et al. (2014) on the effect of magnesium supplementation during pregnancy on the risk of miscarriage.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
340 to 365 milligram / day magnesium versus placebo or aspartic acid or no magnesium[a]	At or before 24 weeks gestation	5 + 1 quasi-RCT	77 / 2,052	88 / 1,652	0.85 (0.49-1.49)	44%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received prenatal vitamins containing 100 milligram of elemental magnesium per day in addition to magnesium supplementation or aspartic acid tablets.[233]

9.2 Perinatal mortality

Summary: Magnesium supplementation during pregnancy and the risk of perinatal mortality.

Aspect	Explanation
Selected studies	One meta-analysis of four RCTs and one quasi-RCT for perinatal death [223]; and meta-analysis of three RCTs and one quasi-RCT for stillbirth and neonatal death prior to hospital discharge.[223]
Heterogeneity	No
Strength of the effect	Perinatal mortality: RR = 1.10 (95%CI 0.72-1.67) Stillbirth: RR = 0.73 (95%CI 0.43-1.25) Neonatal death prior to hospital discharge RR = 2.21 (95%CI 1.02-4.75)
Study population	Women with normal and high-risk pregnancies.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of magnesium supplementation during pregnancy on the risk of perinatal mortality as a whole, or stillbirth and neonatal death prior to hospital discharges separately.

Explanation

Makrides et al. (2014) included four RCTs and also one quasi-randomized trial (Table 79).

They found no significant effect of magnesium supplementation during pregnancy on the risk of perinatal mortality, defined as a combined measure of stillbirth and neonatal death prior to hospital discharge in this review. Also, no significant effect of magnesium supplementation was found for stillbirth separately. However, a possible increased risk of neonatal death prior to hospital discharge was observed in the magnesium-supplemented group.

Overall, the number of cases in the meta-analyses was small and mainly originated from one study, limiting the interpretation of the findings. Therefore, the committee concludes that there is too little research to draw a conclusion on the effect of magnesium supplementation during pregnancy on the risk of perinatal mortality as a whole, or stillbirth and neonatal death prior to hospital discharges separately.

Table 79. Results from the meta-analyses of Makrides et al. (2014) on the effect of magnesium supplementation starting at or before 35 weeks of gestation on the risk of perinatal mortality, stillbirth and neonatal death.

Outcome	Intervention versus control	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Perinatal mortality	128-365 milligram / day magnesium versus placebo or aspartic acid or no magnesium[a]	4 + 1 quasi-RCT	44 / 2,920	41 / 2,983	1.10 (0.72-1.67)	0%
Stillbirth	128-365 milligram / day magnesium versus placebo or aspartic acid or no magnesium	3 + 1 quasi-RCT	23 / 2,733	32 / 2,793	0.73 (0.43-1.25)	0%
Neonatal death prior hospital discharge	128-365 milligram / day magnesium versus placebo or aspartic acid or no magnesium[a]	3 +1 quasi-RCT	20 / 2,655	9 / 2,718	2.21 (1.02-4.75)	0%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received prenatal vitamins containing 100 milligram of elemental magnesium per day in addition to magnesium supplementation or aspartic acid tablets.[233]

9.3 Preterm birth

Summary: Magnesium supplementation during pregnancy and the risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of six RCTs and one quasi-RCT[223] and one additional RCT.[237]
Heterogeneity	No
Strength of the effect	RR = 0.89 (95%CI 0.69-1.14)[223]
Study population	Women with normal and high-risk pregnancies.

Conclusion:

Study findings from RCTs on the effect of magnesium supplementation during pregnancy on the risk of preterm birth are inconclusive.

Explanation

Makrides et al. (2014) included six RCTs and one quasi-randomized trial in their meta-analysis (Table 80).[223]

They found no significant effect of magnesium supplementation during pregnancy on preterm birth. The relative risk estimate is not close to one and the heterogeneity in the direction and size of the effect is moderate. The authors do not explain the heterogeneity. The number of cases is considerable, but largely originate from one study. One additional RCT was found.[237] Fewer participants in the intervention group delivered their baby preterm as compared with the control group. However, the number of cases was small and no effect estimates were presented.

In view of the number of studies (> 5) and cases (> 100 in both arms) and the fact that the risk estimate was not close to 1.00, but not significant either, the committee concludes that study findings on the effect of magnesium supplementation during pregnancy on preterm birth are inconclusive.

Table 80. Results from the meta-analysis of Makrides et al. (2014) and the additional RCT of Zarean et al. (2017) on the effect of magnesium supplementation during pregnancy on the risk of preterm birth.

Study type	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Meta-analysis[223]	128 to 4,000 milligram / day magnesium versus placebo or aspartic acid or no magnesium[a]	At or before 35 weeks of gestation	6	302 / 2,949	329 / 3,032	0.89 (0.69-1.14)	37%
RCT[237]	200 milligram / day magnesium + multiple mineral tablet containing 100 milligram magnesium versus only the multiple mineral tablet daily	One month from 12-14 weeks of gestation	1	6 / 60	16 / 60	n.r.	n.a.

CI: confidence interval; N: number; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received prenatal vitamins containing 100 milligram of elemental magnesium per day in addition to magnesium supplementation or aspartic acid tablets.[233]

9.4 Small for gestational age

Summary: Magnesium supplementation during pregnancy and the risk of small-for-gestational-age infants.

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs and one quasi-RCT.[223]
Heterogeneity	No
Strength of the effect	RR = 0.76 (95%CI 0.54-1.07)
Study population	Women with normal and high-risk pregnancies.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of magnesium supplementation during pregnancy on the risk of small-for-gestational-age infants.

Explanation

Makrides et al. (2014) included two RCTs and one quasi-randomized trial in their meta-analysis (Table 81).

They found no significant effect of magnesium supplementation on the risk of small-for-gestational-age infants.

Due to the limited number of RCTs, the committee concludes that there is too little research to draw a conclusion on the effect of magnesium supplementation during pregnancy on the risk of small-for-gestational-age infants.

Table 81. Results from the meta-analysis of Makrides et al. (2014) on the effect of magnesium supplementation during pregnancy on the risk of small-for-gestational-age infants.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
365 milligram / day magnesium versus placebo or aspartic acid[a]	At or before 24 weeks gestation	2 + 1 quasi-RCT	53 / 639	71 / 652	0.76 (0.54-1.07)	7%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one study, all women received prenatal vitamins containing 100 milligram of elemental magnesium per day in addition to magnesium supplementation or aspartic acid tablets.[233]

9.5 Gestational hypertension

Summary: Magnesium supplementation during pregnancy and the risk of gestational hypertension.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[223]
Heterogeneity	Yes, in size of effect.
Strength of the effect	RR = 0.39 (95%CI 0.11-1.41)
Study population	Pregnant women in general and with low socioeconomic status.

Conclusion (RCTs):

There is too little research on the effect of magnesium supplementation during pregnancy on the risk of gestational hypertension.

Explanation

Makrides et al. (2014) summarised three RCTs and found no significant effect of magnesium supplementation during pregnancy on the risk of pregnancy-induced hypertension (Table 82).

The effect is not close to one, and heterogeneity in the size of the effect is substantial (77%). There are no signs of heterogeneity in the direction of the effect. The authors of the review state that the heterogeneity might be explained by the differing types of magnesium supplement and the differing regimens for administration of use between the included studies. Another explanation they provide is the variation between studies in definitions used for the outcome. The authors, however, did not carry out subgroup analyses. The number of cases is considerable but mainly originates from one study.

In conclusion, there is too little research to draw a conclusion on the effect of magnesium supplementation during pregnancy on the risk of pregnancy-induced hypertension.

Table 82. Results from the meta-analysis of Makrides et al. (2014) on the effect of magnesium supplementation on the risk pregnancy-induced hypertension.

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
128 to 3000 milligram / day[a] magnesium versus placebo	At or before 35 weeks of gestation	3	205 / 2,117	242 / 2,167	0.39 (0.11-1.41)	77%

CI: confidence interval; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] In one RCT, 2,000 milligram / day was supplemented from week 28-30 followed by 3,000 milligram / day from week 30 until birth.[228]

9.6 Pre-eclampsia

Summary: Magnesium supplementation during pregnancy and the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	One meta-analysis of two RCTs and one quasi-RCT[223] and one additional RCT.[237]
Heterogeneity	No
Strength of the effect	RR = 0.87 (95%CI 0.58-1.32)[223]
Study population	Women with normal or high-risk pregnancies.

Conclusion (RCTs):

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

Explanation

Makrides et al. (2014) included two RCTs, and one quasi-randomized trial in their meta-analysis (Table 83).

They found no significant effect of magnesium supplementation during pregnancy on the risk of pre-eclampsia. One additional RCT was found.[237] Fewer participants in the intervention group developed pre-eclampsia as compared with the control group. However, the number of cases was small and no effect estimates were presented.

Due to the limited number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of magnesium supplementation during pregnancy on the risk of pre-eclampsia.

Table 83. Results from the meta-analysis of Makrides et al. (2014) and the RCT of Zarean et al. (2017) on the effect of magnesium supplementation during pregnancy on the risk of pre-eclampsia.

Study type	Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Meta-analysis[223]	365 to 500 milligram / day magnesium versus placebo or aspartic acid[a]	At or before 24 weeks gestation	2 + 1 quasi-RCT	36 / 513	42 / 529	0.87 (0.58-1.32)	0%
RCT[237]	200 milligram / day magnesium + multiple mineral tablet containing 100 milligram magnesium versus only the multiple mineral tablet daily	One month from 12-14 weeks of gestation	1	7 / 60	20 / 60	n.r.	n.a.

CI: confidence interval; N: number; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

[a] In one study, all women received prenatal vitamins containing 100 milligram of elemental magnesium per day in addition to magnesium supplementation or aspartic acid tablets.[233]

9.7 Summary of findings on magnesium

In conclusion this chapter is based on one systematic reviews of intervention studies[223] and one additional RCT.[237] The effect of magnesium supplementation during pregnancy was either inconclusive or there was too little research to draw a conclusion.

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

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	• Perinatal mortality in general or stillbirth and neonatal death prior to hospital discharge specifically (RCTs); • Small for gestational age (RCTs); • Gestational hypertension (RCTs); • Pre-eclampsia (RCTs).
Inconclusive	• Miscarriage (RCTs); • Preterm birth (RCTs).

9.8 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 strong evidence level.

In this chapter, conclusions with strong evidence level are not available. Also, no conclusions with limited evidence level are available. Thus, no recommendation on magnesium supplementation was formulated in the advisory report.

However, there is one finding based on too little research (because of insufficient cases) that reached statistical significance: a meta-analysis based on three RCTs and one quasi-RCT reported that magnesium supplements statistically significantly elevated the risk of neonatal death prior to hospital discharge. Because of the conclusion that there is too little research, this finding has no further implications.

10 fish fatty acids docosahexaenoic acid and eicosapentaenoic acid

This chapter describes the scientific evidence from systematic reviews of intervention studies on the effect of fish-fatty-acid supplementation during pregnancy on the risk of perinatal mortality, congenital anomalies, preterm birth, birth growth measures, a delivery with caesarean section, gestational diabetes, gestational hypertension, pre-eclampsia, postnatal depressive symptoms, neonatal sepsis, allergy in the offspring, cognitive development in the offspring, BMI in the offspring, and visual development in the offspring. For these outcomes, at least two intervention studies were summarised in a review. For other outcomes of interest, the committee did not find systematic reviews summarising at least two cohort studies or two intervention studies.

10.1 Perinatal mortality

Summary: Fish-fatty-acid supplementation and the risk of stillbirth and infant death.

Aspect	Explanation
Selected studies	Two systematic reviews of eight[238] and nine[239] RCTs on stillbirth and six RCTs[238] on infant death.
Heterogeneity	No
Strength of the effect	Stillbirth: RR = 0.80 (95%CI 0.50-1.26)[238] and RR = 0.73 (95%CI 0.49-1.07)[239], low number of cases. Infant death: RR = 0.69 (95%CI 0.38-1.23)[238], low number of cases.
Study population	Healthy pregnant women and women at increased risk of pregnancy hypertension or a history of preterm delivery.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy on the risk of stillbirth or infant death.

Explanation

There are six systematic reviews of long-chain polyunsaturated fatty acids on the risk of stillbirth, infant death or perinatal death (the two combined).[238-243] As Horvath et al. (2008) did not distinguish between studies on docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) supplementation and those on arachidonic acid supplementation, the committee does not consider their systematic review.[240] The four studies summarised in the systematic review of Makrides et al. (2006), the five studies summarised by Saccone et al. (2015) and the two studies summarised by Saccone et al. (2016) were included in the remaining two systematic reviews of Chen et al. (2016) and Imhoff-Kunsch et al. (2012).[238,239,241-243] Chen et al. (2016) summarise nine studies on stillbirth.[239] Imhoff-Kunsch et al. (2012) conducted analyses separately for stillbirth (eight studies) and infant death (six studies).[238] There were seven overlapping studies between the two systematic reviews. Results of both reviews are discussed by the committee (Table 84). The committee did not find any more recent RCTs on fish-fatty-acid supplementation and perinatal mortality.

There was no significant effect of fish-fatty-acid supplementation on the risk of stillbirth in either meta-analysis. However, the number of cases was low and Imhoff-Kunsch et al. (2016) indicate that the allocation concealment was unclear in several trials.[239]

Imhoff-Kunsch et al. (2012) also summarise six RCTs on the effect of fish-fatty-acid supplementation on the risk of infant death. There was no significant effect of fish-fatty-acid supplementation on the risk of infant death. The number of cases was low and the authors indicate that the allocation concealment was unclear in several trials.[238]

In view of the small number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy on the risk of stillbirth or infant death.

Table 84. Results from the meta-analyses of Imhoff-Kunsch et al. (2012) and Chen et al. (2016) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of stillbirth or infant death.

First author	Outcome	Intervention	Start intervention	N RCTs	n / N inter-vention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Imhoff-Kunsch[238]	Stillbirth	0.4-2.1 gram / day DHA and / or 0.1-3 gram / day EPA	> 16 weeks to 30 weeks gestation	8	30 / 3,497	39 / 3,541	0.80 (0.50-1.26)	0%
Imhoff-Kunsch[238]	Infant death	0.4-2.1 gram / day DHA and / or 0.1-3 gram / day EPA	18 weeks to 26 weeks gestation	6	18 / 3,104	27 / 3,131	0.69 (0.38-1.23)	0%
Chen 2016[239]	Stillbirth	0.4-2.1 gram / day DHA and / or 0.1-3 gram / day EPA	> 16 weeks to 30 weeks gestation	9	43 / 3,914	58 / 3,785	0.73 (0.49-1.07)	n.r.

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

In the update, the committee found one new publication on the effect of omega-3 supplementation on miscarriage, stillbirth, neonatal death, perinatal death, and infant death: Middleton et al. (2018).[244] They found results in line with previous meta-analysis and number of cases did not differ substantially. Therefore, the committee's conclusions remained valid.

For miscarriage, Middleton et al. (2018) included eight trials (RR 0.95, 95%CI 0.56-1.60, I^2 0%; 25 cases in intervention group, 26 cases in control group), for stillbirth 13 trials (RR 0.92, 95%CI 0.60-1.42, I^2 0%; 35 cases in intervention group, 39 cases in control group), for neonatal death nine trials (8 provided cases; RR 0.61, 95%CI 0.34-1.11, I^2 0%; 16 cases in intervention group, 27 cases in control group), for perinatal death eight trials (RR 0.71, 95%CI 0.48-1.03, I^2 0%; 44 cases in intervention group, 63 cases in control group), and for infant death four trials (RR 0.74, 95%CI 0.25-2.19, I^2 0%; 4 cases in intervention group; 6 cases in control group).

10.2 Congenital anomalies

Summary: Fish -atty-acid supplementation and the risk of congenital anomalies.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[244]
Heterogeneity	No
Strength of the effect	RR = 1.08 (95%CI 0.61-1.92)
Study population	Pregnant women, regardless of their risk for pre-eclampsia, preterm birth or intrauterine growth restriction from Europe, North America, and Central-America.

Conclusion (RCTs):

There is too little research to draw a conclusion on the use of fish-fatty-acid supplements during pregnancy on the risk of congenital anomalies.

Explanation

There is one meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy on the risk of congenital anomalies (Table 85).[244]

Middleton et al. (2018) included three trials and found no significant effect on congenital anomalies in women who took fish-fatty-acid supplements compared with woman taking placebo. The number of cases was low and there was no heterogeneity.

In view of the low number of cases and the fact that the risk estimate was 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 fish-fatty-acid supplementation during pregnancy on the risk of congenital anomalies.

Table 85. Results from the meta-analysis of Middleton et al. (2018) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of congenital anomalies.

Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
0.4 to 0.864 gram / day DHA and / or 0-0.621 gram / day EPA	At or before 30 weeks of gestation	3	24 / 907	22 / 900	1.08 (0.61-1.92)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

10.3 Preterm birth (< 37 weeks)

Summary: Fish-fatty-acid supplementation and the risk of preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of 30 RCTs (32 comparisons) performed by the committee itself.
Heterogeneity	No
Strength of the effect	RR = 0.87 (95%CI 0.80-0.95)
Study population	Healthy pregnant women and women with a history of pregnancy complications from Europe, Asia, Australia, North America, and Central America.

Conclusion:

Based on RCTs, the use of fish-fatty-acid supplements with 0.1 to 3 gram EPA and / or 0.1 to 2.1 gram DHA per day during pregnancy reduces the risk of preterm birth < 37 weeks of gestation by 13% (95%CI 5% to 20%). Level of evidence: Strong.

Explanation

There are ten systematic reviews of the effect of fish-fatty-acid supplementation during pregnancy on the risk of preterm birth (< 37 weeks).[238-243,245-248] Koletzko et al. (2014) summarise the findings of Makrides et al. (2006), Szajewska et al. (2006) and Horvath et al. (2007).[240,242,246,248] The RCTs in these three systematic reviews and in the systematic reviews of Imhoff-Kunsch et al. (2012), Salvig et al. (2011) and Saccone et al. (2016) are summarised by Saccone et al. (2015), Chen et al. (2016) and Kar et al. (2016).[238,240-243,245,247,248] Among the RCTs on preterm birth summarised in these three systematic reviews, Saccone et al. (2015) and Chen et al. (2016) each summarise three unique RCTs which are not included in the other systematic reviews and Kar et al. (2016) summarise one unique RCT.[239,241,245] Therefore the committee describes the findings of these systematic reviews below (Table 86a). Please note that the conclusion on this topic is based on the update of the literature search and the meta-analysis by the committee, presented after Table 86b.

The systematic review of Saccone et al. (2015) shows no significant effect of fish-fatty-acid supplementation on the risk of preterm birth.[241] Kar et al. (2016) find a significant 17% lower risk.[245] Finally, Chen et al. (2016) find a 10% risk reduction with an upper level of the 95%-confidence interval of 1.00. There were no significant differences in risk estimates between women with a history of pregnancy complications and those without.

There is one large study that contributed for almost 50% to the weight of the estimate in the systematic review of Saccone et al. (2015) for 30% of the weight of the estimate in the systematic review of Kar et al. (2016) and for 16% of the estimate in the systematic review of Chen et al. (2016)[239,241,245] In the latter systematic review, there are two RCTs that are larger (23% and 32% weight contribution). There was no indication of publication bias and heterogeneity was low.[239]

The committee found one more recent RCT in the search until July 2018 (Table 86b).[249] Ostadrahimi et al. (2017) did not find a significant difference in the risk of preterm birth between women receiving a low dose of fish fatty acids versus placebo (RR = 0.74; 0.16-3.42). The risk was in the same direction as in the meta-analysis.

Table 86a. Results from the meta-analyses of Chen et al. (2016), Saccone et al. (2015) and Kar et al. (2016) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of preterm birth (< 37 weeks).

First author	Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Chen[239]	0.6-2.1 gram / day DHA and / or 0.1-3 gram / day EPA	12-27 weeks of gestation	13	503 / 3,494	554 / 3,486	0.90 (0.81-1.00)	6%
Saccone[241]	0.1-1.2 gram / day DHA and / or 0.1-3 gram / day EPA	n.r.	7	140 / 1,807	154 / 1,686	0.90 (0.72-1.11)	0%
Kar [245]	0.5-2.1 gram / day DHA and / or 0.2-2.9 gram / day EPA	12-30 weeks of gestation	9	222 / 2,984	272 / 2,996	0.83 (0.70-0.98)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; n.r.: reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Table 86b. Results from the RCT of Ostadrahimi et al. (2017) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of preterm birth (< 37 weeks).

Intervention	Start intervention	n / N intervention	n / N control	RR estimate (95%CI)
0.12 gram / day DHA and 0.18 gram / day EPA	20 weeks of gestation	3 / 75	4 / 75	0.74 (0.16-3.42)

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

In the update performed in July 2019, the systematic review of Middleton et al. (2018) was identified.[244] They included 18 RCTs, seven of which were not included in earlier meta-analyses. In addition, a large RCT conducted by Makrides et al. (2019). In addition, the meta-analysis of Sun et al. (2020) was put forward by the committee.[250,251] That review included three RCTs that were neither included in the earlier meta-analyses nor identified by the committee itself. The committee could not formulate a conclusion based on the published meta-analyses, because the available meta-analyses only partially overlapped, additional RCTs were found by the committee itself, and because the upper limit of the confidence intervals varied between just below or just above 1.00 (hence, statistically significant or not statistically significant). Therefore, by exception, the committee performed its own meta-analysis to come to a conclusion. This was done by using the risk estimates provided in the identified meta-analyses supplemented with the risk estimates from the individual trials

that were identified by the committee. A fixed-effects model was used in concordance with Middleton et al. (2018) and Sun et al. (2020).

This meta-analysis included 30 RCTs (32 comparisons) on fish-fatty-acid supplementation during pregnancy (figure 1; Table 86c). For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix G. In three trials (Smuts et al. (2003)[252], Smuts et al. (2003)[253] (2019)[250]) the comparison group also received EPA (0.004 gram per day) and / or DHA (0.015 or 0.025 gram). However, because the doses in the control group were very low compared with the doses in the intervention groups the committee did not exclude these studies from the meta-analysis. The meta-analysis showed a statistically significantly reduced risk of preterm birth < 37 week in the intervention group versus placebo. There was no heterogeneity. The committee did not find larger effects in trials that tested a higher dose compared with trials that explored a dose in the lower range of the spectrum. Twenty-five of the 32 risk estimates were below 1.00, i.e. in the direction of a reduced risk of preterm birth. A total of seven trials explored a relatively low dose of fish fatty acids: between 135 to 300 mg DHA per day (mean 210 mg/d) combined with a maximum dose of 384 mg EPA per day.[252-258] All these low-dose trials reported a risk estimate in the direction of a reduced risk of preterm birth. The committee, therefore, assumed that dose in the lower range of the spectrum will also sort an effect. Limited information was available on the baseline fish fatty acid status or the intake of fish.

Some individual studies (five RCTs that were included in the meta-analysis and an additional nested case-control study) indicated that the beneficial effect of fish-fatty-acid supplementation on preterm birth may be more pronounced in pregnant women with a low fish fatty acids status, a low blood concentration of these fatty acids or a low intake of fish.[250,254,259-263]

In a sensitivity analysis, the committee removed the RCT of Hauner et al. (2012) and Mardones et al. (2008) as these RCTs had a co-intervention next to fish-fatty-acid supplementation in the intervention group that was not available for the control group. This did not change the overall results (RR 0.88; 95%CI 0.80-0.96).

The committee concludes that the use of fish-fatty-acid supplements with 0 to 3 gram EPA and / or 0.1 to 2.1 gram DHA during pregnancy reduces the risk of preterm birth < 37 weeks of gestation by 13% (95%CI 5% to 20%). In view of the large number of studies and cases, the statistically significant effect estimate, and the low heterogeneity, the committee judges the level of evidence as strong. The effect may be more pronounced in women with low fish fatty acids status. But more information is needed to confirm the role of fish fatty acids status.

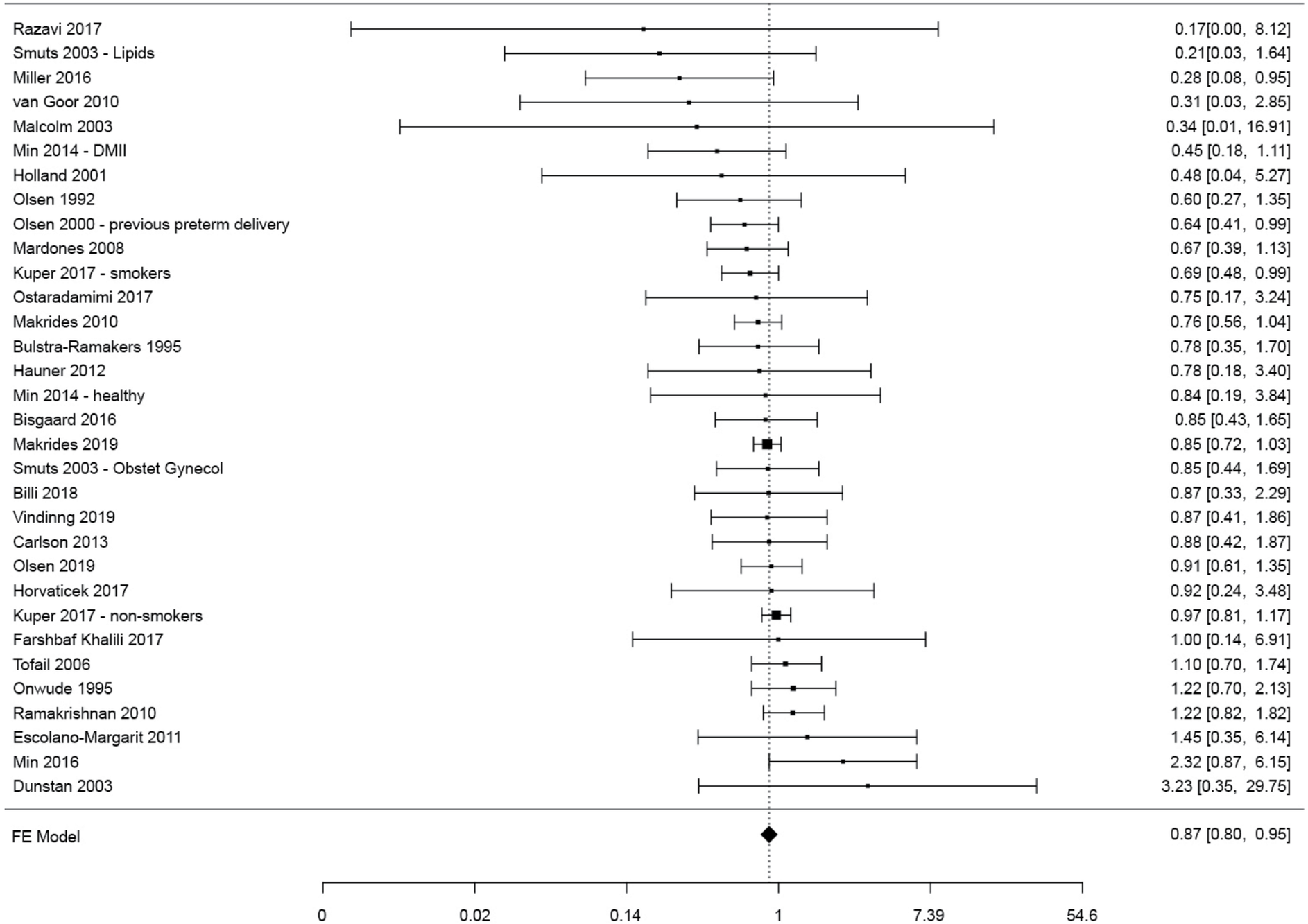

Figure 1. Forest plot of the committee's own meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy versus placebo on the risk of preterm birth (< 37 weeks).

Table 86c. Results of committee's own meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy versus placebo on the risk of preterm birth (< 37 weeks). For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix G.

Intervention	N RCTs	Start intervention	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
0.1-3 gram EPA per day and / or 0.1-2.1 gram DHA per day	32 (30 comparisons)	< 38 weeks of gestation	754 / 9,760	872 / 9,760	0.87 (0.80-0.95)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR, relative risk.

10.4 Preterm birth (< 34 weeks)

Summary: Fish-fatty-acid supplementation and the risk of early preterm birth.

Aspect	Explanation
Selected studies	One meta-analysis of 14 RCTs (15 comparisons) performed by the committee itself.
Heterogeneity	No
Strength of the effect	RR = 0.84 (95%CI 0.70 to 1.01)
Study population	Healthy pregnant women and women with a history of pregnancy complications from Europe, North America, and Australia.

Conclusion:

Based on RCTs, study findings on the effect of fish-fatty-acid supplements during pregnancy on the risk of preterm birth < 34 weeks of gestation are inconclusive.

Explanation

There are three systematic reviews of the effect of fish-fatty-acid supplementation during pregnancy on the risk early preterm birth (< 34 weeks).[238,239,245] Chen et al. (2016) summarise the five RCTs in the systematic reviews of Imhoff-Kunsch et al. (2012) in combination with two other RCTs.[238,239] Kar et al. (2016) summarise six RCTs, one of which is not included in the systematic review of Chen et al. (2016)[239,245] Therefore, the committee describes the findings of the two systematic reviews of Kar et al. (2016) and Chen et al. (2016) below (Table 87).

Kar et al. (2016) find that fish-fatty-acid supplementation lowers the risk of early preterm birth. However, the number of cases was small, limiting the interpretation of the finding.[245]

Chen et al. (2016) also find a significantly lower risk (22% risk reduction). Heterogeneity was moderate and was mostly present in the size of the effect. Two studies contributed for respectively 44% and 23% of the weight of the estimate. Nevertheless, there was no indication of publication bias.[239]

The committee did not find any more recent studies on fish-fatty-acid supplementation and the risk of early preterm birth in the search until July 2018.

Table 87. Results from the meta-analyses of Chen et al. (2016) and Kar et al. (2016) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of early preterm birth (< 34 weeks).

First author	Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
Chen[239]	0.5-2.1 gram / day DHA and / or 0.1-3 gram / day EPA	12-27 weeks of gestation	7	152 / 2,398	192 / 2,400	0.78 (0.64-0.95)	39%
Kar [245]	n.r.	12-28 weeks of gestation	6	27 / 2,097	68 / 2,096	0.42 (0.27-0.66)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

In the update of systematic reviews published between July 2018 and July 2019, the committee found one new publication: Middleton et al. (2018).[244] They included eight RCTs, four of which were not included in the earlier meta-analyses. In addition, a large RCT conducted by Makrides et al. (2019) and the meta-analysis of Sun et al. (2020) was put forward by the committee.[250,251] That review included one additional RCT that was neither included in the earlier meta-analyses nor identified by the committee itself. The committee could not formulate a conclusion based on the published meta-analyses, because the additional RCT by Makrides et al. (2019) and the additional RCT from Sun et al. (2020) were not in line with the earlier meta-analyses. Therefore, by exception, the committee performed its own meta-analysis to come to a conclusion. A fixed-effects model was used in concordance with Middleton et al. (2018) and Sun et al. (2020).

This meta-analysis included 14 RCTs (15 comparisons) on fish-fatty-acid supplementation during pregnancy (figure 2; Table 87b) and showed an effect estimate in the direction of a risk reduction, but was not statistically significant. Heterogeneity was moderate. For information on the original studies (supplement doses, start moments, dietary intakes), see Appendix G. In one trial (Makrides et al. (2019)[250]), the control group received some EPA (0.004 gram per day) and DHA (0.015 gram per day) as well. Because the doses were very low the committee did not exclude this study from the meta-analysis.

In a sensitivity analysis, the committee removed the RCT of Mardones et al. (2008) as this RCT had a co-intervention in addition to fish-fatty-acid supplementation in the intervention group that was not available for the control group. This did not change the overall results (RR 0.86; 95%CI 0.71-1.04).

In view of the large number of studies and cases and an effect estimate that is not close to one, but not statistically significant either, the committee concludes that the effect of fish-fatty-acid supplements during pregnancy on the risk of preterm birth is inconclusive.

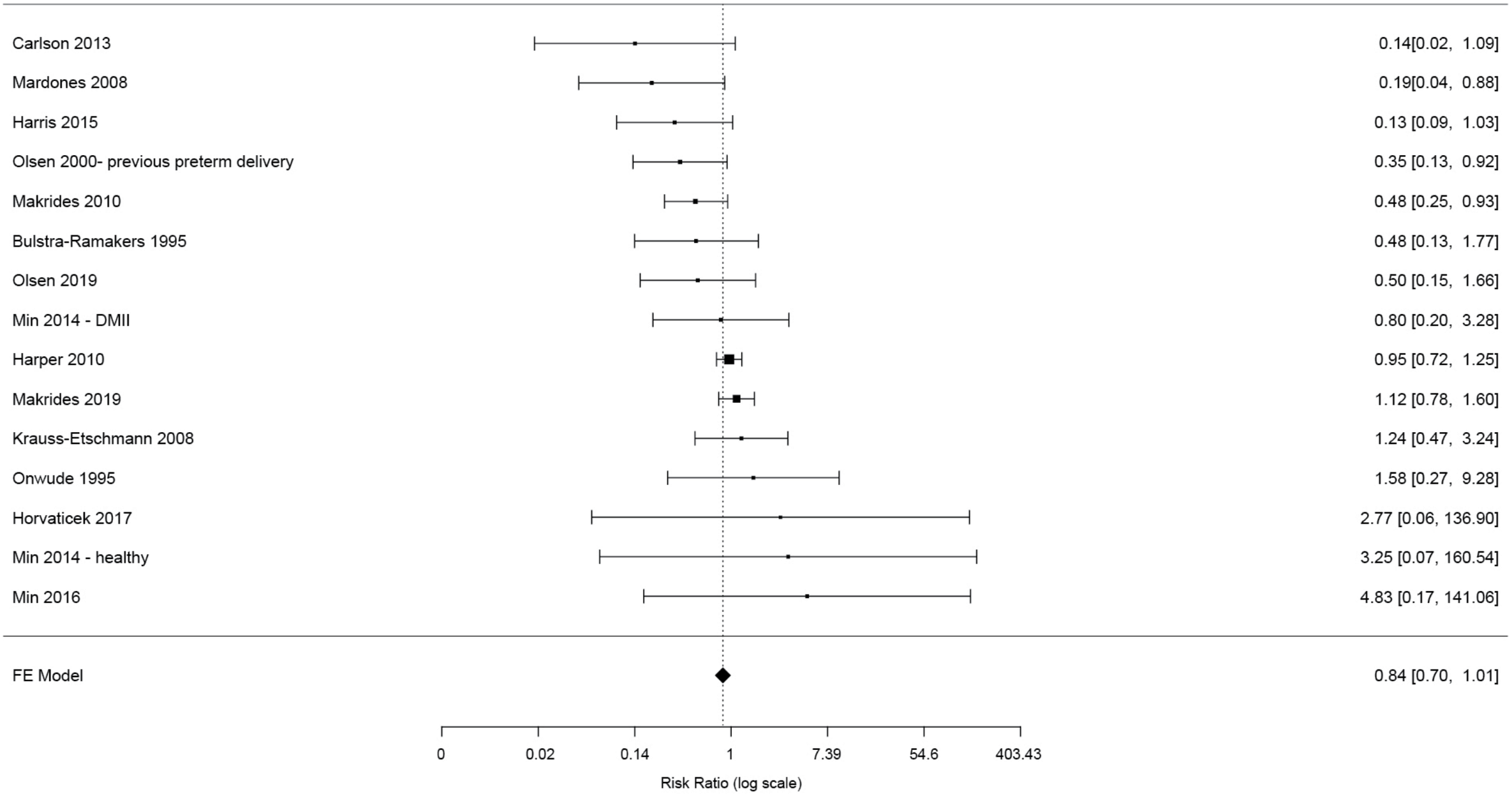

Figure 2. Forest plot of the committee's own meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy versus placebo on the risk of preterm birth (< 34 weeks).

Table 87b. Results of committee's own meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy versus placebo on the risk of preterm birth (< 34 weeks).

Intervention	N RCTs	Start intervention	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
0.1-3 gram EPA per day and / or 0.5-2.1 gram DHA per day	14 RCTs (15 comparisons)	< 38 weeks of gestation	193 / 7,434	232 / 7,336	0.84 (0.70-1.01)	38.2%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR, relative risk.

10.5 Small for gestational age

Summary: Fish-fatty-acid supplementation and the risk of an infant that is small for gestational age.

Aspect	Explanation
Selected studies	One systematic review of five RCTs.[238]
Heterogeneity	No
Strength of the effect	RR = 1.06 (95%CI 0.92-1.21)
Study population	Healthy pregnant women and women at increased risk of pregnancy hypertension or a history of intrauterine growth retardation.

Conclusion:

Study findings from RCTs on the effect of fish-fatty-acid supplementation during pregnancy on the risk of an infant that is small for gestational age are inconclusive.

Explanation

There are five systematic reviews of fish-fatty-acid supplementation during pregnancy and the risk of intrauterine growth restriction.[238-240,243,264] Saccone et al. (2016) refer in their systematic review to their systematic review from 2015.[243,264] The three RCTs in their 2015 meta-analysis are also summarised by Chen et al. (2016) and Imhoff-Kunsch et al. (2012) in combination with two other RCTs (respectively seven and five comparisons).[238,239] These also include the one RCT in the systematic review of Horvath et al. (2007).[240] Chen et al. (2016) treat three RCTs that were performed within the same multicentre setting as independent RCTs, whereas Imhoff-Kunsch et al. (2012) combined the risk estimates from the three RCTs because they are not independent.[238,239]Therefore, the committee describes the findings of Imhoff-Kunsch et al. (2012) below (Table 88).[238] The committee did not find any more recent studies on fish fatty acids supplementation and the risk of an infant that is small for gestational age.

The authors find that fish-fatty-acid supplementation does not significantly reduce the risk of an infant that is small for gestational age. The number of cases was considerable and heterogeneity was low.

In view of the large number of cases, the low heterogeneity, and the fact that the effect estimate is not close to one, but not statistically significant either, the committee concludes that study findings on the effect of fish

fatty acids supplementation during pregnancy on the risk of an infant that is small for gestational age are inconclusive.

Table 88. Results from the meta-analysis of Imhoff-Kunsch et al. (2012) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of an infant that is small for gestational age.

Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
0.22-2.1 gram / day DHA and 0.03-3 gram / day EPA	12-33 weeks of gestation	5	342 / 1,744	323 / 1,717	1.06 (0.92-1.21)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

In the update of systematic reviews the committee found one new publication: Middleton et al. (2018).[244] They included five RCTs, and found results in line with the previous meta-analysis: RR 1.05, 95%CI 0.93-1.20, I^2 0%. Therefore, the committee did not change its conclusion.

10.6 Large for gestational age

Explanation

There is one meta-analysis on the effect of fish-fatty-acid supplementation on the risk of an infant that is large for gestational age.[244] Middleton et al. (2018) summarised two RCTs and found a non-significantly increased risk of an infant that is large for gestational age (RR 1.19, 95%CI 0.99-1.43). However, one of the studies was small and provided only one infant that was large for gestational age to the total number of cases. It was born to a woman with pre-existing diabetes. As this small study had a negligible effect on the summarised estimate, the estimate was actually based on just one (large) study. As one study is too little research to base conclusions on, the committee left this outcome out of the evaluation.

10.7 Caesarean section

Summary: Fish-fatty-acid supplementation and the risk of caesarean section.

Aspect	Explanation
Selected studies	One systematic review of 19 RCTs.[244]
Heterogeneity	No
Strength of the effect	RR = 0.98 (95%CI 0.92-1.06)
Study population	Pregnant women, regardless of their risk for pre-eclampsia, preterm birth or intrauterine growth restriction from Europe, North America, Central-America, Asia, and Australia.

Conclusion:

Based on RCTs, the effect of fish-fatty-acid supplementation during pregnancy on the risk of a caesarean section is unlikely.

Explanation

There is one meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy on the risk of a caesarean section (Table 89).[244]

Middleton et al. (2018) included 19 trials and found no effect of supplementation. There was no heterogeneity. One study was specifically on emergency caesarean sections, and one specifically on elective caesarean sections. However, no distinction was made in the other studies. Therefore, it was not possible to draw separate conclusions.

In view of the large number of RCTs and cases, the relative risk that was close to one with a rather narrow confidence interval, and the fact that there was no heterogeneity, the committee concludes that the effect of fish-fatty-acid supplementation during pregnancy on the risk of a caesarean section is unlikely.

Table 89. Results from the meta-analysis of Middleton et al. (2018) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of caesarean section.

Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
0-2.07 gram / day DHA and 0-3 gram / day EPA versus placebo	At or before 30 weeks of gestation	19	975 / 3,286	990 / 3,251	0.98 (0.92-1.06)	4%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

10.8 Gestational diabetes

Summary: Fish-fatty-acid supplementation and the risk of gestational diabetes.

Aspect	Explanation
Selected studies	One systematic review of seven RCTs.[244]
Heterogeneity	No
Strength of the effect	RR = 1.02 (0.80-1.30)
Study population	Pregnant women.

Conclusion:

Based on RCTs, an effect of fish-fatty-acid supplementation during pregnancy on the risk of gestational diabetes is unlikely.

Explanation

There are four systematic reviews of the effect of fish fatty acids supplementation during pregnancy on the risk of gestational diabetes.[244,248,265,266] Ostadrahimi et al. (2016) describe in their systematic review one RCT which is also described by Chen et al. (2015) in combination with five other RCTs.[265] These also include the two RCTs summarised by Szajewska et al. (2006). Chen et al. (2015) did not only include RCTs on omega-3 supplements only but also on studies that used combined omega-3 supplements with food/diet advice in the intervention. The meta-analysis of Middleton et al. (2018) included seven RCTs on omega-3 supplements only. As this was the most complete and recent review, the committee describes the findings of Middleton et al. (2018)

below (Table 90).[244] The committee did not find any more recent studies on fish-fatty-acid supplementation and the risk of gestational diabetes.

Middleton et al. (2015) found no significant effect of fish-fatty-acid supplementation on the risk of gestational diabetes. Heterogeneity was low. However, results were dominated by one large RCT with 196 cases in total. In the other six RCTs, the number of cases was small (ranging from 0 to 16).[244]

In view of the fact that the number of studies was considerable, the relative risk estimate was close to one, and there was no heterogeneity, the committee concludes that an effect of fish-fatty-acid supplementation during pregnancy on the risk of gestational diabetes is unlikely.

Table 90. Results from the meta-analysis of Middleton et al. (2018) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of gestational diabetes.

Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
0.2-0.9 gram / day DHA and / or 0-1.3 gram / day EPA	Before 20 weeks of gestation	7 (6 provided cases)	123 / 1,893	118 / 1,833	1.02 (0.80-1.30)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

10.9 Gestational hypertension

Summary: Fish-fatty-acid supplementation and the risk of high blood pressure.

Aspect	Explanation
Selected studies	One meta-analysis of six RCTs.[244]
Heterogeneity	No
Strength of the effect	RR = 1.05 (95%CI 0.90-1.22)
Study population	Pregnant women, regardless of their risk for pre-eclampsia, preterm birth or intrauterine growth restriction from Europe, North America, and Australia.

Conclusion:

Study findings from RCTs on the effect of fish-fatty-acid supplementation during pregnancy on the risk of high blood pressure during pregnancy are inconclusive.

Explanation

There is one meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy on the risk of high blood pressure during pregnancy (Table 91).[244]

Middleton et al. (2018) included six RCTs and found no statistically significant effect. There was no heterogeneity.

In view of the risk estimate that is not close to one, but not statistically significant either, the wide confidence interval and the large number of available trials, the committee concludes that study findings on the effect

of fish-fatty-acid supplementation on the risk of high blood pressure during pregnancy are inconclusive.

Table 91. Results from the meta-analysis of Middleton et al. (2018) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of gestational hypertension

Intervention versus control	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
0-3 gram / day EPA and / or 0-1.08 gram / day DHA versus placebo or no supplement	At or before 30 weeks of gestation	6	276 / 2,203	268 / 2,228	1.05 (0.90-1.22)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

10.10 Pre-eclampsia

Summary: Fish-fatty-acid supplementation and the risk of pre-eclampsia.

Aspect	Explanation
Selected studies	One systematic review of ten RCTs.[266]
Heterogeneity	No
Strength of the effect	RR = 0.93 (95%CI 0.74-1.16)
Study population	Healthy pregnant women and pregnant women with a history of pregnancy complications.

Conclusion:

Study findings from RCTs on the effect of fish-fatty-acid supplementation during pregnancy on the risk of pre-eclampsia are inconclusive.

Explanation

There are six systematic reviews of the effect of fish-fatty-acid supplementation during pregnancy on the risk of pre-eclampsia.[238,240,242,243,248,266] Chen et al. (2015) summarise in their systematic review all the RCTs that exclusively studied fish fatty acids in women without hypertension from the other systematic reviews. Therefore, the committee focuses below on the findings of Chen et al. (2015) (Table 92).[266] The committee did not find any more recent studies on fish-fatty-acid supplementation and the risk of pre-eclampsia.

Chen et al. (2015) find no significant effect of fish-fatty-acid supplementation on the risk of pre-eclampsia. There was one large study with 110 cases that contributed for 39% of the weight of the estimate. Heterogeneity was low.

As the risk estimate is not close to one but not statistically significant either, and the confidence interval is rather wide, the committee concludes that study findings on the effect of fish-fatty-acid supplementation on the risk of pre-eclampsia are inconclusive.

Table 92. Results from the meta-analysis of Chen et al. (2015) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of pre-eclampsia.

Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Hetero-geneity I^2
0.6-2.0 gram / day DHA and / or 0.1-3 gram / day EPA	14 to 30 weeks gestation	10 (12 comparisons)	134 / 2,831	150 / 2,854	0.93 (0.74-1.16)	5%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

Update July 2018 - July 2019

In the update of systematic reviews, the committee found one new publication: Middleton et al. (2018).[244] They included 13 RCTs, and found results in line with the previous meta-analysis: RR 0.95, 95%CI 0.76-1.19, I^2 0%. The final conclusion is therefore not changed by the committee.

10.11 Postnatal depressive symptoms

Summary: Fish-fatty-acid supplementation and the risk of perinatal depressive symptoms.

Aspect	Explanation
Selected studies	Three RCTs.[267-269]
Heterogeneity	No
Strength of the effect	No significant effects or risks.
Study population	Healthy pregnant women and pregnant women at increased risk of depressive symptoms.

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy until birth or until 3 months postpartum on the risk of postnatal depressive symptoms.

Explanation

There are five systematic reviews on the effect of fish-fatty-acid supplementation during pregnancy on the risk of postnatal depression providing information on three RCTs.[243,246,270,271] Wojcicki and Heyman (2011) summarise five RCTs, three of which were carried out in women with major depressive disorders. In one of the two remaining studies, supplementation is carried out perinatally (Doornbos et al. (2009)) and in the other after birth.[267,270] Therefore, only the RCT of Doornbos et al. (2009) was of interest to the committee (Table 93).

Doornbos et al. (2009) find no significant change in scores on the Edinburgh Postnatal Depression Scale in women using 220 milligram / day DHA from 16 weeks of gestation until 3 months postpartum.[267]

The other systematic reviews describe two additional RCTs (Table 91).[268,269] The committee did not find any more recent studies on fish-fatty-acid supplementation and the risk of postnatal depressive symptoms.

In the RCTs, there was also no significant effect on postnatal depressive symptoms measured by the Edinburgh Postnatal Depression Scale score or Beck's Depression Inventory Scale of 0.8 gram / day DHA supplementation or two combinations of DHA with EPA supplementation during pregnancy.

In conclusion, in view of the small number of studies the committee concludes that there is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy until birth or until 3 months postpartum on the risk of postnatal depressive symptoms.

Table 93. Results of the RCTs of Doornbos et al. (2009), Makrides et al. (2010) and Mozurkewich et al. (2013) on the effect of fish-fatty-acid supplementation during pregnancy on postnatal depressive symptoms.

First author	Intervention	Start and end intervention	Follow-up measurement	N inter-vention	N control	Difference in depressive symptoms (95%CI)
Doornbos[267]	0.22 gram / day DHA	16 weeks of gestation until 3 months postpartum	6 weeks postpartum	38	32	0[a] (n.s.)
Makrides[268]	0.8 gram / day DHA	Before 21 weeks gestation until birth	6 months postpartum	1,197	1,202	RR = 0.85[b] (0.70-1.02)
Mozurkewich[269]	0.9 gram / day DHA and 0.18 gram / day EPA	Before 20 weeks gestation until 6 weeks postpartum	6-8 weeks postpartum	38	41	-0.20[c] (-2.61 to +2.21)
Mozurkewich[269]	0.27 gram / day DHA and 1.06 gram / day EPA	Before 20 weeks gestation until 6 weeks postpartum	6-8 weeks' postpartum	39	41	+0.70[c] (-1.78 to +3.18)

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; n / N: number of cases / total number of participants; n.s.: not significant; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Edinburgh Postnatal Depression Scale. [b] % women with a Edinburgh Postnatal Depression Scale score> 12. [c] Beck's Depression Inventory Scale. Estimate derived from systematic review of Miller et al. (2013).[271]

Update July 2018 - July 2019

In the update of systematic reviews the committee found one new publication: Middleton et al. (2018).[244] They included four RCTs on various measures of depressive symptoms. Two of these studies were already included by the committee. The other RCTs were small (respectively n = 32 and n = 42) and found no statistically significant effect of omega-3 supplementation on postpartum depressive symptoms measured on the Edinburgh Postnatal Depression Scale (RR 1.89, 95%CI 0.54-6.60)[272] and the Postpartum Depression Screening Scale (RR 0.37, 95%CI 0.04-3.25).[273] Therefore, the committee did not change its conclusion.

10.12 Neonatal sepsis

Summary: Fish-fatty-acid supplementation and the risk of neonatal sepsis.

Aspect	Explanation
Selected studies	One meta-analysis of three RCTs.[244]
Heterogeneity	No
Strength of the effect	RR = 0.97 (95%CI 0.44-2.14)
Study population	Pregnant women, regardless of their risk for pre-eclampsia, preterm birth or intrauterine growth restriction from Europe, North America, and Australia.

Conclusion (RCTs):

There is too little research to draw a conclusion on the use of fish-fatty-acid supplements during pregnancy on the risk of neonatal sepsis.

Explanation

There is one meta-analysis on the effect of fish-fatty-acid supplementation during pregnancy on the risk of neonatal sepsis (Table 94).[244]

Middleton et al. (2018) included three trials and found a no significant effect on congenital anomalies in women who took fish-fatty-acid supplements compared with woman taking placebo. The number of cases was low and there was no heterogeneity.

In view of the low number of cases, the committee concludes that there is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy on the risk of neonatal sepsis.

Table 94. Results from the meta-analysis of Middleton et al. (2018) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of neonatal sepsis.

Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
0.8-1.183 gram / day DHA and / or 0.1-1.2 gram / day EPA	16 to 22 weeks of gestation	3	24 / 907	22 / 900	1.08 (0.61-1.92)	0%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

10.13 Allergy in the offspring

There are four systematic reviews of fish-fatty-acid supplementation and the risk of allergy.[246,274-276] Koletzko et al. (2014) summarise the findings of Klemens et al. (2011) and describe several additional RCTs.[246,276] The RCTs from the two systematic reviews are also included in the systematic reviews of Best et al. (2016) and / or Gunaratne et al. (2015).[274,275]
Best et al. (2016) summarise seven RCTs in total, four of which are also summarised by Gunaratne et al. (2015) in combination with four other RCTs. Therefore, the committee describes the findings of the two systematic reviews below for various allergic endpoints.

10.13.1 Asthma-like symptoms

Summary: Fish-fatty-acid supplementation and the risk of asthma-like symptoms.

Aspect	Explanation
Selected studies	One systematic review of four relevant RCTs [274], one additional RCT[277], and one additional publication on an RCT already included in the systematic review.[278]
Heterogeneity	No measure of heterogeneity available.
Strength of the effect	No summarised effect measure.
Study population	Healthy pregnant women and pregnant women with a history of allergy or atopic disease.

Conclusion:

Study findings from RCTs on the effect of fish-fatty-acid supplementation during pregnancy or pregnancy and lactation on the risk of asthma-like symptoms in the offspring are inconclusive.

Explanation

There are two systematic reviews of the effect of fish-fatty-acid supplementation during pregnancy on the risk of asthma-like symptoms and wheeze.[274,275] Gunaratne et al. (2015) summarise four RCTs, two of which are also summarised by Best et al. (2016).[275] As fish fatty acids were only supplied after birth in the other two RCTs, the committee focuses on the findings of Best et al. (2016) (Table 95).[274]

Best et al. (2016) describe five RCTs with publications at different ages and a variety of outcome measures, which prevented meaningful meta-analysis.[279-283] In one of the five RCTs in the systematic review of Best et al. (2016) the intervention consisted of fatty fish rather than fish fatty acids and it is therefore not reviewed below.[279] Of the other four RCTs, three provided fish-fatty-acid supplements during pregnancy and one during pregnancy and lactation. According to Best et al. (2016), there were no differences in asthma-like symptoms or wheeze with or without sensitization at 12 months, 24 months, 0-24 months, or 3 years.
In addition, in one RCT with a 16-year follow-up, there was a significant reduction in the risk of asthma in the fish fatty acids group compared with the olive oil group, but not compared with the ‘no oil’ group. The number of cases was very low, which limits the interpretation of the finding.[274]

The committee found two more recent publications on fish-fatty-acid supplementation during pregnancy and the risk of persistent wheezing or

asthma. In the larger RCT, there was a significant 31% reduction in the risk of recurrent wheeze and asthma at 3 years of age (RR = 0.69; 0.49 to 0.97).[277] The other publication is on the 6-year follow-up of an RCT of which data on shorter follow-up periods were summarised by Best et al. (2016) earlier.[278,283] The authors found no significant effect of fish-fatty-acid supplementation during pregnancy on the risk of wheeze / asthma at six years.[278]

In conclusion, there are a large number of studies reporting on this topic and a sufficient number of cases. However, no consistency in the direction of the effect was found. But all confidence intervals overlapped, indicating no significant heterogeneity in the direction of the effect. Therefore, the committee concluded that the study findings on the effect of fish-fatty-acid supplementation during pregnancy or pregnancy and lactation on the risk of asthma-like symptoms in the offspring are inconclusive.

Table 95. Results from the RCTs included in the systematic review of Best et al. (2016) and one additional RCT on the effect of fish-fatty-acid supplementation during pregnancy on the risk of asthma and asthma-like symptoms in the offspring.

First author	Outcome	Intervention	Start intervention	n / N intervention	n / N control	Infant age at moment of outcome assessment	RR estimate (95%CI)
Dunstan[280]	Wheeze, asthma or asthma-like symptoms	2,1 gram / day DHA and 1,0 gram / day EPA	20 weeks of gestation	2 / 40	6 / 43	12 months	0.36 (0.08-1.67)
Olsen[281]	Wheeze, asthma or asthma-like symptoms	2.7 gram / day n-3 PUFA versus no oil	30 weeks of gestation	8 / 263	3 / 129	16 years	0.37 (0.15-0.92)
Olsen[281]	Wheeze, asthma or asthma-like symptoms	2.7 gram / day n-3 PUFA versus olive oil	30 weeks of gestation	8 / 263	11 / 136	16 years	0.29 (0.08-1.03)
Furuhjelm[282]	Wheeze, asthma or asthma-like symptoms	2.1 gram / day DHA and 1.1 gram / day EPA	20 to 25 weeks gestation	7 / 54	8 / 64	24 months	P = 0.19
Palmer[283]	Wheeze, asthma or asthma-like symptoms	0.8 gram / day DHA and 0.1 gram / day EPA	Before 21 weeks of gestation	6 / 368	5 / 338	3 years	1.00[a]
Best[278]	Wheeze with sensibilization	0.8 gram / day DHA and 0.1 gram / day EPA	Before 21 weeks of gestation	60 / 367	45 / 336	6 years	1.24 (0.83-1.85)
Best[278]	Wheeze, asthma or asthma-like symptoms	0.8 gram / day DHA and 0.1 gram / day EPA	Before 21 weeks of gestation	79 / 367	73 / 336	6 years	1.01 (0.75-1.37)
Bisgaard[277]	Recurrent wheeze or asthma	0.89 gram / day DHA and 1.3 gram / day EPA	24 weeks of gestation	58 / 346	83 / 349	3 years	0.69 (0.49-0.97)

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; n.a.: not applicable; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Unadjusted risk estimate.

Update July 2018 - July 2019

The committee found one new meta-analysis.[284] Vahdaninia et al. (2019) included seven RCTs in their meta-analysis, four of which were already included in the evaluation of the committee. The analysis showed results in line with the conclusion of the committee: RR = 0.87, 95%CI 0.71-1.07, I^2 43.1%. Three out of seven studies were conducted in high-risk populations. However, that did not explain heterogeneity. The committee did not change its overall conclusion.

10.13.2 Food allergy

Summary: Fish-fatty-acid supplementation and the risk of food allergy.

Aspect	Explanation
Selected studies	One systematic review of three RCTs.[274]
Heterogeneity	No
Strength of the effect	RR = 0.58 (95%CI 0.45-0.75)
Study population	Pregnant women with a history of allergy or atopic disease from Australia and Europe.

Conclusion:

Based on RCTs, fish-fatty-acid supplementation during pregnancy until delivery or until the first months postpartum reduces the risk of food allergy in the offspring at 1 year of age.
Level of evidence: Limited.

Based on the literature, update the committee adds that there is too little research (RCTs) to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy on the risk of food allergy in the offspring later in life.[a]

Explanation

There are three systematic reviews of the use of fish-fatty-acid supplements during pregnancy on the risk of food allergy.[274,275,285] Best et al. (2016) summarise three RCTs which provided fish fatty acids to the mother during pregnancy until birth or until the first months postpartum. Food allergy was defined as a positive skin prick test to any food extract in the offspring in the first 12 months of life.[274] Garcia-Larsen et al. (2018) summarise two RCTs, one of which is also summarised by Best et al. (2016). In the other RCT, fish fatty acids were provided to the infants after birth instead of to the mothers during pregnancy. It is, therefore, excluded from the analysis by the committee.[285] Gunaratne et al. (2015) summarise one of the three RCTs from the systematic review of Best et al. (2016). This RCT not only provides follow-up data on infants up to 12 months, but also on infants of 12 to 36 months old and beyond. Gunaratne et al. (2015) combine the data on 12 to 32 months with data from another RCT. However, in this RCT, fish fatty acids were provided to the infants after birth instead of to the mothers during pregnancy.[275] Therefore, the committee focuses on the results of Best et al. (2016) (table 96).[274]

[a] As the new studies do not provide new insights, and do not change the conclusion drawn before the update, the data are not shown in the table.

The committee did not find any more recent RCTs on fish-fatty-acid supplementation during pregnancy and the risk of food allergy.

Best et al. (2016) show that the use of fish-fatty-acid supplements reduces the risk of food allergy. Heterogeneity was low. In the remaining RCT there was no significant effect of fish fatty acids on the risk of allergic sensitization to any food allergen.

In conclusion, fish-fatty-acid supplementation during pregnancy until birth or until the first months postpartum reduces the risk of food allergy. In view of the small number of RCTs and cases, the committee judges the level of evidence as limited.

Update July 2018 - July 2019

In the update, the committee found one new meta-analysis on this topic.[284] The results of Vahdaninia et al. (2019) results were not in line with Best et al. (2016): RR = 0.91, 95%CI 0.66-1.27, I^2 50.3%, four RCTs. However, the studies in Best et al. (2016) all reported on follow-up until the age of 12 months, while Vahdaninia et al. (2019) summarised four studies with four different follow-up lengths that were mainly performed in high-risk populations and until the age of 12 months, 24 months, 36 months, and 6 years. This may explain the difference in findings. Therefore, the committee adds to the earlier conclusion on children up to 1 year of age that there is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation later in life.

Table 96. Results from the meta-analysis of Best et al. (2016) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of food allergy in the offspring.

Intervention	Start intervention	N RCTs	n / N intervention	n / N control	RR estimate (95%CI)	Heterogeneity I^2
0.8-2.1 gram / day DHA and 0.1-1.1 gram / day EPA	20 to 25 weeks gestation	3	73 / 457	123 / 440	0.58 (0.45-0.75)	8%

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio).

10.13.3 Eczema

Summary: Fish-fatty-acid supplementation and the risk of eczema.

Aspect	Explanation
Selected studies	One systematic review with three relevant RCTs[274] and one additional publication on an already included RCT.[278]
Heterogeneity	No
Strength of the effect	No summarised effect estimates. For age 12 months statistically significantly lower risks. For 2 to 6 years of age not significant.
Study population	Pregnant women with a history of allergy or atopic disease from Australia and Europe.

Conclusion:
Based on RCTs, fish-fatty-acid supplementation during pregnancy or pregnancy and lactation reduces the risk of eczema in the offspring up to 1 year of age.
Level of evidence: Limited.

Conclusion (RCTs):
There is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy or pregnancy and lactation on the risk of eczema in children aged 2 to 6 years.

Explanation
There are two systematic reviews of the use of fish-fatty-acid supplements during pregnancy on the risk of eczema.[274,275] Best et al. (2016) describe the findings of four RCTs described in six publications. Gunaratne et al. (2015) summarise two RCTs, one of which is also reviewed by Best et al. (2016). In the other RCT, additional fish fatty acids were provided to the infants after birth instead of to the mothers during pregnancy.[275] The committee focuses, therefore, on the four RCTs in the systematic review of Best et al. (2016) below (table 97).[274]

In one of the four RCTs in the systematic review of Best et al. (2016) the intervention consisted of fatty fish rather than fish-fatty-acid supplements and the RCT is therefore not reviewed below.[279] Dunstan et al. (2003) found no significant effect of fish-fatty-acid supplementation during pregnancy on the risk of eczema in the first year.[280] Both other RCTs found a significant protective effect of fish fatty acids during pregnancy or during pregnancy and lactation on the risk of atopic eczema (eczema with a positive skin prick test) in the first year. The number of cases was small, however.[286,287] There was no significant effect at 2 or 3 years of age.[282,283]

The committee found one more recent publication on the RCT of Palmer et al. (2012) on the risk of eczema at 6 years of age. Again, there was no significant effect. The confidence interval was relatively broad.[278]

The committee concludes that fish-fatty-acid supplementation during pregnancy or pregnancy and lactation reduces the risk of eczema in infants up to 1 year of age. In view of the limited number of RCTs (N = 3), the level of evidence is limited.

In view of the small number of RCTs and cases, the committee concludes that there is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy or during pregnancy and lactation on the risk of eczema in children aged 2 to 6 years.

Table 97. Results from the RCTs included in Best et al. (2016) on the effect of fish-fatty-acid supplementation during pregnancy on the risk of atopic eczema in the offspring.

First author	Intervention	Start intervention	n / N intervention	n / N control	Age at outcome assessment	RR estimate (95%CI)
Dunstan[280]	2,1 gram / day DHA and 1,0 gram / day EPA	20 weeks of gestation	18 / 40	13 / 43	12 months	Not estimable
Furuhjelm[a 287]	2,1 gram / day DHA and 1,1 gram / day EPA	20 to 25 weeks gestation	4 / 52	16 / 63	12 months	0.30 (0.11-0.85)
Furuhjelm[a 282]	2,1 gram / day DHA and 1,1 gram / day EPA	20 to 25 weeks gestation	3 / 54	6 / 63	24 months	0.58 (0.15-2.22)
Palmer[b286]	0,8 gram / day DHA and 0,1 gram / day EPA	Before 21 weeks of gestation	26 / 368	39 / 338	12 months	0.61 (0.38-0.98)
Palmer[b283]	0.8 gram / day DHA and 0.1 gram / day EPA	Before 21 weeks of gestation	44 / 368	48 / 338	36 months	0.86 (0.58-1.27)
Best[b278]	0.8 gram / day DHA and 0.1 gram / day EPA	Before 21 weeks of gestation	36 / 367	36 / 336	6 years	0.95 (0.59-1.53)

CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; n.a.: not applicable; n / N: number of cases / total number of participants; RCT: randomized controlled trial; RR: relative risk estimate (can also be an odds ratio or hazard ratio). [a] Two publications on the same RCT but different follow-up moments. [b] Three publications on the same RCT but different follow-up moments.

Update July 2018 - July 2019

The committee found one new meta-analysis in the update.[284] Vahdaninia et al. (2019) included six RCTs, three of which were already included in the evaluation of the committee. The analysis showed no effect of supplementation on eczema; however, the confidence interval was wide and there was substantial heterogeneity: RR = 1.02, 95%CI 0.77-1.34, I^2 = 55.5%. Three out of six studies were performed in high-risk populations. That did not explain the heterogeneity, however. Because Vahdaninia et al. (2019) did not distinguish between age groups, the comparison with the evaluation of the committee was difficult. Therefore, the committee did not change its conclusion based on this new meta-analysis.

10.14 Cognitive development in the offspring

Conclusion:

Study findings from RCTs on the effect of fish-fatty-acid supplementation during pregnancy on children's cognitive development are inconclusive.

Explanation

There are six systematic reviews of fish-fatty-acid supplementation during pregnancy and offspring cognitive development.[56,243,246,288-290] The committee describes the findings of the three systematic reviews below: Gould et al. (2013), Freedman et al. (2018), and Rangel-Huerta et al. (2018)[56,288,289] The other systematic reviews are not described as Koletzko et al. (2014) describe the results of the systematic review of Gould et al. (2013); the two RCTs described by Dziechciarz et al. (2010) are also summarised by Gould et al. (2013); and the four RCTs from the systematic review of

Saccone et al. (2016) are also described in the systematic reviews of Gould et al. (2013), Rangel-Huerta et al. (2018) and / or Freedman et al. (2018).

Gould et al. (2013) summarise eight RCTs, four of which are unique, i.e. are not described in other systematic reviews; Freedman et al. (2018) summarise eight RCTs, four of which unique; and Rangel-Huerta and Gill (2018) summarise seven RCTs, again four of which are unique.

Gould et al. (2013) are the only authors who summarised the effects on cognitive development from RCTs quantitatively. However, as there were only one or two RCTs available per analysis, the committee does not present the combined effect estimates. The authors concluded that the evidence does not conclusively support or refute that fish-fatty-acid supplementation during pregnancy improves cognitive function in children up to 12 years of age.[288] Rangel-Huerta and Gill (2018) summarised seven RCTs, in which follow-up ranged from 3 months to 12 years. Supplementation with fish fatty acids during pregnancy had no significant effect except in one RCT, in which there was a significant improvement in attention using the Connors' Kiddie Continuous Performance test of 5-year old children (0.4 gram / day DHA during pregnancy).[289] Freedman et al. (2018) describe that four RCTs showed a beneficial effect of maternal DHA-supplementation on attention and neurological signs in the first 5 years of life, but that four other RCTs have not shown differences. However, the interpretation of this finding is limited by the fact that Freedman et al. (2018) combined studies on cognitive and behavioural outcomes in their systematic review.[56]

The committee found three more recent RCTs.[291-293] Hurtado et al. (2015) assigned 110 pregnant women to a fish-oil enriched dairy drink (0.4 gram / day DHA and EPA) or a control dairy drink. No differences were observed on a Bayley test at 12 months.[291] Colombo et al. (2016) carried out an RCT in which 230 women received 0.6 gram / day DHA or placebo during the last two trimesters of pregnancy. Infants were tested on visual habituation at 4, 6 and 9 months. Infants of supplemented mothers maintained high levels of sustained attention and had improved attention on habituation tasks, especially at 6 and 9 months.[292] Ostadrahimi et al. (2018) supplied 150 pregnant women with a fish oil supplement (0.12 gram / day DHA and 0.18 gram / day EPA) or placebo. Neurodevelopment was assessed using the Ages and Stages Questionnaire at 4 and 6 months. The fish oil supplemented infants scored better on neurodevelopment at 4 months, but not at 6 months.[293]

In conclusion, in view of the fact that most studies find no significant effect and the large variety in cognitive outcome measures and the age at which they were assessed, the committee concludes that study findings on the effect of fish-fatty-acid supplementation on cognitive development in the offspring are inconclusive.

10.15 BMI in the offspring

Summary: Fish-fatty-acid supplementation and offspring BMI.

Aspect	Explanation
Selected studies	Three systematic reviews of two[294], six[295], five[296] (BMI) and four[296] RCTs (BMI z-score).
Heterogeneity	In one of the four analyses.
Strength of the effect	Change in BMI: -0.001 (95%CI -0.088 to +0.086) [296]; 0.06 (95%CI -0.15 to +0.26) [294]; +0.09 (95%CI -0.05 to +0.23) [295] kg / m^2 Change in BMI z-score = +0.034 (95%CI -0.044 to +0.113)[296]
Study population	Healthy pregnant women or obese pregnant women with gestational diabetes.

Conclusion:

Based on RCTs, an effect of fish-fatty-acid supplementation during pregnancy alone or during pregnancy and lactation on BMI or BMI z-score in in children up to 10 years of age is unlikely.

Explanation

There are six systematic reviews of the effect of fish-fatty-acid supplementation during pregnancy on offspring BMI.[246,294-298] Koletzko et al. (2014) summarise the systematic reviews of Muhlhausler et al. (2010) and Rodriguez et al. (2012) and two non-systematic reviews.[246,297,298] Muhlhausler et al. (2010) included only studies in which the use of long-chain n-3 fatty acids supplements during lactation was studied and is, therefore, excluded.[297] Rodriguez et al. (2012) summarise two RCTs in which the effect of long-chain n-3 fatty acids supplement use during pregnancy and lactation on offspring BMI was studied in combination with two other studies in which fish fatty acids were supplemented during lactation. As the former studies are also included in the other systematic reviews, the findings of Rodriguez et al. (2012) are not further described.[298]

Three other systematic reviews are included as they either solely studied supplementation during pregnancy or combined studies during pregnancy with those during pregnancy and lactation, offering the possibility to compare the results (Table 98).[294-296]

Stratakis et al. (2014) included two RCTs in which fish fatty acids were supplemented during pregnancy. They found no significant effect on BMI at 1.5 or 4 years. Heterogeneity was moderate.[294]

Li et al. (2018) summarise eight RCTs on the effect of fish fatty acids on BMI at age 1 to 7. In three of the eight RCTs, fish fatty acids were not only supplemented during pregnancy, but also during lactation. They found no significant effect. Heterogeneity was moderate. When one RCT contributing for 71% of weight to the risk estimate was excluded, the effect became significant according to the authors (no data reported). However, the remaining studies were relatively small and the authors did not report on the risk of publication bias.[295]

Finally, Vahdaninia et al. (2018) summarise five RCTs on the effect of fish fatty acids on BMI and four RCTs on BMI z-score. In three of the five RCTs

on BMI, fish fatty acids were also supplemented to mothers or infants postnatal. This was the case in one of the four RCTs on BMI z-score. The authors did not find any significant effect on BMI at 5 to 7 year of age or BMI z-score at 4 to 6 years of age. Heterogeneity was low for BMI and considerable for BMI z-score. Excluding an RCT on prenatal supplementation in a high-risk population decreased the heterogeneity, without basically changing the effect estimate.[296]

In view of the fact that none of the systematic reviews found a significant effect and in view of the large number of studies and subjects, the committee concludes that an effect of fish fatty acids during pregnancy alone or during pregnancy and lactation on BMI or BMI z-score in children up to 10 years of age is unlikely.

Table 98. Results from the meta-analyses of Stratakis et al. (2012), Li et al. (2018), and Vahdaninia et al. (2018) on the effect of fish-fatty-acid supplementation during pregnancy on BMI and BMI z-score in the offspring.

First author	Intervention	Start intervention	N RCTs	N inter-vention	N control	Change in BMI in kg / m^2 or BMI z-score (95%CI)	Hetero-geneity I^2
Stratakis[294]	0.4-0.5 gram / day DHA and / or 0.15 gram / day EPA	20 weeks gestation	2	701	704	+0.06 (-0.15 to +0.26)	41%
Li[295]	0.5-1.02 gram / day DHA and / or 0.1-0.6 gram / day EPA	15 weeks of gestation to start at lactation (1 RCT)	6	n.r. [a]	n.r.	+0.09 (-0.05 to +0.23)	43%
Vahdaninia[296]	0.2 to 1.1 gram / day DHA and / or 0.06 to 4.3 gram / day EPA	18 to 37 weeks of gestation	5	1,038	1,013	-0.001 (-0.088 to +0.086)	0%
Vahdaninia[296]	0.2 to 0.08 milligram DHA and 0.06 milligram EPA[b]	18 to 29 weeks of gestation	4	1,248	1,263	+0.034[c] (-0.044 to +0.113)	59%

BMI: body mass index; CI: confidence interval; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; N: number; n / N: number of cases / total number of participants; n.r.: not reported; RCT: randomized controlled trial.
[a] 2,724 participants in total. [b] Not reported in two RCTs. [c] BMI z-score.

10.16 Visual development in the offspring

Conclusion (RCTs):

There is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy or during pregnancy and lactation on visual development of the offspring.

Explanation

There are four systematic reviews of fish-fatty-acid supplementation during pregnancy on visual outcomes.[243,246,288,290] The RCTs summarised by Koletzko et al. (2015) and Dziechciarz et al. (2010) are also summarised by Gould et al. (2013).[246,288,290] Saccone et al. (2016) summarise two RCTs, one of which is not included in the systematic review of Gould et al. (2013). The latter RCT did not include visual outcomes and is, therefore, not further reviewed.[243] Therefore, the committee describes the findings of Gould et al. (2013) and the remaining RCT from the systematic review of Saccone et al. (2016).

Gould et al. (2013) describe that visual outcomes were measured with a variety of assessments at the age of 2-3 days to 6 months, so that it was not possible to combine the results in a meta-analysis. Of the seven RCTs, two reported an improved visual outcome at 2 months and 4 months respectively.[288]

The committee found one more recent RCT in which the effect on visual development of a dairy drink with 0.4 gram / day EPA and DHA was compared with a control dairy drink in pregnant women. Hurtado et al. (2015) found no significant effect on visual development of the offspring as measured with the pattern reversal visual evoked potentials at 2.5 and 7.5 months.[291]

In conclusion, in view of the variety of outcome measures, the committee concludes that there is too little research to draw a conclusion on the effect of fish-fatty-acid supplementation during pregnancy or pregnancy and lactation on visual development of the offspring.

10.17 Summary of findings on fish fatty acids

In conclusion this chapter is based on 13 systematic reviews of intervention studies [56,238,239,241,244,245,266,274,288,289,294-296] and nine additional RCTs.[249,267-269,277,278,291-293] The committee found strong evidence for a protective effect of fish-fatty-acid supplements during pregnancy on early preterm birth. Further, limited evidence was found for a protective effect on preterm birth, food allergy in the offspring, and eczema in the offspring.

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

Committee's conclusion	Outcome
Strong evidence	• Preterm birth (< 37 weeks): Based on RCTs, the use of fish-fatty-acid supplements with 0.1 to 3 gram EPA and / or 0.1 to 2.1 gram DHA during pregnancy reduces the risk of preterm birth < 37 weeks of gestation by 13% (95%CI 5% to 20%).
Limited evidence	• Food allergy in the offspring up to one year of age: Based on RCTs, fish-fatty-acid supplementation during pregnancy until delivery or until the first months postpartum reduces the risk of food allergy in the offspring at one year of age. • Eczema in the offspring up to one year of age: Based on RCTs, fish-fatty-acid supplementation during pregnancy or pregnancy and lactation reduces the risk of eczema in the offspring up to one year of age.
Unlikely	• Caesarean section: Based on RCTs, the effect of fish-fatty-acid supplementation during pregnancy on the risk of a caesarean section is unlikely. • Gestational diabetes: Based on RCTs, an effect of fish-fatty-acid supplementation during pregnancy on the risk of gestational diabetes is unlikely. • BMI in the offspring: Based on RCTs, an effect of fish-fatty-acid supplementation during pregnancy alone or during pregnancy and lactation on BMI or BMI z-score in in children up to 10 years of age is unlikely.
Contradictory	No conclusions with contradictory evidence
Too little research	• Perinatal mortality (i.e. stillbirth and infant death) (RCTs); • Congenital anomalies (RCTs); • Postnatal depressive symptoms (RCTs); • Neonatal sepsis (RCTs); • Food allergy in the offspring age one year and over (RCTs); • Eczema in children aged two to six years (RCTs); • Visual development in the offspring (RCTs).
Inconclusive	• Preterm birth < 34 weeks (RCTs); • Small for gestational age (RCTs); • Gestational hypertension (RCTs); • Pre-eclampsia (RCTs); • Asthma-like symptoms in the offspring (RCTs); • Cognitive development in the offspring (RCTs).

10.18 Findings cited in the advisory report

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

In this chapter, this applies to the reduced risk of preterm birth < 37 weeks. This is in line with the conclusion that the consumption of fish two or three times per week is associated with a lower risk of preterm birth (conclusion based on cohort studies) in the background document *Health effects of food consumption and dietary patterns during pregnancy*.[194]

The committee notes here that there are two conclusions with limited evidence level in this background document, which are not mentioned in the advisory report. Both conclusions point in the same direction as the conclusion with strong evidence level: a reduced risk of food allergy in the offspring up to the age of 1 year, and a reduced risk of eczema in the offspring up to 1 year of age when mothers took fish-fatty-acid supplementation during pregnancy or during pregnancy and lactation.

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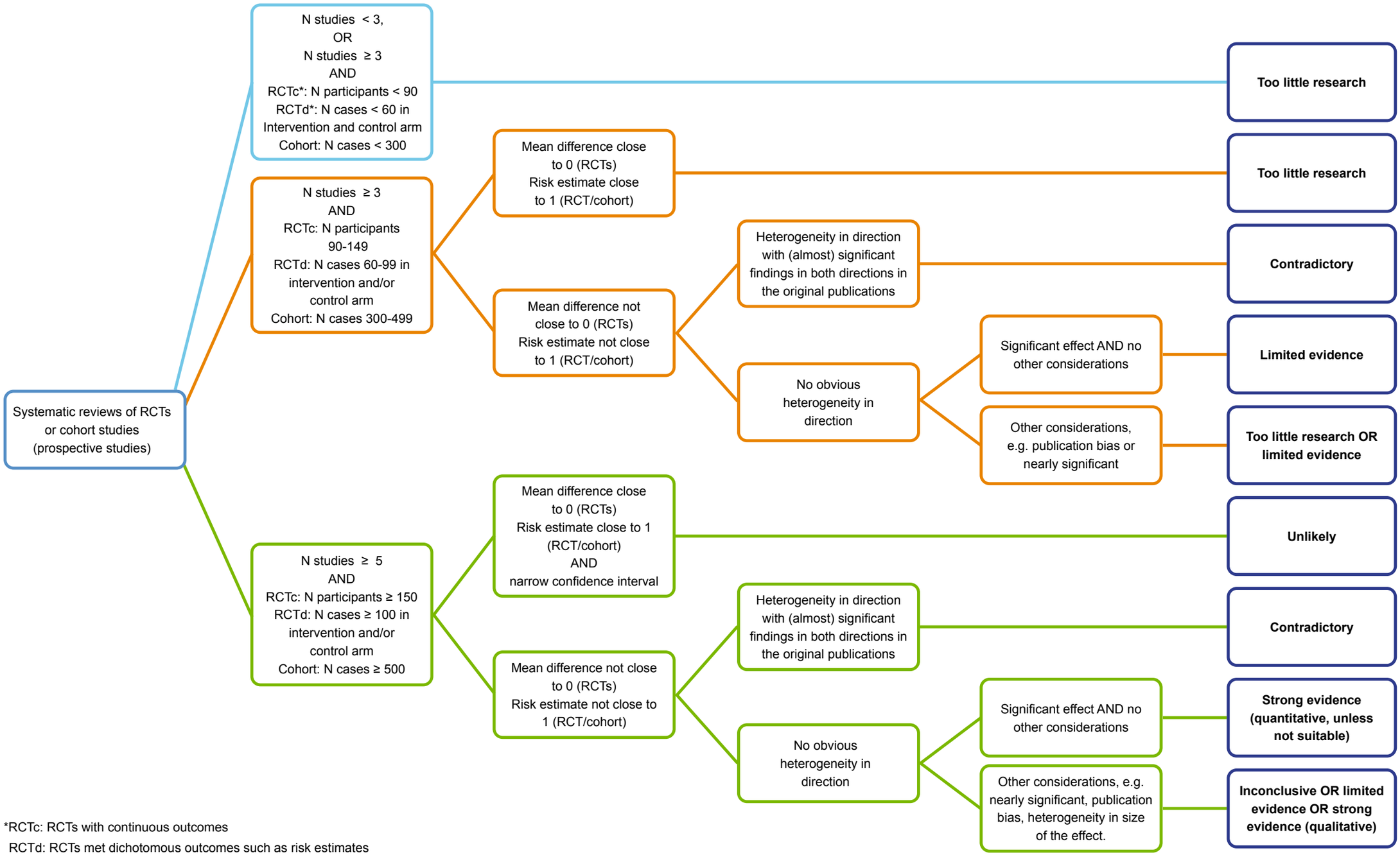
annexes

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 general search in PubMed to identify systematic reviews on health effects of maternal supplementation 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 and 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

B.1 Folic Acid

General search on 2 May 2018:

(((folic acid[Title / Abstract]) OR folic acid[MeSH Terms])) AND ((((((pregnan*[Title / Abstract]) OR maternal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnancy[MeSH Terms]) Filters: Meta-Analysis; Systematic Reviews.

Addtional specific searches in PubMed on 2 May 2018:

Fetal loss, miscarriage and stillbirth

(((((((fetal loss[Title / Abstract]) OR miscarriage*[Title / Abstract]) OR stillbirth[Title / Abstract]) OR abortion, spontaneous[MeSH Terms]) OR fetal death[MeSH Terms])) AND ((folic acid[Title / Abstract]) OR folic acid[MeSH Terms]))) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnan[Title / Abstract])

Congenital malformations other than neural tube defects

((((folic acid[Title / Abstract]) OR folic acid[MeSH Terms])) AND ((((congenital heart*[Title / Abstract]) OR congenital cardiovascular*[Title / Abstract]) OR oral cleft*[Title / Abstract]) OR abnormalities, congenital[MeSH Terms]))

Preterm birth

(((((preterm birth[Title / Abstract]) OR premature birth[Title / Abstract]) OR premature birth[MeSH Terms])) AND ((folic acid[Title / Abstract]) OR folic acid[MeSH Terms])) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnan[Title / Abstract])

Small for gestational age

(((((small for gestational age[Title / Abstract]) OR SGA[Title / Abstract]) OR infant, small for gestational age[MeSH Terms])) AND ((folic acid[Title / Abstract]) OR folic acid[MeSH Terms])) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnan[Title / Abstract])

Twinning

(((((twin*[Title / Abstract]) OR twins[MeSH Terms])) AND ((folic acid[Title / Abstract]) OR folic acid[MeSH Terms]))) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnan[Title / Abstract])

Pre-eclampsia

(((((((maternal hypertension[Title / Abstract]) OR pre-eclampsia[Title / Abstract]) OR pre-eclampsia[Title / Abstract]) OR hypertension) OR pre-eclampsia[MeSH Terms])) AND ((folic acid[Title / Abstract]) OR folic acid[MeSH Terms])) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnan[Title / Abstract])

Wheezing and asthma

(((((asthma[Title / Abstract]) OR wheez*[Title / Abstract]) OR asthma[MeSH Terms])) AND ((folic acid[Title / Abstract]) OR folic acid[MeSH Terms])) AND ((((((pregnancy[MeSH Terms]) OR maternal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnan[Title / Abstract])

Autism spectrum disorders

((((autism*[Title / Abstract]) OR autism spectrum disorder[MeSH Terms])) AND
((folic acid[Title / Abstract]) OR folic acid[MeSH Terms])) AND
((((((pregnancy[MeSH Terms]) OR maternal*[Title / Abstract]) OR prenatal*[Title / Abstract]) OR perinatal*[Title / Abstract]) OR gestational*[Title / Abstract]) OR pregnan[Title / Abstract])

B.2 Multiple micronutrients

Update until July 2019

(“multivitamins” OR “dietary supplements”[MeSH Terms] OR “multivitamins”[Title / Abstract] OR “dietary supplements”[Title / Abstract]) AND (pregnancy [MeSH Terms] 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]) AND (autism OR autistic OR ASD OR Asperger* OR pervasive developmental disorder* OR PDD)

Filter August 1st 2018 Until July 2019 → 0 hits.

B.3 Vitamin D

General search in PubMed on 19 June 2018

(((((vitamin D[Title / Abstract]) OR vitamin D[MeSH Terms])) AND (((supplement[Title / Abstract]) OR supplementation[Title / Abstract]))) AND (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])) AND

(review[pt] OR meta-analysis[pt] OR “systematic review”[tiab] OR “systematic literature review”[tiab] OR meta-analysis[tiab])

Date:19 / 6 / 2018

Addtional, specific search in PubMed on 20 June 2018

(((((vitamin D[MeSH Terms]) OR vitamin D[Title / Abstract])) AND (supplement or supplementation)) AND ((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]))) AND ((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])))

Date: 28 / 6 / 2018.

B.4 Calcium

General search in PubMed on July 20 2018

(((((calcium[Title / Abstract]) OR calcium[MeSH Terms])) AND (((supplement[Title / Abstract]) OR supplementation[Title / Abstract]))) AND (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])) AND

(review[pt] OR meta-analysis[pt] OR “systematic review”[tiab] OR “systematic literature review”[tiab] OR meta-analysis[tiab])

Date: 20 / 7 / 2018 retrieving 278 hits

Addtional, specific search in PubMed on August 6 2018:

(((((calcium[MeSH Terms]) OR calcium[Title / Abstract])) AND (supplement OR supplementation)) AND ((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])))) AND ((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 trial[tiab] 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])))

Filter: May 2014 until today
Date: 06 / 08 / 2018 retrieving 17 hits.

Search systematic reviews and meta-analyses

(((“multivitamins”[MeSH Terms]) OR “multivitamins”[Title / Abstract] OR multi-vitamins[tiab])) AND (pregnancy [MeSH Terms] 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]))

Date: 25 juni 2018
Filters: systematic review en meta-analyses
Number of hits: 40

((“dietary supplements”[MeSH Terms]) AND (pregnancy [MeSH Terms] 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]))

Date: 25 juni 2018
Filters: systematic review en meta-analyses
Number of hits: 442

((((((Pregnancy[MeSH Terms]) OR pregnan*[Title / Abstract])) OR (((((((((carrying[Title / Abstract]) OR expecting[Title / Abstract]) OR expectant[Title / Abstract]) OR gestating[Title / Abstract]) OR gestational[Title / Abstract]) OR gravid[Title / Abstract]) OR parous[Title / Abstract]) OR parturient[Title / Abstract]) OR enceinte[Title / Abstract])))) AND ((((((((review[Publication Type]) OR meta-analysis[Publication Type]) OR meta-analysis[MeSH Terms]) OR meta-analysis[Title / Abstract]) OR systematic review[Publication Type]) OR systematic review[Title / Abstract]) OR systematic literature review[Title / Abstract]) OR Review[MeSH Terms])) AND ((Minerals[MeSH Terms]) OR Minerals[Title / Abstract]) Filters: Publication date to 2018 / 07 / 01; Humans; English

Number of hits: 309

Aanvullende search RCTs na maart 2015

((((((“multivitamins” OR “dietary supplements”[MeSH Terms])) OR (“multivitamins”[Title / Abstract] OR “dietary supplements”[Title / Abstract]))) AND ((pregnancy [MeSH Terms] 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]))))) AND (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])

Filter: verschenen na 1-3-2015

Number of hits: 416

Aanvullende search Cohorten na feb 2015

(((((((“multivitamins” OR “dietary supplements”[MeSH Terms])) OR (“multivitamins”[Title / Abstract] OR “dietary supplements”[Title / Abstract]))) AND ((pregnancy [MeSH Terms] 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]))))) AND (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])))

Filter: verschenen na 1-2-2015

Number of hits: 52

B.5 Calcium and Vitamin D

Search systematic reviews and meta-analyses

(Calcium[MeSH Terms] OR Calcium[Title / Abstract]) AND (vitamin d[MeSH Terms] OR vitamin d[Title / Abstract]) AND (Pregnancy[MeSH Terms] OR pregnan*[Title / Abstract] OR carrying[Title / Abstract]) OR expecting[Title / Abstract] OR expectant[Title / Abstract] OR gestating[Title / Abstract] OR gestational[Title / Abstract] OR gravid[Title / Abstract] OR parous[Title / Abstract] OR parturient[Title / Abstract] OR enceinte[Title / Abstract]) AND (review[Publication Type]) OR meta-analysis[Publication Type] OR meta-analysis[MeSH Terms] OR meta-analysis[Title / Abstract] OR systematic review[Publication Type] OR systematic review[Title / Abstract] OR systematic literature review[Title / Abstract] OR Review[MeSH Terms]

Date: 4 February 2019

Filters: Publication date to 01 / 07 / 2018; Humans; English

Number of hits: 265

Additional search RCTs preterm birth after January 2015

(calcium[MeSH Terms] OR calcium[Title / Abstract]) AND (vitamin D[mesh terms] OR vitamin D[tiab]) AND AND (preterm birth[tiab] OR premature birth[Mesh terms] OR premature birth [tiab]) AND (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 trial[tiab] OR Multicenter Study[pt] NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt] OR congresses[pt] OR “cross-sectional study”[tiab]))

Filter: published after 1-1-2015
Number of hits: 4
Search date: May 15 2019

Additional search RCTs pre-eclampsia after July 2017

(calcium[MeSH Terms] OR calcium[Title / Abstract]) AND (vitamin D[mesh terms] OR vitamin D[tiab]) AND (pre-eclampsia [tiab] OR pre-eclampsia [Mesh terms] OR pre-eclampsia [tiab]) AND (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 trial[tiab] OR Multicenter Study[pt] NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt] OR congresses[pt] OR “cross-sectional study”[tiab]))

Filter: published after July 2017
Number of hits: 4
Search date: May 15 2019

B.6 Iron

General search in PubMed on 5 July 2018

((((((iron[MeSH Terms]) OR iron[Title / Abstract])) AND ((supplement[Title / Abstract]) OR supplementation[Title / Abstract]))) AND (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])) AND (review[pt] OR meta-analysis[pt] OR “systematic review”[tiab] OR “systematic literature review”[tiab] OR meta-analysis[tiab])

Additional, specific search in PubMed 11 July 2018

((((((iron[MeSH Terms]) OR iron[Title / Abstract])) AND ((supplement[Title / Abstract]) OR supplementation[Title / Abstract])) AND (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]))) AND (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]))

Additional, specific search in PubMed on 16 December 2019

((iron[MeSH Terms] OR iron[Title / Abstract]) AND (supplement[Title / Abstract] OR supplementation[Title / Abstract]) AND (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]) AND (clinical trial[publication type] OR RCT[tiab] OR trial[tiab]) AND (anemia[MeSH Terms] OR anemia[tiab] OR anaemia) AND (“2014/01/01”[PDat] : “2019/12/31”[PDat]))

49 hits, 0 relevant.

Additional, specific search in PubMed on 16 December 2019

((iron[MeSH Terms] OR iron[Title / Abstract]) AND (supplement[Title / Abstract] OR supplementation[Title / Abstract]) AND (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]) AND (clinical trial[publication type] OR RCT[tiab] OR trial[tiab]) AND (preterm birth[tiab]) AND (“2014/01/01”[PDat] : “2019/12/31”[PDat]))

6 hits, 0 relevant.

B.7 Iodine

Search systematic reviews and meta-analyses

(iodine[MeSH Terms] OR iodine[Title / Abstract]) AND (Pregnancy[MeSH Terms] OR pregnan*[Title / Abstract] OR carrying[Title / Abstract] OR expecting[Title / Abstract] OR expectant[Title / Abstract] OR gestating[Title / Abstract] OR gestational[Title / Abstract] OR gravid[Title / Abstract] OR parous[Title / Abstract] OR parturient[Title / Abstract] OR enceinte[Title / Abstract]) AND (review[Publication Type] OR meta-analysis[Publication Type] OR meta-analysis[MeSH Terms] OR meta-analysis[Title / Abstract] OR systematic review[Publication Type] OR systematic review[Title / Abstract] OR systematic literature review[Title / Abstract] OR Review[MeSH Terms])

Filters: Humans; English; until 01 / 07 / 2018

Search date: 04 / 02 / 2019

Hits: 592

Additional search RCTs published after search of included systematic reviews

(iodine[MeSH Terms] OR iodine[Title / Abstract]) AND (Pregnancy[MeSH Terms] OR pregnan*[Title / Abstract] OR carrying[Title / Abstract] OR expecting[Title / Abstract] OR expectant[Title / Abstract] OR gestating[Title / Abstract] OR gestational[Title / Abstract] OR gravid[Title / Abstract] OR parous[Title / Abstract] OR parturient[Title / Abstract] OR enceinte[Title /

Abstract]) AND (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 trial[tiab] OR Multicenter Study[pt] NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt] OR congresses[pt] OR “cross-sectional study”[tiab]))

Filter Humans; English; until 01 / 07 / 2018
Search date: 17 / 05 / 2019
Hits: 35

B.8 Magnesium

General search in PubMed on 19 July 2018

(((((magnesium[Title / Abstract]) OR magnesium[MeSH Terms])) AND (((supplement[Title / Abstract]) OR supplementation[Title / Abstract]))) AND (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])) AND

(review[pt] OR meta-analysis[pt] OR “systematic review”[tiab] OR “systematic literature review”[tiab] OR meta-analysis[tiab])

Date:19 / 7 / 2018 retrieving 84 hits

Addtional, specific search in PubMed on 20 July 2018:

(((((magnesium[MeSH Terms]) OR magnesium[Title / Abstract])) AND

(supplement or supplementation)) AND

((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]))) AND
((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 trial[tiab] 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]))

Date: 20 / 7 / 2018 retrieving 32 hits.

B.9 Fish fatty acids

General search in PubMed on 2 October 2018

((((omega-3 fatty acids[Title / Abstract]) OR (((Docosahexaenoic Acids[Title / Abstract]) OR Eicosapentaenoic Acid[Title / Abstract]))) OR “Fatty Acids, Omega-3”[MeSH Terms])) AND (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]) Limits: meta-analysis, systematic reviews

Additional searches in PubMed 10 October 2018

(((((((omega-3 fatty acids[Title / Abstract]) OR (((Docosahexaenoic Acids[Title / Abstract]) OR Eicosapentaenoic Acid[Title / Abstract]))) OR "Fatty Acids, Omega-3"[MeSH Terms])) AND (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]))) AND ((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] NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt] OR congresses[pt] OR "cross-sectional study"[tiab])))) AND (enceinte[Title / Abstract]) AND (review[Publication Type]) OR meta-analysis[Publication Type] OR meta-analysis[MeSH Terms] OR meta-analysis[Title / Abstract] OR systematic review[Publication Type] OR systematic review[Title / Abstract] OR systematic literature review[Title / Abstract] OR Review[MeSH Terms])

Filters: Humans; English; until 01 / 07 / 2018
Search date: 04 / 02 / 2019
Hits: 180 hits

Reproducing the search including Cobalomine as additional search term did not retrieve additional relevant systematic reviews.

B.10 Vitamin B12

(vitamin b 12[MeSH Terms] OR vitamin b 12[Title / Abstract]) AND (Pregnancy[MeSH Terms] OR pregnan*[Title / Abstract] OR carrying[Title / Abstract] OR expecting[Title / Abstract] OR expectant[Title / Abstract] OR gestating[Title / Abstract]) OR gestational[Title / Abstract] OR gravid[Title / Abstract] OR parous[Title / Abstract] OR parturient[Title / Abstract] OR

C vitamin D trials

C.1 Small for gestational age

Individual trials that underlie the conclusion on vitamin D supplementation and the risk of a small-for-gestational-age infant.

Table C.1. Underlying individual RCTs from the meta-analysis by Bi et al. (2018)[107] on the effect of vitamin D supplementation during pregnancy on the risk of a small-for-gestational-age infant.

Reference Country	Study population	Dietary vitamin D intake (mean µg/d (sd)); total = dietary + supplement (rough estimation of mean in µg/d); vitamin D status at baseline (nmol/L)	Intervention (vitamin D supplement µg/d; n; start moment)	Control (n)	Small for gestational age Relative Risk (95%CI)	Note
Brooke 1980[299] United Kingdom	Pregnant Asian women	Dietary intake not reported. Mean plasma concentration in study population 20.1 (sd 1.9) nmol/L. No significant difference between intervention and control at baseline.	Ergocalciferol 25 µg/d; n=59; start at third trimester until term	Placebo (n=67)	0.54 (0.26-1.10)	
Yu 2009[300] United Kingdom	Pregnant women	No information on dietary intake presented. Median vit D level in the control group was 25 nmol/L (IQR 21-38); 26 nmol/L (IQR 20-37) in the daily dose group; and 26 nmol/L (IQR 21-41) in the high dose group.	Ergocalciferol 20 µg/d or cholecalciferol single dose of 5,000 µg; n=120; start at 27 weeks of gestation until delivery	No treatment (n=59)	0.84 (0.41-1.71)	
Sablok 2015[301] India	Prima gravida with singleton pregnancy at 14-20 weeks of gestation without preexisting osteomalacia, hyperparathyroidism, renal or liver dysfunction, tuberculosis, or sarcoidosis	No information on dietary intake presented. Median vitamin D level in control group 24 nmol/L and 38 nmol/L in intervention group (no sd reported). 77.5% had a vitamin D serum level < 50 nmol/L.	Cholecalciferol: 1 dose of 1,500µg at 20 weeks, if women had a vit D level >50 nmol/L; 2 doses of 3,000 µg at 20 and 24 weeks, if women had vit D level 25-50 nmol/L; 4 doses of 3,000 µg at 20, 24, 28, and 32 weeks if women had vit D level <25 nmol/L; n=108	No supplementation (n=57)	0.43 (0.19-0.98)	

Reference Country	Study population	Dietary vitamin D intake (mean µg/d (sd)); total = dietary + supplement (rough estimation of mean in µg/d); vitamin D status at baseline (nmol/L)	Intervention (vitamin D supplement µg/d; n; start moment)	Control (n)	Small for gestational age Relative Risk (95%CI)	Note
Hossain 2014[302] Pakistan	Women with singleton pregnancies	No information on dietary intake. Confusing information on vitamin D status. In Table 1 the control group had a median serum level of 5.31 ng/dL (=0.0531 ng/mL=0.133 nmol/L) and the intervention group a median level of 4.74 ng/dL (=0.0474 ng/mL=0.119 nmol/L).	Routine care + Cholecalciferol 100µg/d; n=86; start at 20 weeks of gestation until delivery	Routine care (2x 200 mg Fe + 600 mg Ca) (n=89)	1.09 (0.62-1.94)	We assume the reported serum levels of vitamin D are incorrect as the extremely low values are implausible. Furthermore, the abstract reported different baseline values than Table 1 (abstract: control = 6.32 ng/dL; intervention = 8.82 ng/dL) but these still represent extremely low values. According to the meta-analysis of Roth et al. (2017)[106] the mean baseline status was 13.7 nmol/L in the control group. No sd presented.
Dawodu 2013[303] United States	Arab expectant mothers, singleton pregnancies	Mean dietary intake of vitamin D in intervention A=3.3 µg/d (sd 3.1); in intervention B=2.7 µg/d; in control group=2.3 µg/d (sd 1.6). Total intake in intervention A=53.3 µg/d; in intervention B=102.7 µg/d; in control group at least 12.3 µg/d. Mean serum concentration intervention A 20.5 nmol/L (11.9); in intervention B 19.6 nmol/L (sd 7.7); in control group 21.5 nmol/L (sd 13.0)	Cholecalciferol A: 50 µg/d or B: 100 µg/d; n=84; start between 12 and 16 weeks of gestation until delivery	10 µg/d (n=42)	0.63 (0.18-2.21)	
Hashemipour 2014[304] Iran	Pregnant women with vitamin D deficiency	No information on dietary intake. Mean serum concentration intervention group = 17.6 ng/ml (sd 4.8) (=44 nmol/L (sd 12)); control group = 15.9 ng/ml (sd 5.6) (=39.5 nmol/L (sd14))	Cholecalciferol 1,250 µg/week; n=55; start between 26 to 28 weeks of gestation for a duration of 8 weeks	10 µg/d (n=54)	0.33 (0.01-7.86)	

C.2 Gestational diabetes

Individual trials that underlie the conclusion on vitamin D supplementation and the risk of gestational diabetes.

Table C.2. Underlying individual RCTs from the meta-analysis by Roth et al. (2017) used in the background document on the effect of vitamin D supplementation during pregnancy on the risk of gestational diabetes.

Reference Country	Study population	Dietary vitamin D intake (mean mg/d (sd)); vitamin D status at baseline (nmol/L)	Intervention (vitamin D supplement µg/d; n; start moment)	Control (n)	Gestational diabetes Relative Risk (95%CI)	Note
Shahgheibi et al. (2016)[305] Iran	Pregnant women at high risk of gestational diabetes indicated by BMI > 25, history of macrosome neonate, positive family history for diabetes and gestational diabetes, history of gestational diabetes in previous pregnancies, and glycosuria	No information on dietary vitamin D intake. Mean baseline vitamin D status 17.4 nmol/L (sd 14.9) in control group and 13.5 nmol/L (sd 7.6) in intervention group.	125 µg/d from 12 weeks of gestation until 26 weeks of gestation; n=44	Placebo (n=43)	0.33 (0.13-0.82)	Satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017)
Tehrani et al. (2017)[306] Iran	Healthy pregnant women with a vitamin D status of < 10 nmol/L	No information on dietary vitamin D intake and baseline status.	1,250 µg every 2 weeks from 14-16 weeks of gestation for a duration of 10 weeks (n=70)	Placebo (n=70)	0.88 (0.34-2.28)	Low vitamin D status at entry. Satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017)
Hossain et al. (2014)[302] Pakistan	Women with singleton pregnancies	No information on dietary intake. Confusing information on vitamin D status. In Table 1 the control group had a median serum level of 5.31 ng/dL (=0.0531 ng/mL=0.133 nmol/L) and the intervention group a median level of 4.74 ng/dL (=0.0474 ng/mL=0.119 nmol/L).	Routine care + Cholecalciferol 100 µg/d; n=86; start at 20 weeks of gestation until delivery	Routine care (2x 200 mg Fe + 600 mg Ca) (n=89)	1.72 (0.66-4.54)	Satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017). We assume the reported serum levels of vitamin D are incorrect as the extremely low values are implausible. Furthermore, the abstract reported different baseline values than Table 1 (abstract: control = 6.32 ng/dL; intervention = 8.82 ng/dL) but these still represent extremely low values. According to Roth et al. (2017)[106] the mean baseline status was 13.7 nmol/L in the control group (no sd reported).

Reference Country	Study population	Dietary vitamin D intake (mean mg/d (sd)); vitamin D status at baseline (nmol/L)	Intervention (vitamin D supplement µg/d; n; start moment)	Control (n)	Gestational diabetes Relative Risk (95%CI)	Note
Mojibian et al. (2015)[307] Iran	Healthy pregnant women with a vitamin D status of < 75 nmol/L	No information on dietary vitamin D intake. Mean baseline vitamin D status 38.2 nmol/L (sd 12.9) in control group and 36.2 nmol/L (sd 12.9) in intervention group	Cholecalciferol 1,250 µg every 2 weeks from 12-16 weeks of gestation until delivery; n=224	10µg/d vitamin D (n=246)	0.50 (0.28-0.89)	Satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017)
Yap et al. (2014)[308] Australia	Healthy pregnant women with a vitamin D status of < 80 nmol/L.	No information on dietary vitamin D intake. Mean baseline vitamin D status 44.9 nmol/L (sd 17.5) in control group and 50 nmol/L (sd 17.5) in the intervention group	125µg/d from 20 weeks of gestation until delivery; n=78	10µg/d vitamin D (n=80)	0.60 (0.25-1.44)	Satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017)
Asemi et al. (2013)[309] Iran	Healthy pregnant women	Mean baseline vitamin D status in control group 36.2 nmol/L (sd 3.0); in intervention group 44.5 nmol/L (sd 3.2).	10 µg/d from 25 weeks of gestation for 9 weeks + folic acid and iron (n=27)	Folic acid and iron (n=27)	0.33 (0.01-7.84)	NOT satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017).
Grant et al. (2014)[131] New Zealand	Healthy pregnant women	Median baseline vitamin D status in control group 55 nmol/L (IQR 32.5-80); in 25 µg group 57.5 nmol/L (IQR 40-90); in 50 µg group 55 nmol/: (IQR 32.5-87.5)	25 µg/d (n=80) or 50 µg/d (n=77) from 27 weeks of gestation until delivery	Placebo (n=42)	25 µg/d: 1.82 (0.39-8.35) 50 µg/d: 0.54 (0.18-1.60)	NOT satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017). Infant received either placebo, 10 µg/d, or 20 µg/d.
Sablok et al. (2015)[301] India	Prima gravida with singleton pregnancy at 14-20 weeks of gestation without preexisting osteomalacia, hypterparathyroidism, renal or liver dysfunction, tuberculosis, or sarcoidosis	No information on dietary intake presented. Median vit D level in control group 24 nmol/L and 38 nmol/L in intervention group (no sd reported). 77.5% had a vitamin D serum level < 50 nmol/L.	Cholecalciferol: 1 dose of 1,500µg at 20 weeks, if women had a vit D level >50 nmol/L; 2 doses of 3,000µg at 20 and 24 weeks, if women had vit D level 25-50 nmol/L; 4 doses of 3,000µg at 20, 24, 28, and 32 weeks if women had vit D level <25 nmol/L; n=108	No supplementation (n=57)	0.53 (0.03-8.28)	NOT satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017).
Hollis et al. (2011)[310] United States (South Carolina)	Healthy pregnant women	Mean baseline vitamin D status in control group 61.6 nmol/L (sd 27.1); in 50 µg group 58.3 nmol/L (sd 22.3); in 100 µg group 58.2 nmol/: (sd 21.8).	50 µg/d (n=117) or 100 µg/d (n=122) from 12-16 weeks of gestation until delivery	10 µg/d vitamin D (n=56)	50 µg/d: 0.57 (0.16-2.04) 100 µg/d: 0.36 (0.08-1.54)	NOT satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017).
Zerofsky et al. (2016)[311] United States (California)	Healthy pregnant women	Mean baseline vitamin D status in study population 75.3 nmol/L (sd 18.2).	50 µg/d from 20 weeks of gestation until delivery (n=25)	10 µg/d vitamin D (n=26)	0.12 (0.01-2.04)	NOT satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017).

Reference Country	Study population	Dietary vitamin D intake (mean mg/d (sd)); vitamin D status at baseline (nmol/L)	Intervention (vitamin D supplement µg/d; n; start moment)	Control (n)	Gestational diabetes Relative Risk (95%CI)	Note
Chawes et al. (2016)[129] Denmark	Healthy pregnant women	Mean baseline serum concentration in study population 77.4 nmol/L (sd 25)	70 µg/d vitamin D from 24 weeks of gestational age until 1 week postpartum (n=315)	10 µg/d vitamin D (n=308)	0.54 (0.18-1.60)	NOT satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017).
Hashemipour et al. (2013)[304] Iran	Pregnant women with vitamin D deficiency	No information on dietary intake. Mean serum concentration intervention group = 17.6 ng/ml (sd 4.8) (=44 nmol/L); control group = 15.9 ng/ml (sd 5.6) (=39.5 nmol/L)	Cholecalciferol 1,250 µg/week; n=55; start between 26 to 28 weeks of gestation for a duration of 8 weeks	10 µg/d (n=54)	3.00 (0.12-72.31)	NOT satisfy the criteria for case definition and method of ascertainment for gestational diabetes as defined by Roth et al. (2017).

C.3 Asthma-like symptoms and wheeze in the offspring

Individual trials that underlie the conclusion on vitamin D supplementation and the risk of gestational diabetes.

Table C.3. Underlying individual RCTs from the meta-analysis by Roth et al. (2017) used in the background document on the effect of vitamin D supplementation during pregnancy on the risk of asthma-like symptoms and wheeze in the offspring.

Reference Country	Study population	Dietary vitamin D intake (mean mg/d (sd)); vitamin D status at baseline (nmol/L)	Intervention (vitamin D supplement mg/d; n; start moment)	Control (n)	Asthma-like symptoms and wheeze in the offspring Relative Risk (95%CI)	Note
Chawes et al. (2016)[129] Denmark	Healthy pregnant women	No information on dietary vitamin D intake, Mean baseline serum concentration in study population 77.4 nmol/L (sd 25)	60 + 10µg/d vitamin D from 24 weeks of gestational age until 1 week postpartum (n=295)	Placebo + 10 µg/d vitamin D (n=286)	0.80 (0.56-1.13)	Satisfy the criteria for case definition and method of ascertainment for asthma-like symptoms or wheeze in the offspring as defined by Roth et al. (2017).
Litonjua et al. (2016)[312] United States (Massachusetts, Missouri, San Diego)	Healthy pregnant women at high risk of having children with asthma.	Dietary vitamin D intake not specified. Mean baseline serum concentration in control group 56.2 nmol/L (sd 25.2); in intervention group 58.2 nmol/L (sd 25.2)	100 + 10 µg/d vitamin D from 10-18 weeks of gestation until delivery (n=405)	Placebo + 10 µg/d vitamin D (n=401)	0.81 (0.64-1.02)	Satisfy the criteria for case definition and method of ascertainment for asthma-like symptoms or wheeze in the offspring as defined by Roth et al. (2017).
Grant et al. (2014)[131] New Zealand	Healthy pregnant women	Median baseline vitamin D status in control group 55 nmol/L (IQR 32.5-80); in 25µg group 57.5 nmol/L (IQR 40-90); in 50µg group 55 nmol/: (IQR 32.5-87.5)	25 µg/d (n=80) or 50 µg/d (n=76) from 27 weeks of gestation until delivery	Placebo (n=40)	25 µg/d: 0.05 (0.00-0.90) 50 µg/d: 0.35 (0.09-1.44)	Meta-analysis of Roth et al. used Grant et al. (2014) as the main reference for this trial. However the values presented here originate from another publication (Grant et al. (2016)[REF]). Relative risks are calculated by Roth et al.(2017). NOT satisfy the criteria for case definition and method of ascertainment for asthma-like symptoms or wheeze in the offspring as defined by Roth et al. (2017).
Yu et al. (2009)[300] United Kingdom	Pregnant women	No information on dietary intake presented. Median vit D level in the control group was 25 nmol/L (IQR 21-38); 26 nmol/L (IQR 20-37) in the daily dose group; and 26 nmol/L (IQR 21-41) in the high dose group.	Ergocalciferol 20 µg/d (n=56) or cholecalciferol single dose of 5,000 µg (n=52); start at 27 weeks of gestation until delivery	No treatment (n=25)	single dose of 5,000 µg: 1.24 (0.40-3.86) 20 µg/d: 1.02 (0.32-3.27)	NOT satisfy the criteria for case definition and method of ascertainment for asthma-like symptoms or wheeze in the offspring as defined by Roth et al. (2017).

Reference Country	Study population	Dietary vitamin D intake (mean mg/d (sd)); vitamin D status at baseline (nmol/L)	Intervention (vitamin D supplement mg/d; n; start moment)	Control (n)	Asthma-like symptoms and wheeze in the offspring Relative Risk (95%CI)	Note
Sahoo et al. (2016)[132] India	Healthy pregnant women	Median baseline vitamin D status in control group 28.5 nmol/L (IQR 16.0-54.5); intervention every 4 weeks 30.3 nmol/L (IQR 16.5-41.0); intervention every 8 weeks 24.3 nmol/L (IQR 11.5-34.0)	1,500 µg every 4 weeks (n=23) or 1,500 µg every 8 weeks (n=13) from 14-20 weeks of gestation until delivery	10 µg/d vitamin D (n=8)	1,500 µg/d every 4 weeks: 0.70 (0.03-18.82) 1,500 µg/d every 8 weeks: 1.23 (0.05-32.66)	NOT satisfy the criteria for case definition and method of ascertainment for asthma-like symptoms or wheeze in the offspring as defined by Roth et al. (2017). Numbers in Table 1 interpreted as median with IQR. Measures not stated.

D calcium trials

D.1 Preterm birth

Individual trials that underlie the conclusion on calcium supplementation and the risk of preterm birth < 37 weeks. Separate tables are presented on trials in populations with an adequate calcium intake from the diet (mostly defined as ≥ 900 mg/d), a low-calcium diet, and trials with unknown dietary calcium intake.

Note: The analysis from Buppasiri et al. (2015) without the study by Taherian et al. (2002) (RR = 1.55 (95%CI 1.00-2.41)) was used by the committee, because the intervention in that study consisted of calcium + vitamin D instead of calcium alone.[179]

Table D.1a. Underlying individual studies from the meta-analyses used in the background document on the effect of calcium supplementation during pregnancy on the risk of preterm birth < 37 weeks in women with **adequate calcium diet**.

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Relative Risk (95%CI)	Note
Boggess et al. (1997)[313] USA	Healthy pregnant women	Control group Baseline: median 1,450 mg/d (range 575 to 4,100). After 6 weeks: median 1,100 mg/d (range 800 to 2,960). Total: estimated 1,300 to 1,700 mg/d. Calcium group Baseline: median 1,878 mg/d (range 1,260 to 2,700) After 6 weeks: median 1,305 mg/d (range 927 to 6,136) Total: estimated 3,005 to 3,628 mg/d	1,500 mg/d (n=12) for six weeks during the third trimester (starting at week 28 to 31 of gestation).	Placebo	RR = 0.13 (0.01-2.30)	Included in Buppasiri et al (2015). Hofmeyr et al. (2014) excluded this trial, unclear for what reason. All participants received 200 to 250 mg calcium per day in standard prenatal vitamin-mineral preparations.
Crowther et al. (1999)[314] Australia	Nulliparous women with normal blood pressure	Adequate calcium diet.[136] Control group: 1,268 (range 10 to 3,768) mg/d (n=148). Calcium group: 1,144 (range 35 to 4,171) mg/d in the calcium group (n=140); total calcium intake 2,944 mg/d.	1,800 mg/d starting at week 20 of gestation for a duration of 18 weeks (n=227).	Placebo (n=229)	RR = 0.44 (0.21-0.90)	Included in Hofmeyr and in Buppasiri.
Levine et al. (1997)[177] US	Healthy nulliparous women	Adequate calcium diet.[136] Control group: 1,135 mg/d (675); total calcium intake 1,185 mg/d. Calcium group: 1,113 (691) mg/d; total calcium intake 3,163 mg/d.	2,000 mg/d starting at week 20 of gestation for a duration of 19 weeks (n=2,295).	Placebo (n=2,294)	RR = 1.09 (0.92-1.29)	Included in Hofmeyr and in Buppasiri. Effect estimate in Buppasiri et al. (2015) slightly different due to differences in denominator RR = 1.08 (0.91-1.28). Hofmeyr et al. (2014) performed the analysis on participants with complete data: control n=2,173; calcium n=2,163. Buppasiri et al. (2015) based the analysis on all randomized participants.
Villar et al. (1987)[315] Baltimore, Argentina	Healthy nulliparous and primiparous women	Adequate calcium diet.[136] Control group: 914 (478) mg/d; total calcium intake in control group 1,114 mg/d. Calcium group: 1,129 (736) mg/d; total calcium intake in calcium group 2,829 mg/d.	1,500 mg/d from 26 weeks of gestation (n=25). Based on Hofmeyr et al. (2014) mean dietary calcium intake was estimated at 26 weeks.	Placebo (n=27)	-	No cases of preterm birth in neither the intervention nor the control group.
Villar et al. (1990)[178] Baltimore	Pregnant adolescents (≤ 17 yr)	Adequate calcium diet.[136] Control group: 1,336 (796) mg/d; total calcium intake in control group 1,536 mg/d. Calcium group: 1,119 (677) mg/d; total calcium intake in calcium group 3,319 mg/d.	2,000 mg/d starting at week 24 of gestation for a duration of 15 weeks (n=90).	Placebo (n=88)	RR = 0.35 (0.16-0.80)	

Table D.1b. Underlying individual studies from the meta-analyses used in the background document on the effect of calcium supplementation during pregnancy on the risk of preterm birth < 37 weeks in women with **low calcium diet**.

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Relative Risk (95%CI)	Note
Belizan et al. (1991)[316] Argentina	Nulliparous without high blood pressure.	Low calcium diet.[136] Control group: 642 mg/d (448). Calcium group: 646 mg/d (396); total calcium intake in the calcium group estimated at 2,646 mg/d.	2,000 mg/d starting at week 23 of gestation for a duration of 15 weeks (n=579).	Placebo (n=588)	RR = 0.92 (0.58-1.44)	Included in Hofmeyr et al. (2014) and Buppasiri et al. (2015). Effect estimate differ slightly between these meta-analyses due to differences in denominator RR = 0.91 (0.58-1.43). Inclusion of participants either or not restricted to those with complete data.
Lopez Jaramillo et al. (1989)[317] Ecuador	Healthy nulliparous women ≤ 25 years.	Low calcium diet.[136] Population: 292 (sd 126) mg/d[318]; total calcium intake in the calcium group estimated at 2,292 mg/d.	2,000 mg/d starting at week 24 of gestation until delivery (n=49-55).	Placebo (n=43-51)	- No cases of preterm birth in neither the intervention nor the control group	Included in Buppasiri et al. (2015).
Lopez Jaramillo et al. (1990)[319] Ecuador	Healthy nulliparous women (mean age 19 year) from a population with high frequency of pregnancy induced hypertension.	Low calcium diet.[136] Population: 934 mg/d [320]; total calcium intake in the calcium group estimated at 2,934 mg/d.	2,000 mg/d starting at week 30 of gestation for a duration of 8 weeks (n=22).	Placebo (n=34)	RR = 0.17 (0.01-2.99)	Included in Hofmeyr et al. (2014).
Lopez Jaramillo et al. (1997)[321] Ecuador	Teenage pregnant girls.	Low calcium diet.[136] Control group: 605 mg/d. Calcium group: 628 mg/d; total intake in the calcium group 2,628 mg/d.	2,000 mg/d starting at week 20 and continuing until delivery (n=125).	Placebo (n=135)	- Note: no cases of preterm birth in either the intervention nor the control group.	Included in Hofmeyr et al. (2014).
Kumar et al. (2009)[322] India	Healthy nulliparous women with a normal blood pressure.	Low calcium diet.[136] Study population: 314 mg/d (range 86-911; sd 203); total intake calcium in the calcium group 2,314 mg/d.	2,000 mg/d starting at week 12-25 of gestation (n=273).	Placebo (n=251)	RR = 0.55 (0.32-0.94)	Included in Hofmeyr et al. (2014) and Buppasiri et al. (2015).
Purwar et al. (1996)[323] India	Healthy nulliparous women.	Low calcium diet.[136] Control group: 352 (142) mg/d. Calcium group: 336 (156) mg/d; total intake calcium in the calcium group 2,336 mg/d.	2,000 mg/d starting at week 20 of gestation for a duration of 18 weeks (n=97).	Placebo (n=93)	RR = 0.32 (0.07-1.54)	Included in Hofmeyr et al. (2014) and Buppasiri et al. (2015).

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Relative Risk (95%CI)	Note
Sanchez Ramos et al. (1994)[325] USA; Florida	Pregnant women with elevated risk on pre-eclampsia based on positive roll-over test.	Low calcium diet.[136]	2,000 mg/d starting at week 26 of gestation for a duration of 12 weeks (n=29).	Placebo (n=34)	RR = 0.73 (0.27-1.99)	Included in Hofmeyr et al. (2014) and in Buppasiri et al. (2015). Only available as abstract.
Villar et al. (2006)[175] Argentina, India, Egypt, Peru, South Africa, Vietnam	Nulliparous women with normal blood pressure.	Low calcium diet.[136] Study population: < 600 mg/d; total calcium intake in the calcium group estimated to not exceed a mean of 2,100 mg/d.	1,500 mg/d starting at week 16 of gestation for a duration of 22 weeks (n=4,151).	Placebo (n=4,161)	RR = 0.91 (0.80-1.04)	Included in Hofmeyr et al. (2014) and in Buppasiri et al. (2015).
Wanchu et al. (2001)[326] India	Pregnant women without comorbidity.	< 900 mg/d according to Imdad et al. (2012).[139]	2,000 mg/d (n=50) from < 20 weeks of gestation continuing until delivery.	No treatment (n=50)	RR = 1.00 (0.21-4.72)	Included in Buppasiri et al. et al. (2015) Excluded from Hofmeyr et al. (2014) because no placebo group was used.

Table D.1c. Underlying individual studies from the meta-analyses used in the background document on the effect of calcium supplementation during pregnancy on the risk of preterm birth < 37 weeks in women with **unknown calcium diet**.

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Relative Risk (95%CI)	Note
Almirante (1998)[182] Philippines	Nulliparous pregnant women (including adolescents). Classified as high risk pregnancies by Khaing et al. (2017)[122]	Not reported.	500 mg/d (n=212) from 18 weeks of gestation for a duration of 20 weeks.	Not clear what control group received (n=210).	RR = 0.40 (0.21-0.75)	Full text unavailable, therefore the information was retrieved from meta-analysis of Hofmeyr et al. (2014)[136]. The RCT was excluded by Buppasiri et al (2015) because of insufficient data.

Table D.1d. Number of RCTs on the outcome preterm birth, starting at or after 20 weeks of pregnancy versus before 20 weeks of pregnancy.

Dietary calcium intake	Intervention started >20 weeks of pregnancy	Intervention started <20 weeks of pregnancy	Number of RCTs with variable or unknown intervention start (not included to calculate the percentage of RCTs starting at 20 weeks or more)
• Adequate	5 (100%)	0	0
• Low	3 (60%)	2 (start in week 16 and <20)	1 (start in week 12-25)
• Unknown	0	1 (start in week 18)	0
Total	8 (73%) started in week >20	3 (27% started in week <20)	1

D.2 Gestational hypertension and pre-eclampsia

Individual trials that underlie the conclusions on calcium supplementation and the risk of gestational hypertension and pre-eclampsia. Separate tables are presented on trials in populations with an adequate mean value for calcium intake from the diet (mostly defined as ≥ 900 mg/d), trials in populations with low mean values for dietary calcium intake, and trials not reporting information on the dietary calcium intake.

Note: Two individual trials on the outcome pre-eclampsia are not specified in table 2a, because the interventions in both trials consisted of supplements with calcium plus vitamin D instead of calcium alone: (1) the trial by Taherian et al. (2002)[179] (RR = 0.37; 95%CI 0.18-0.75) from the meta-analysis by Imdad et al. (2012), and the trial by Marya et al. (1987)[186] (RR = 0.65; 95%CI 0.31-1.38) from the meta-analysis by Bucher et al. (1996).

Table D.2a. Underlying individual RCTs from the meta-analyses used in the background document on the effect of calcium supplementation during pregnancy on the risk of gestational hypertension and pre-eclampsia in women with **adequate calcium diet**.

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean in mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Gestational hypertension (with or without proteinuria) Relative Risk (95%CI)	Pre-eclampsia Relative Risk (95%CI)	Note
Crowther et al. (1999)[314] Australia	Nulliparous women with normal blood pressure	Adequate calcium diet.[156] Control group: 1,268 (range 10 to 3,768) mg/d (n=148). Calcium group: 1,144 (range 35 to 4,171) mg/d in the calcium group (n=140); total calcium intake 2,944 mg/d.	1,800 mg/d starting at week 20 of gestation for a duration of 18 weeks (n=227).	Placebo (n=229)	RR = 0.90 (0.59-1.38)	RR = 0.44 (0.21-0.90)	
Levine et al. (1997)[177] US	Healthy nulliparous women	Adequate calcium diet.[156] Control group: 1,135 mg/d (675); total calcium intake 1,185 mg/d. Calcium group: 1,113 (691) mg/d; total calcium intake 3,163 mg/d.	2,000 mg/d starting at week 20 of gestation for a duration of 19 weeks (n=2,295).	Placebo (n=2,294)	Excluding pre-eclampsia: RR = 0.88 (0.77-1.01) All hypertensive disorders (including pre-eclampsia): RR = 0.91 (0.81-1.00)	RR = 0.94 (0.77-1.16)	All women received a daily prenatal supplement containing 50 mg of elemental calcium.
Villar et al. (1987)[315] Baltimore, Argentina	Healthy nulliparous or primiparous women	Adequate calcium diet.[156] Control group: 914 (478) mg/d; total calcium intake in control group 1,114 mg/d. Calcium group: 1,129 (736) mg/d; total calcium intake in calcium group 2,829 mg/d.	1,500 mg/d from 26 weeks of gestation (n=25).	Placebo (n=27)	RR = 0.36 (0.04-3.24)	RR = 0.36 (0.04-3.24)	All women received 200 mg of calcium per day via vitamin preparations. Mean dietary intake retrieved from description of the study in the meta-analysis of Hofmeyr et al. (2014).
Villar et al. (1990)[178] Baltimore	Pregnant adolescents (≤ 17 yr)	Adequate calcium diet.[156] Control group: 1,336 (796) mg/d; total calcium intake in control group 1,536 mg/d. Calcium group: 1,119 (677) mg/d; total calcium intake in calcium group 3,319 mg/d.	2,000 mg/d starting at week 24 of gestation for a duration of 15 weeks (n=90).	Placebo (n=88)	Gestational hypertension: RR = 0.59 (0.14-2.38) All hypertensive disorders: RR = 0.37 (0.10-1.34)	RR = 0.14 (0.01-2.67)	All women received 200 mg of calcium per day via vitamin preparation.

Table D.2b. Underlying individual RCTs from the meta-analyses used in the background document on the effect of calcium supplementation during pregnancy on the risk of gestational hypertension and pre-eclampsia in women with **low-calcium diet**.

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean in mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Gestational hypertension (with or without proteinuria) Relative Risk (95%CI)	Pre-eclampsia Relative Risk (95%CI)	Note
Belizan et al. (1991)[316] Argentina	Nulliparous without high blood pressure.	Low calcium diet.[156] Control group: 642 mg/d (448). Calcium group: 646 mg/d (396); total calcium intake 2,646 mg/d.	2,000 mg/d starting at week 23 of gestation for a duration of 15 weeks (n=579).	Placebo (n=588)	RR = 0.68 (0.47-0.98)	RR = 0.66 (0.35-1.26)	
Lopez Jaramillo et al. (1989)[317] Ecuador	Healthy nulliparous women ≤ 25 years	Low calcium diet.[156] Population: 292 (sd 126) mg/d.[318]; total calcium intake calcium group estimated at 2,292 mg/d.	2,000 mg/d starting at week 24 of gestation until delivery (the number of participants used in the meta-analyses differed and ranged from 49 to 55).	Placebo (the number of participants used in the meta-analyses differed and ranged from 43 to 51)	RR = 0.15 (0.03-0.62)	RR = 0.15 (0.04-0.66)	
Lopez Jaramillo et al. (1990)[319] Ecuador	Healthy nulliparous women (mean age 19 year) from a population with high frequency of pregnancy induced hypertension.	Low calcium diet.[156] Population: 933.7 mg/d[320]; total calcium intake calcium group estimated at 2,933.7 mg/d.	2,000 mg/d starting at week 30 of gestation for a duration of 8 weeks (n=22).	Placebo (n=34)	RR = 0.19 (0.07-0.57)	RR = 0.09 (0.01-1.48)	Publication type: letter to the editor.
Lopez Jaramillo et al. (1997)[321] Ecuador	Teenage pregnant girls.	Low calcium diet.[156] Control group: 605 mg/d. Calcium group: 628 mg/d; total intake calcium intake calcium group 2,628 mg/d.	2,000 mg/d starting at week 20 and continuing until delivery (n=125).	Placebo (n=135)	Not applicable	RR = 0.21 (0.07-0.58)	
Kumar et al. (2009)[322] India	Healthy nulliparous women with a normal blood pressure.	Low calcium diet.[156] Study population: 313.83 mg/d (range 85.71-910.71; sd 203.25); total intake calcium in calcium group 2,313.83 mg/d.	2,000 mg/d starting at week 12-25 of gestation (n=273).	Placebo (n=251)	RR = 0.34 (0.17-0.66)	RR = 0.34 (0.17-0.66)	For gestational hypertension Hofmeyr et al. (2014) used the risk of pre-eclampsia.
Puwar et al. (1996)[323] India	Healthy nulliparous women	Low calcium diet.[156] Control group: 352 (142) mg/d. Calcium group: 336 (156) mg/d; total intake calcium in calcium group 2,336 mg/d.	2,000 mg/d starting at week 20 of gestation for a duration of 18 weeks (n=97).	Placebo (n=93)	Gestational hypertension or pre-eclampsia: RR = 0.28 (0.14-0.59)	RR = 0.17 (0.04-0.77)	

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean in mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Gestational hypertension (with or without proteinuria) Relative Risk (95%CI)	Pre-eclampsia Relative Risk (95%CI)	Note
Rogers et al. (1999)[176] Hong Kong	Nulliparous women with an elevated blood pressure.	Population: 670 (sd 300) mg/d.[324] A total calcium intake in calcium group estimated at 1,270 mg/d from week 22 until week 32, and 1,870 mg/d from week 32 until delivery.	600 mg/d from week 22 until week 32 of gestation, from week 32 until delivery they received 1,200 mg/d (n=144).	Not specified (n=75)	Gestational hypertension: RR = 0.61 (0.35-1.07) All hypertensive disorders including pre-eclampsia: RR = 0.60 (0.38-0.95)	Not applicable	
Sanchez Ramos et al. (1994)[325] USA; Florida	Pregnant women with elevated risk of pre-eclampsia based on positive roll-over test.	Low calcium diet.[156]	2,000 mg/d starting at week 26 of gestation for a duration of 12 weeks (n=29).	Placebo (n=34)	Hypertension only: RR = 0.84 (0.30-2.36) All hypertensive disorders including pre-eclampsia: RR = 0.48 (0.26-0.87)	RR = 0.31 (0.12-0.84)	Only available as abstract.
Villar et al. (2006)[175] Argentina, India, Egypt, Peru, South Africa, Vietnam	Nulliparous women with normal blood pressure.	Low calcium diet.[156] Study population: < 600 mg/d; total calcium intake in calcium group estimated to not exceed a mean of 2,100 mg/d.	1,500 mg/d starting at week 16 of gestation for a duration of 22 weeks (n=4,151).	Placebo (n=4,161)	Gestational hypertension: RR = 0.97 (0.85-1.09) All hypertensive disorders including pre-eclampsia and eclampsia: RR = 0.95 (0.86-1.05)	RR = 0.92 (0.75-1.13)	Women were allowed to take iron and folic acid during the trial.
Wanchu et al. (2001)[326] India	Pregnant women without comorbidity.	< 900 mg/d according to Imdad et al. (2012).[139]	2,000 mg/d (n=50) from < 20 weeks of gestation continuing until delivery.	No treatment (n=50)	Not applicable	All cases (mild + severe): RR = 1.13 (0.47-2.68) RR mild cases: RR = 1.50 (0.58-3.90)	Excluded from Hofmeyr et al. (2014) because no placebo group was used.

Table D.2c. Underlying individual RCTs from the meta-analyses used in the background document on the effect of calcium supplementation during pregnancy on the risk of gestational hypertension and pre-eclampsia in women **without data on dietary calcium intake**.

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean in mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Gestational hypertension (with or without proteinuria) Relative Risk (95%CI)	Pre-eclampsia Relative Risk (95%CI)	Note
Aghamohammadi et al. (2015)[327] Iran	Pregnant women over 35 years of age with normal blood pressure.	Not reported	1,000 mg/d (n=40) from week 19 of gestation for a duration of 19 weeks.	Placebo (n=40)	Not applicable	RR = 0.43 (0.18-1.00)	
Almirante (1998)[182] Philippines	Nulliparous pregnant women (including adolescents). Classified as high risk pregnancies by Khaing et al. (2017).	Not reported	500 mg/d (n=212) from 18 weeks of gestation for a duration of 20 weeks.	Not clear what control group received (n=210)	Not applicable	RR = 0.34 (0.19-0.60)	Full text unavailable, info retrieved from meta-analyses.[122,136] Excluded by Imdad et al. (2012) because of insufficient data.
Bassaw et al. (1998)[174] Bangladesh	Pregnant women with obstetric history of pre-eclampsia. None of the participants had any underlying medical disorders.	Not reported	Khaing et al. (2017) used: 1,200 mg/d (n=81) from 19 weeks of gestation for a duration of 20 weeks. Hofmeyr et al. (2014) used: 600 mg/d calcium + 80 mg/d aspirin (n=84).	Khaing et al. (2017) used: placebo (n=250). Hofmeyr et al. (2014) used: 80 mg/d aspirin (n=87).	High-dose calcium vs. placebo: RR = 0.06 (0.00-0.94) Low-dose calcium + aspirin vs. aspirin: RR = 0.60 (0.38-0.95)	High-dose calcium vs. placebo: RR = 0.08 (0.01-0.60) Low-dose calcium + aspirin vs. aspirin: RR = 0.30 (0.06-1.38)	All participants received ferrous sulphate (200 mg) and folic acid (5 mg/d).
Cong et al. (1993) (1995) [184,328] China	Healthy nulliparous women.	Not reported	120 mg/d or 240 mg/d (n=112) starting from 20-28 weeks of gestation until delivery.	No calcium (n=56)	RR = 0.45 (0.19-1.04)	RR = 0.10 (0.00-2.07)	
Montanaro et al. (1990)[329] Not known	Not known.	Not known	Total n = 170	Not known	Not applicable	RR = 0.25 (0.06-1.03)	Conference presentation (not retrievable). Imdad et al. (2012) excluded this study because of insufficient data. Hofmeyr et al. (2014) excluded this study because no placebo was used.

Reference Country	Study population	Dietary calcium intake (mean mg/d (sd)); total = dietary + supplement (rough estimation of mean in mg/d)	Intervention (calcium supplement mg/d; n; start moment)	Control (n)	Gestational hypertension (with or without proteinuria) Relative Risk (95%CI)	Pre-eclampsia Relative Risk (95%CI)	Note
Nenad et al. (2011)[183] Serbia	Healthy nulliparous women.	Not reported	2,000 mg/d starting at week 19 of gestation for a duration of 19 weeks (n=4,590).	Placebo (n=4,588)	RR = 0.88 (0.81-0.97)	RR = 0.94 (0.76-1.16)	No trial registration number available. Report of the trial was only available as conference abstract.
Niromanesh et al. (2001)[330] Iran	Pregnant women with at least one risk factor for pre-eclampsia and a positive rollover test.	No difference in baseline calcium intake between the intervention and the control group. Control group: 5.3 (4.4) glass milk/ week; 33.1 (39.4) spoons yoghurt/ week; 109 (103.8) gram cheese/ week; 393.2 (189) gram other dairy/ week. Calcium group: 3.8 (2.3) glass milk/ week; 24.7 (26.1) spoons yoghurt/ week; 117 (75.7) gram chees/ week; 365.5 (160.7) gram other dairy/ week.	2,000 mg/d starting at week 30 of gestation for a duration of 9 weeks (n=15).	Placebo (n=15)	Hypertension only: RR = 2.25 (0.88-5.73) Hypertensive disorders including pre-eclampsia: RR = 0.91 (0.57-1.45)	RR = 0.14 (0.02-1.02)	

Table D.2d. Number of RCTs on the outcome gestational hypertension, starting at or after 20 weeks of pregnancy versus before 20 weeks of pregnancy.

Dietary calcium intake	Intervention started >20 weeks of pregnancy	Intervention started <20 weeks of pregnancy	Number of RCTs with variable or unknown intervention start (not included to calculate the percentage of RCTs starting at 20 weeks or more)
• Adequate	4 (100%)	0	0
• Low	6 (75%)	2 (start in week 16 and <20)	1 (start in week 12-25)
• Unknown	2 (50%)	2 (start in week 19 and <20)	0
Total	12 (75%) started in week >20	4 (25%) started in week <20	1

Table D.2e. Number of RCTs on the outcome pre-eclampsia, starting at or after 20 weeks of pregnancy versus before 20 weeks of pregnancy.

Dietary calcium intake	Intervention started >20 weeks of pregnancy	Intervention started <20 weeks of pregnancy	Number of RCTs with variable or unknown intervention start (not included to calculate the percentage of RCTs starting at 20 weeks or more)
• Adequate	4 (100%)	0	0
• Low	6 (75%)	2 (start in week 16 and <20)	1 (week 12-25)
• Unknown	2 (33%)	4 (start in week 18, 19, 19 and 19)	1 (not known)
Total	12 (66%) started in week >20 16 (89%) started in week >18	6 (33%) started in week <20 2 (11%) started in week <18	2

E iron trials

Individual trials that underlie the conclusion on iron supplementation and the risk of maternal anaemia. Separate tables are presented on trials in high-income countries and trials in middle or low-income countries.

Table E.a. Underlying individual RCTs in high-income countries from the meta-analysis by Imdad and Bhutta (2012)[199] and the two additional RCTs used in the background document on the effect of iron supplementation during pregnancy on the risk of anaemia at term.

Reference High-income country	Study population	Iron status at the start	Intervention (iron supplement mg/d; n; start moment)	Control (n)	Anaemia at term Relative Risk (95%CI)	Note
Chanarin & Rothman 1971 [331] UK	Anaemic and non-anaemic pregnant women	Group mean Hb values ranged between 108 and 119 g/L; SDs between 6 and 9.	Not clear, either 30 or 120 mg/d, starting from pregnancy week 20 until delivery, or 1 gram intravenously at the start followed by 60 mg/day (each n=49)	Placebo (n=46)	RR = 0.10 (0.01-0.79)	Chanarin and Rothman had four intervention groups with different interventions, three of which included 49 participants. One of these three interventions is included in the meta-analysis by Imdad and Butte.
Milman et al. 1991 [332] Denmark	Anaemic and non-anaemic pregnant women	17% of women: Hb <110 g/L; 6%: low Hb ánd ferritin <20 mcg/L.	66 mg/d, starting from week 16 until delivery (n=100)	Placebo (n=107)	RR = 0.03 (0.00-0.57)	The risk estimate reported in the meta-analysis by Imdad & Butta appears to be lower than findings of Milman et al.
Pritchard & Hunt 1958 [333] USA	Anaemic and non-anaemic pregnant women with low social-economic status	34-48% of the women had Hb <110 g/L	115 mg/day starting point during pregnancy not specified (n=74)	Placebo (n=49)	RR = 0.17 (0.08-0.39)	
Chisholm et al. 1966 [334] UK	Non-anaemic pregnant women	Hb ≥110 g/L, serum Fe ≥60 µg/100mL were inclusion criteria	900 mg/d (n=60) starting from week 28 until delivery	Placebo (n=60)	RR = 0.15 (0.05-0.48)	

Reference High-income country	Study population	Iron status at the start	Intervention (iron supplement mg/d; n; start moment)	Control (n)	Anaemia at term Relative Risk (95%CI)	Note
Cogswell et al. 2003 [335] USA	Non-anaemic pregnant women	Hb ≥110 g/L, ferritin ≥20 µg/L were inclusion criteria	30 mg/d starting from week 28 until delivery (n=149)	Week <20 to 28: placebo; Week 28 until delivery: placebo if ferritin >20 µg/L; 30 mg/d if ferritin 12-20 µg/L; 60 mg/d if ferritin < 12 µg/L (n=129)	RR = 0.75 (0.35-1.59)	In the meta-analysis by Imdad and Butte, the experimental group comprised 90 women and the control group 62 women.
De Benaze et al. 1989 [336] France	Non-anaemic pregnant women	exclusion if at start anaemic or iron or if the woman used folic acid supplements in the past 6 months	15 mg/d starting between week 12 and 18, until delivery (n=44)	Placebo (n=25)	RR = 0.21 (0.06-0.73)	
Eskeland et al. 1997 [337] Norway	Non-anaemic pregnant women	Hb 110-148 g/L	27 mg/d starting from week 20 until delivery (n=48)	Placebo (n=23)	RR = 0.06 (0.00-0.97)	The risk estimate presented in this table (from the meta-analysis by Imdad and Butte) is lower than findings by Eskeland et al.
Hemminki & Rimpelä 1991 [338] Finland	Non-anaemic pregnant women	Hb >110 g/L, packed cell volume >0.32 were inclusion criteria	100 mg/day starting from week 16 or earlier in pregnancy, until delivery (n=1336)	No placebo (n=1358) If Hb <100/105 g/L in two consecutive visits, the control women received iron supplements until Hb >110 g/L.	RR = 0.27 (0.15-0.48)	
Holly 1995 [339] USA	Non-anaemic pregnant women	Hb >100 g/L was inclusion criterion	115 mg/day starting from week 26 or earlier in pregnancy, until delivery (n=94)	No placebo (n=55)	RR=0.03 (0.00-0.18)	
Makrides et al. 2003 [340] Australia	Non-anaemic pregnant women	Hb >110 g/L was inclusion criterion	20 mg/day starting from week 20 until delivery (n=200)	Placebo (n=193)	RR = 0.45 (0.25-0.82)	
Puolakka 1980 [341] Finland	Non-anaemic pregnant women	Hb >110 g/L was inclusion criterion	200 mg/d starting from week 16 or earlier in pregnancy, until delivery (n=16)	No placebo (n=15)	RR = 0.07 (0.00-1.18)	
Romslo et al. 1983 [342] Norway	Mostly non-anaemic	unselected	200 mg/day starting from week 10 or earlier in pregnancy, until delivery (n=22)		RR = 0.15 (0.02-1.12)	
Meier et al. 2003 [203] USA	111 non-anaemic pregnant women (37 adolescents and 74 adults), all women used 1 mg/day folic acid	Hb range 110-170 g/L	60 mg/day starting point ranged between week 7 and 18 of pregnancy, until delivery (n=58)	Placebo (n=53)	Adolescents: RR = 0.34 (0.13-0.89) Adults: RR = 0.32 (0.13-0.78)	This RCT was not included in the meta-analysis by Imdad and Butte, but is presented as an additional RCT in this background document

Reference High-income country	Study population	Iron status at the start	Intervention (iron supplement mg/d; n; start moment)	Control (n)	Anaemia at term Relative Risk (95%CI)	Note
Siega-Riz et al. 2006 [204] USA	non-anaemic women	Hb>110 g/L and ferritin >40 µg/L were inclusion criteria	30 mg/day, starting from week 20 or earlier in pregnancy, until week 26-29 of pregnancy (n=218)	Multivitamin with no iron (n=211)	RR = 1.11 (0.71-1.71)	This RCT was not included in the meta-analysis by Imdad and Butte, but is presented as an additional RCT in this background document

Table E.b. Underlying individual RCTs in middle and low-income countries from the meta-analysis used in the background document on the effect of iron supplementation during pregnancy on the risk of anaemia at term.

Reference Middle- or low-income country	Study population	Iron status at the start	Intervention (iron supplement mg/d; n; start moment)	Control (n)	Anaemia at term Relative Risk (95%CI)	Notes
Batu et al. 1976 [343] Birma	Anaemic and non-anaemic pregnant women	72% had Hb <110 g/L	120 mg/day starting from week 22-25 of pregnancy until delivery (n=30)	Placebo (n=22)	RR = 0.55 (0.38-0.80)	
Preziosi et al. 1997 [344] Niger	Anaemic and non-anaemic pregnant women	65-70% had Hb <110 g/L	100 mg/day starting from week 27 until delivery (n=99)	Placebo (n=98)	RR = 0.59 (0.45-0.77)	

F iodine trials

F.1 Maternal goitre

Individual trials that underlie the conclusion on the use of iodine supplements during pregnancy and the risk of maternal goitre.

Table F.1. Underlying individual RCTs from the meta-analysis by Harding et al. (2017)[211] on the effect of iodine supplementation during pregnancy on the risk of maternal goitre.

Reference Country	Study population	Dietary iodine intake	Intervention (iodine supplement µg/d; n; start moment)	Control (n)	Maternal goitre at term Relative Risk (95%CI), as reported in the meta-analysis by Harding et al. [211]	Notes
Glinoer et al. 1993 [216,217] Belgium	Euthyroid pregnant women with excessive thyroid stimulation	Mean dietary iodine intake: 40 µg/day. Mean total iodine intake in iodine-supplementation group 1: 40 µg/day. Mean total iodine intake in iodine-supplementation group 2: 200 µg/day.	Iodine-supplementation group 1: 100 µg/day (n=60); Iodine-supplementation group 2: 161 µg/day (n=60); Starting on average from pregnancy week 14.4 (standard error of the mean 0.2)	Placebo (n=60)	RR = 0.60 (0.23-1.55) The percentages of women developing goitre during pregnancy were: 16% in the control group; 10% in iodine-supplementation group 1; 3% in iodine-supplementation group 2.	Excessive thyroid stimulation was defined as the combination of serum thyroglobuline > 20 µg/L and free T4 index < 1,23 (T4 index was based on the T4/TBG-ratio) and/or a T3/T4 ratio > 0,025.
Gowachirapant et al. 2014 [219,345,346] Thailand	Pregnant women from the general population, excluding women with increased TSH values	Mean dietary intake was not reported, but the authors note that 90% of the participants used iodized salt at home. Mean urinary iodine excretion was 110 µg/L at the start.	200 µg/day starting, on average, from pregnancy week 10.7, with standard deviation of 2.7 (n=64)	Placebo (n=67)	RR = 1,89 (0,56-6,34)	

F.2 Neonatal thyroid volume

Individual trials that underlie the conclusion on the effect of iodine supplements by pregnant women on neonatal thyroid volume.

Table F.2: Underlying individual RCTs from the meta-analysis by Harding et al. (2017)[211] on the effect of iodine supplementation during pregnancy on neonatal thyroid volume.

Reference Country	Study population	Dietary iodine intake	Intervention (iodine supplement µg/d; n; start moment)	Control (n)	Neonatal thyroid volume	Notes
Glinoer et al. 1993 [216,217] Belgium	Euthyroid pregnant women with excessive thyroid stimulation	Mean dietary iodine intake: 40 µg/day. Mean total iodine intake in iodine-supplementation group 1: 40 µg/day. Mean total iodine intake in iodine-supplementation group 2: 200 µg/day.	Iodine-supplementation group 1: 100 µg/day (n=60); Iodine-supplementation group 2: 161 µg/day (n=60); Starting on average from pregnancy week 14.4 (standard error of the mean 0.2)	Placebo (n=60)	Iodine-supplementation group 1: -0,19 mL (-20%) Iodine-supplementation group 2: -0,20 mL (-19%) Differences between both intervention groups and the control group were statistically significant (p=0,0001) Neonatal thyroid volumes were reported per group (standard error of the mean = SEM): Placebo group: 1.05 (SEM 0.05) mL Iodine-supplementation group 1: 0.76 (SEM 0.05) mL Iodine-supplementation group 2: 0.75 (SEM 0.05) mL	Excessive thyroid stimulation was defined as the combination of serum thyroglobuline > 20 µg/L and free T4 index < 1,23 (T4 index was based on the T4/TBG-ratio) and/or a T3/T4 ratio > 0,025.
Liesen-kotter et al. 1996 [218] Germany	Pregnant women visiting a hospital for pregnancy care	The average dietary iodine intake was not reported. At the start of the study the urinary iodine/ creatinine ratio was 53 µg iodine per gram creatinine	230 µg of iodine (300 µg potassium iodide) per day. N=38 Start between 10 and 12 weeks of gestation.	Placebo (n=70)	-0.80 mL (-1.09 tot -0.51) (p<0.004) (-53%) Neonatal thyroid volumes per group (mean and standard deviation = SD): Placebo group 1.5 (SD 1.1) mL Iodine group 0,7 (SD 0.4) mL	At the initial contact, 14 of the participating pregnant women (13%) noted that they had had goitre, and 7 participants (6,5%) appeared to have goitre. Based on their measurements of thyroid volume of all participating women in early pregnancy, Liesenkotter et al. estimated - definining goitre as a thyroid volume of at least 18 mL - that 43% of the participating women had goitre. Thyroid volumes in early pregnancy did not differ between the intervention group and the placebo group (16.2 mL and 16.8 mL, respectively). Liesenkotter et al. did not observe an effect of iodine supplements on maternal thyroid volume. Urinary iodine/creatinine ratio increased by the use of iodine supplements with approximately 50 µg iodine per gram creatinine.

Reference Country	Study population	Dietary iodine intake	Intervention (iodine supplement µg/d; n; start moment)	Control (n)	Neonatal thyroid volume	Notes
Gowachi-rapant et al. 2014 [345] Thailand	Pregnant women from the general population, excluding women with increased TSH values	Mean dietary intake was not reported, but the authors note that 90% of the participants used iodized salt at home. Mean urinairy iodine excretion was 110 µg/L at the start.	200 µg/day starting, on average, from pregnancy week 10.7, with standard deviation of 2.7 (n=64)	Placebo (n=67)	-0.09 mL (-0.18 to 0.00) (p=0,274) (-13%) Neonatal thyroid volumes per group (mean and standard deviation = SD): Placebo group 0.72 (SD 0.2) mL Iodine group 0.63 (SD 0.3) mL	Gowachirapant et al. excluded women with increased TSH, considering that it was unethical to not giving these women iodine supplements.

G fish fatty acid trials

Results from the individual trials that underlie the conclusion on fish-fatty-acid supplementation and the risk of preterm birth < 37 weeks and < 34 weeks.

Table G: Underlying individual RCTs from the meta-analyses performed by the committee on the effect of fish-fatty-acid supplementation during pregnancy on the risk of preterm birth < 37 weeks and preterm birth < 34 weeks.

Reference Country	Study population; in/ exclusion criteria in relation to fish of fish fatty acids intake	Baseline dietary fish intake; baseline fish fatty acids intake; baseline fish fatty acids status	Intervention (fish fatty acid supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Effect size (95%CI)	Preterm birth < 34 weeks Effect size (95%CI)	Note
Bisgaard et al. 2016[277] Denmark	Pregnant women between 22 and 26 weeks of gestation were eligible. No in/exclusion criteria regarding fish or fish oil.	Fish fatty acids intake: median 0.9EN% n-3 LCPUFA (inter tertile range 0.8-1.0). EPA 130mg/d (90-170); DHA 320mg/d (230-410). Fish intake: 26g/d (19-33.5). No sensitivity analysis available for high/low baseline intake.	2,400 mg/d n-3 LCPUFA (55% EPA; 37% DHA) N=365 Start 24 weeks of gestation (stop 1 week after delivery)	Olive oil. N=371	0.85 (0.43-1.65)	n.a.	Blood levels of EPA and DHA increased in intervention group. Int: mean 4.9% (SD 1.3%) to 6.1% (2.0%). Cont: 4.9% (1.2%) to 3.7% (1.1%)
Bulstra-Ramakers et al. 1995[347] Netherlands	Women with a history of IUGR (BW < 10th centile) in previous pregnancy. No in/exclusion criteria regarding fish of fish oil.	No information on baseline intake or status	3,000 mg/d EPA + not specified amount of DHA N=32 Start between 12-14 weeks of gestation	Coconut oil N=31	0.78 (0.35-1.70)	0.48 (0.13-1.77)	Most preterm births were caesarean sections due to IUGR or pregnancy induced hypertension.
Carlson et al. 2013[348] USA	Pregnant women between 8 and 20 weeks of gestation were eligible. Women who took a DHA supplement < 300 mg/d were not excluded.	Fish fatty acids intake from supplements: 9% (mean 20mg/d (SD 66)) of intervention group and 15% (mean 33mg/d (SD 79)) of control group took DHA supplements. DHA Status: 4.3% (SD 1.1) int; 4.3% (SD 1.3) cont. n-3 LCPUFA intake at baseline: not estimated. During trial: 10% of int and 17% of cont took DHA supplements not provided by the study.	600 mg/d DHA from marine algae-oil. N=154 Start between 8 and 20 weeks of gestation (stop at birth)	Half soybean, half corn oil, containing ± 90 mg/d of ALA (a precursor of DHA) N=147	0.88 (0.42-1.87)	0.14 (0.02-1.09)	

Reference Country	Study population; in/ exclusion criteria in relation to fish of fish fatty acids intake	Baseline dietary fish intake; baseline fish fatty acids intake; baseline fish fatty acids status	Intervention (fish fatty acid supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Effect size (95%CI)	Preterm birth < 34 weeks Effect size (95%CI)	Note
Dilli et al. 2018[258] Turkey	Pregnant women with GDM. No in/exclusion criteria related to fish or fish oil intake.	No information on baseline intake or status	Fish oil capsules EPA 384 mg/d + DHA 252 mg/d N=52 Start 24 to 28 weeks of gestation.	Capsules sunflower oil. N=68	0.87 (0.33-2.29)	n.a.	
Dunstan et al. 2003[280] Australia	Atopic pregnant women. Excluded if they had seafood allergy or if their normal dietary intake exceeded 2 times fish per week	No information on baseline intake or status	3,700 mg/d n-3 PUFAs; 56% DHA, 27,7% EPA N=40 Start 20 weeks of gestation (stop at delivery)	Capsules olive oil. N=43	3.23 (0.35-29.75)	n.a.	
Escolano-Margarit et al. 2011[349] Spain, Germany, Hungary	Healthy pregnant women. Women were not supplemented with fish oil at baseline	No information on baseline intake or status	Milk containing 500mg DHA + 150mg EPA per day N=43 Start 20 weeks of gestation (stop at delivery)	Placebo N=47	1.46 (0.35-6.14)	n.a.	On this RCT also the publication of Cantena 2015[350] was identified. Results of Escolano-Margarit are included in the meta-analysis since they use the largest sample.
Farshbaf Khalili et al. 2017[351] Iran	Healthy pregnant women. Participants with history of allergy to fish oil or other fish products and those who consumed fish 2 or more times a week were excluded.	Fish intake: 2/3 of the participants reported no fish intake in the month prior to the trial. Status: DHA 0.19% (sd 0.1) in intervention and control group. EPA 0.15-0.16% (sd 0.1) in intervention group and control group respectively.	Fish oil supplements containing 120 mg/d DHA and 180 mg/d EPA N=75 Start 21 weeks of gestation (until delivery)	Placebo N=75	1.00 (0.14-6.91)	n.a.	
Harris et al. 2015[352] USA	Pregnant women. Excluded if they consumed salmon, mackerel, rainbow trout, sardines at least once weekly or fish allergy.	Information on DHA status is not presented in the paper.	Capsules with 300 mg/d OR 600 mg/d algal derived DHA N=224 Start 20 weeks of gestation (until delivery)	Olive oil placebo N=121	n.a.	0.31 (0.09-1.03)	

Reference Country	Study population; in/ exclusion criteria in relation to fish of fish fatty acids intake	Baseline dietary fish intake; baseline fish fatty acids intake; baseline fish fatty acids status	Intervention (fish fatty acid supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Effect size (95%CI)	Preterm birth < 34 weeks Effect size (95%CI)	Note
Hauner et al. 2012[353] Germany	Healthy pregnant women. Excluded if they took n3 LCPUFA supplementation prior randomization.	DHA status: mean 4.55% (sd 1.61%) in intervention group; 4.54% (1.24) in control group. EPA status: 0.42% (0.18) intervention group; 0.42% (0.15) in control group. Dietary intake of DHA at 32 weeks of gestation was mean 201.2 mg/d (sd 258.3) in intervention group and 198.8mg/d (sd 220.1) in control group.	Capsule 1,020 mg/d DHA; 180mg/d EPA + diet advice to reduce arachidonic acid + vitamin E (9mg) N=92 Start 15 weeks of gestation (until 4 months of lactation)	Brief semi structured counselling on a healthy balanced diet according to German guidelines + asked not to take fish oil or DHA supplements N=96	0.78 (0.18-3.40)	n.a.	
Helland et al. 2001[354] Norway	Healthy pregnant women. Excluded if n3 fatty acids supplements were taken prior to study entry.	DHA intake from diet: 300 mg/d in intervention and control group. EPA intake from diet: 200 mg/d in intervention and control group.	10 ml cod liver oil (1,183 mg/d DHA; 803 mg/d EPA) N=301 Start 17-19 weeks of gestation (until 3 months after delivery)	10ml corn oil N=289	0.48 (0.04-5.27)	n.a.	
Horvaticek et al. 2017[355] Croatia	Pregnant women with type I diabetes. No in/exclusion criteria related to fish or fish oil intake.	No information on baseline intake or status	Diabetic diet + supplement with 120 mg/d EPA and 616 mg/d DHA. N=51 Start 9 weeks of gestation.	Diabetic diet + placebo with corn oil N=47	0.92 (0.24-3.48)	2.77 (0.12-66.36)	
Krauss-Etschmann et al. 2008[356] Spain, Hungary, Germany	Apparently healthy women. Excluded if fish oil supplementation was used after 16 weeks of gestation.	No information on baseline intake or status	Fish oil milk based preparation: 500 mg/d DHA + 150 mg/d EPA. N=74. Start 22 weeks of gestation.	Milk based placebo N=80	n.a.	1.24 (0.47-3.24)	
Kuper et al. 2017[357] USA	Pregnant women with a history of preterm delivery. All women received 17α-hydroxyprogesterone. Intake of > 500 mg/wk in prior month, allergy to fish were exclusion criteria.	Fish intake: median in intervention group 1.0 times a week (IQR 0.0-1.5); in control group 0.5 times per week (IQR 0.0-1.5). 18% of intervention group and 19% of control group had at least 2 servings of fish per week.	Supplement with 1,200 mg/d EPA; 800 mg/d DHA. Non-smokers N=370 smokers N=64 Start 16-22 weeks of gestation (until 36 weeks)	Placebo Non-smokers N=345 smokers N=72	Non-smokers: 0.98 (0.81-1.18) Smokers: 0.69 (0.48-0.99).	n.a.	On this trial also the publication of Harper 2010[358] was identified. Since Kuper 2017 reported a separate analysis on smokers and non-smokers (as they found effect modification by this variable) Kuper 2017 was included in meta-analysis.

Reference Country	Study population; in/ exclusion criteria in relation to fish of fish fatty acids intake	Baseline dietary fish intake; baseline fish fatty acids intake; baseline fish fatty acids status	Intervention (fish fatty acid supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Effect size (95%CI)	Preterm birth < 34 weeks Effect size (95%CI)	Note
Makrides et al. 2010[268] Australia	Pregnant women. Excluded if they were already taking prenatal DHA supplements.	Not measured. In the discussion they state: women in Australia are known to have low dietary intakes of n3 LCPUFAs.	Capsules with 800 mg/d DHA and 100 mg/d EPA N=1,197 Start around 20 weeks of gestation (until delivery)	Capsules with vegetable oil N=1,202	0.76 (0.56-1.04)	0.48 (0.25-0.93)	
Makrides et al. 2019[250] Australia	Pregnant women. Excluded if they took supplements containing > 150 mg/d n3 LCPUFAs before start RCT	Median maternal DHA level 2.7% (IQR 2.3-3.1) in intervention and control group.	Capsules with 800 mg/d DHA and 100 mg/d EPA N=2,734 Start around 14 weeks of gestation (until 34 weeks of delivery)	Capsules with vegetable oil (with 15 md/d DHA and 4 mg/d EPA) N=2,752	0.86 (0.72-1.03)	1.12 (0.78-1.60)	Subgroup analysis baseline DHA-status: <34 weeks: seems trend towards lower baseline status à larger effect of intervention. Very small numbers. For the outcome <37 weeks trend was less clear.
Malcom et al. 2003[255] UK	Healthy pregnant women. Excluded if allergy to fish products	Fish intake: not significantly different between intervention and control group at baseline and follow-up Status: idem. At follow-up DHA status intintervention group mean 3% (range 0.3-5%); control group 2% (0.5-4%)	Capsule of 200 mg/d DHA N=31 Start 15 weeks of gestation (until delivery)	Placebo N=32	0.34 (0.01-8.13)	n.a.	
Mardones et al. 2008[359] Chile	Mainly women with low-income, ethnically mixed families. No in/ exclusion criteria related to fish or fish oil intake.	No information on baseline intake or status	Powdered milk fortified with multiple micronutrients, ALA (n3 fatty acids; ±600 mg/d) N=493 Start before 20 weeks of gestation. Around 10th week of gestation.	Powdered milk fortified with small amounts of iron sulphate, copper, zinc and vitamin C. N=477	0.67 (0.39-1.13)	0.19 (0.04-0.88)	Intervention and control condition differed not only in omega-3 intake but also in other micronutrients.
Miller et al. 2016[254] USA	Healthy pregnant women. Excluded if allergies to seafood or fish oils.	Dietary DHA intake: mean 101 mg/d (sd 99). Intake DHA from supplements: mean 209 mg/d (sd 239). Total DHA intake: mean 468 mg/d (sd 278). Maternal plasma DHA status: intervention group 4.97% (sd 1.53); control group 5.17% (sd 1.36).	Tuna oil supplement 300 mg/d DHA + 67 mg/d EPA N=60 Start last trimester (± 26 weeks of gestation) (until 3 months of lactation)	Sunola oil placebo N=55	0.28 (0.08-0.95)	n.a.	Analysis in subgroups: 22% preterm births group with DHA intake up to 300 mg/d; 7% in group with DHA intake up to 300-600 mg/d; 9% in group with DHA intake of 600 mg/d or more.

Reference Country	Study population; in/ exclusion criteria in relation to fish of fish fatty acids intake	Baseline dietary fish intake; baseline fish fatty acids intake; baseline fish fatty acids status	Intervention (fish fatty acid supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Effect size (95%CI)	Preterm birth < 34 weeks Effect size (95%CI)	Note
Min et al. 2014[360] UK	Pregnant women with type 2 diabetes and healthy pregnant women. No in/ exclusion criteria related to fish or fish oil intake.	DHA plasma status varied between 4-5%	Fish oil capsules with 600 mg/d DHA and 100 mg/d EPA N=60 (N=28 with DMII; N=32 healthy) Start around 10 weeks of gestation.	Capsules with sunflower oil. N=57 (N=30 with DMII; N=27 healthy)	DMII group: 0.45 (0.18-1.11) Healthy group: 0.84 (0.19-3.84)	DMII group: 0.80 Healthy group: 3.24 (1 vs. 0 cases)	
Min et al. 2016[361] UK	Women diagnosed with GDM. Excluded if women took omega-3 supplements prior to trial.	DHA plasma status 4.5% in intervention group (sd 1.0); 4.6% in control group (sd 1.5)	Fish oil capsules with 600 mg/d DHA and 82 mg/d EPA N=58 Start between 17-33 weeks of gestation	Capsules with sunflower seed oil N=56	2.32 (0.87-6.15)	4.83 (0.24-98.44)	
Olsen et al. 1992[263] Denmark	Healthy pregnant women in week 30 of pregnancy. Excluded if allergic to fish and regular intake of fish oil.	Low fish intake (≤ 5 times fish per month) N=103; moderate fish intake (> 5 and ≤ 20 times fish per month) N=327; high fish intake (> 20 times fish per month) N=103.	Fish oil capsules containing 2700 mg/d omega 3 fatty acids N=266 Start at 30 weeks of gestation.	Olive oil supplement or no supplement N=267	0.60 (0.27-1.35)	n.a.	Effect modification in analysis on gestational age (continuous) by fish consumption at baseline. The higher the fish intake the lower the difference between groups.
Olsen et al. 2000[362] Denmark, Scotland, Sweden, England, Italy, The Netherlands, Norway, Belgium, Russia	High-risk pregnancies (4 prophylactic: twin pregnancy or previous PTB, IUGR, PIH. 2 therapeutic: threatening PE, suspected IUGR). Women with regular intake of fish oil were excluded, just like women with allergy to fish products.	High, medium and low baseline fish intake groups were formed in publication of Olsen 2006 (about the same trial). No cutoff's of intake are presented, but authors estimated that the high intake group consumed 36 g/d fish; the medium group 23 g/d; and the low group 16 g/d.	Fish oil 1,300 mg/d EPA + 900 mg/d DHA. N=108 in previous PTB trial Starting around 20 weeks of gestation (until delivery)	Olive oil N=120 in previous PTB trial	0.54 (0.30-0.98)	0.32 (0.11-0.89)	In the meta-analysis only the results of the prophylactic previous PTB trial are used. Authors found that gestational age in days was shorter in those in the low and middle fish intake group compared with the high intake group. And that the effect of fish oil seemed larger in the low intake group (however p for interaction n.s. (0.1)). These results apply to the combination of the prophylactic previous problems trials (PTB, IUGR, and PIH).

Reference Country	Study population; in/ exclusion criteria in relation to fish of fish fatty acids intake	Baseline dietary fish intake; baseline fish fatty acids intake; baseline fish fatty acids status	Intervention (fish fatty acid supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Effect size (95%CI)	Preterm birth < 34 weeks Effect size (95%CI)	Note
Olsen et al. 2019[260] China	Healthy pregnant women. Excluded if allergy to fish or fish oil, users of fish oil (> 1 wk) were also excluded.	Fish intake: 42-43% of population had fish intake of ≤2 g/d. Aggregated low fish areas: median fish intake 2.1 g/d (IQR 0-8.9) Aggregated high fish areas: 14.3 g/d (7.1-30.4).	Fish oil capsules 2000 mg/d LC n3 PUFAs N=1,706 Start 20 weeks of gestation (until 37 weeks)	Olive oil capsules N=1,717	0.90 (0.60-1.35)	0.50 (0.15-1.67)	In general the effect estimates are larger in those with a low baseline fish intake compared with those with a high baseline fish intake. However, none of the individual effect estimates are statistically significant. Analysis of high compared with low fish intake reflect observational, nonrandomized settings.
Onwude et al. 1995[363] UK	Women at risk of PIH or IUGR or with a history of unexplained stillbirth. No in/exclusion criteria related to fish or fish oil intake.	No information on baseline intake or status	Capsules containing 1,620 mg/d EPA, 1,080 mg/d DHA. N=113 Start mostly between 19-26 weeks of gestation.	Air filled capsules N=119	1.22 (0.70-2.13)	1.57 (n.s.)	
Ostadrahimi et al. 2017[249] Iran	Pregnant women. Excluded if allergic to fish or fish products and mothers who consumed more than 2 servings of fish per week	EPA serum phospholipid level: mean 0.15-0.16 (sd 0.1). DHA serum level: mean 0.19 (sd 0.1). *not clear on what scale serum levels were measured.*	180 EPA and 120mg DHA and 400 mg ALA N=75 Start end of 20 weeks of gestation (until 1 month after delivery)	Capsules liquid paraffin N=75	0.75 (0.17-3.24)	n.a.	
Ramakrishnan et al. 2010[364] Mexico	Pregnant women with medium-to-low SES, Excluded if fish oil or DHA supplements were regularly used	Median DHA dietary intake: 55 mg/day (25th centile 38 mg/d; 75th centile 93 mg/d) Median EPA dietary intake: 18 mg/day (25th centile 10 mg/d; 75th centile 37 mg/d)	400 mg/day of algal DHA N=487 Start at 18 to 22 weeks of gestation (until delivery)	Placebo N=486	1.22 (0.82-1.82)	n.a.	
Razavi et al. 2017[256] Iran	Pregnant women with GDM. No in/exclusion criteria related to fish or fish oil intake.	No information on baseline intake or status	360 mg/d EPA + 240 mg/d DHA with or without vitamin D (89 mcg/d) N=60 Start at 24 to 28 weeks of gestation for a duration of 6 weeks	Placebo N=30	0.17 (0.01-4.04)	n.a.	

Reference Country	Study population; in/ exclusion criteria in relation to fish of fish fatty acids intake	Baseline dietary fish intake; baseline fish fatty acids intake; baseline fish fatty acids status	Intervention (fish fatty acid supplement mg/d; n; start moment)	Control (n)	Preterm birth < 37 weeks Effect size (95%CI)	Preterm birth < 34 weeks Effect size (95%CI)	Note
Smuts et al. 2003 – Obstet Gynecol[253] US	Healthy pregnant women. Predominantly women from African-American origin. No in/exclusion criteria related to fish or fish oil intake.	In general women in the US consume little n-3 LCPUFA's, including less than 100 mg DHA per day. Red blood cell phospholipid DHA: intervention group 5.45 g/100g (sd 1.0) fatty acids; control group 5.49 g/100g (sd 1.2) fatty acids.	DHA-enriched eggs (mean 133 mg DHA per egg) – intake average 7.2 eggs per week N=142 Start at 24 to 28 weeks of gestation (until delivery).	Ordinary eggs (mean 33 mg DHA per egg) – intake average 7.3 eggs per week N=149	0.86 (0.44-1.69)	n.a.	
Smuts et al. 2003 - Lipids[252] US	Healthy pregnant women predominantly form African-American origin. No in/exclusion criteria related to fish or fish oil intake.	DHA intake at baseline: intervention group 51 mg/d (sd 19); control group: 104 mg/d (sd 32). Baseline red blood cell plasma concentration: intervention group 4.82 g/100g fatty acids; control group 5 g/100g fatty acids	DHA-enriched eggs (mean DHA 183 mg/d (sd 71.4)) N=18 Start at 24 to 28 weeks of gestation (until delivery)	Ordinary eggs (mean DHA 35.1 mg/d (sd 13.2)) N=19	0.21 (0.03-1.64)	n.a.	
Tofail et al. 2006[365] Bangladesh	Pregnant women with high illiteracy, poverty, overcrowding, poor housing, poor hygiene. No in/exclusion criteria related to fish or fish oil intake.	No information on baseline intake or status	1,200 mg/d DHA and 1,800 mg/d EPA. N=125 Start at 25 weeks of gestation (until delivery)	Soy oil N=124	1.10 (0.70-1.74)	n.a.	
Van Goor et al. 2010[366] Netherlands	Apparently healthy pregnant women Excluded if vegetarian or vegans	The average fish intake in the present study population amounts to 0.94 meals per week, of which 0.45 meals include fatty fish. Fish intake was not different between intervention and control group and did not change over time.[267]	220 mg/d DHA N=42 Start at 14-20 weeks of gestation (most 15.6-17.4 weeks).	Soy oil N=39	0.39 (0.03-2.63)	n.a.	
Vinding et al. 2019[367] Denmark	Healthy pregnant women. Excluded if they used vitamin D-supplements (>15 mcg/d)	Daily fish intake before inclusion: 28 g/d (sd 17 g/d); Pretreatment EPA+DHA blood concentration: 4.9% (sd 1.2%)	1,300 mg/d EPA and 900 mg/d DHA. N=346 Start between 22 to 26 weeks of gestation.	Olive oil N=353	0.87 (0.41-1.86)	n.a.	

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