Health effects related to weight change during pregnancy

No. 2021/26-A4e, 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 document, the effects related to weight change during pregnancy on pregnancy outcomes and offspring health are described. The committee described her working method in a separate background document.[1] The committee did not include health effects for which no systematic review was available, nor health effects for which only one Randomized Controlled Trial (RCT) or cohort study was described in systematic reviews. The committee used a decision tree to formulate the conclusions in the background documents (Appendix A). The conclusions in the background documents are not dietary recommendations; recommendations for pregnant women are formulated in the advisory report.

In this background document on gestational weight change, the standardised approach described in the background document on the working method of the committee[1] is not applied for describing the findings of observational research (see paragraph 2.1). Instead, Chapter 2 includes a short description of two issues:

- The optimal or adequate gestational weight gain range (these criteria are based on observational research).
- The role of pre-pregnancy Body Mass Index (BMI) in the association between gestational weight gain and pregnancy outcomes (observational research shows that the association differs between the BMI groups).

Weight gain during pregnancy consists of the growth of tissues of the child (foetus, placenta, amniotic fluid) and mother (uterus, blood volume, breast tissue, fat reserves), but is also influenced by the mother's degree of fluid retention (oedema). If gestational weight gain is high, it may be due to relatively strong growth of maternal and / or child tissues and / or excessive fluid retention. The origin of the weight gain is, therefore, in a sense a "black box".

The committee carried out systematic literature searches in PubMed to retrieve systematic reviews (with or without meta-analysis) on *a priori* selected exposures. The literature search terms for this advisory report are specified in Appendix B. The initial searches were performed until July 2018 and updated in the summer of 2019 (until July 2019). A public consultation round took place in the autumn of 2019, asking explicitly for potentially missed publications. The committee is, therefore, confident that the relevant publications published until the autumn of 2019 have been considered.

02 observational studies

2.1 The standardised approach of the committee is not applied in this specific background document

The committee has a prevention perspective and therefore describes research in which exposure is determined before outcome

The committee formulates nutritional recommendations for pregnant women to prevent pregnancy complications or other undesirable outcomes. The advisory report is not about the role of nutrition in the treatment of those pregnancy complications. Because of the prevention perspective, the background documents generally describe research in which the exposure (the intake of nutrient or food, the diet) is determined before complications or undesirable outcomes of pregnancy were present. In these studies, it is unlikely that the exposure measurements are influenced by the outcome measures.[1]

Gestational weight change is not a real "exposure", and is determined by the end of pregnancy, when certain outcomes have already developed

This specific background document differs from the other background documents because the "exposure" weight change during pregnancy covers the whole duration of pregnancy, and is therefore partly determined by the weight at the end of the pregnancy, which – in turn – is partly dependent on the duration of pregnancy. Since some outcomes directly affect either the duration of the pregnancy or the body weight at the end of the pregnancy, the "exposure" weight change during pregnancy can be influenced by the outcome measures. These are pregnancy complications that may have an effect on gestational weight gain:

- Preterm birth, by definition, means that the duration of pregnancy is short, so there is less time to gain weight. Therefore, gestational weight gain – on average – is lower when the baby is born preterm compared with at term.
- Women with gestational hypertension and pre-eclampsia are prone to developing more oedema, leading to a higher gestational weight gain.
- The outcome measures large / small birth weight for gestational age (LGA and SGA) are related to gestational weight change, because the weight of the baby is part of the total weight change during pregnancy.
- And in general: pregnancy complications can lead to a medically induced preterm birth, which – on average, like other preterm births – is associated with shorter pregnancy duration and a relatively lower weight change compared with a full-term delivery.

Please note that gestational weight gain, on average, is larger in twin or multiple pregnancies than in singleton pregnancies, but that there is insufficient research on the association between gestational weight gain in twin pregnancies with pregnancy outcomes.[2]

Associations of gestational weight change with pregnancy complications (observational research) may therefore be influenced by *reversed causation*

Due to the effects of outcome measures on the “exposure” gestational weight change, part of the associations between weight change and pregnancy complications can be caused by these complications. For instance: the effect of pre-eclampsia on water retention (oedema) may cause or enhance an association between a higher gestational weight gain and a higher risk of pre-eclampsia. This is called *reversed causation*, because we are interested in the opposite causal pathway: the impact of a relatively high gestational weight gain as a causal factor in the development of pre-eclampsia. In practice, associations between gestational weight change and pregnancy complications may be partly caused by “exposure” and partly by the complication. If *reversed causation* exists, its impact on findings of cohort studies cannot be determined, which complicates etiological interpretations of these data, so that these findings have limited relevance for the committee’s prevention perspective: the formulation of nutritional recommendations for pregnant women for the prevention of undesirable outcomes. This is why the standardised approach[1] to formulating conclusions based on cohort studies on the associations between exposure and outcome is not applied in this background document. Still, the findings in observational studies are used by the committee to address two issues:

- The criteria for determining whether gestational weight gain is adequate, inadequate or excessive, which depend on pre-pregnancy BMI.
- The effect of pre-pregnancy BMI on the association between gestational weight gain and specific pregnancy outcomes.

Please note that intervention studies are not subject to *reversed causation*

In the intervention studies (Chapter 3), pregnant women without complications are randomly divided into groups that receive an intervention or control treatment in order to study whether the intervention has an effect on the development of pregnancy complications or other undesirable outcomes. The assignment to groups and the start of the treatments occurred before the pregnancy complications develop. Therefore, the findings from intervention research are not influenced by the pregnancy complications, i.e. there is no *reversed causation* in the findings from intervention studies.

2.2 Criteria for too low or too high gestational weight gain are widely used and depend on pre-pregnancy BMI

Based on considerations that gestational weight gain may be either too low, adequate, or too high, criteria have been established, using findings from observational research on the associations of a substantial number of adverse pregnancy outcomes (combined) with gestational weight gain.

In 2009, the Institute of Medicine (IOM, now called National Academy of Medicine or NAM) published criteria for an adequate gestational weight gain for women who are underweight, normal weight, overweight, and obese before conception (Table 1).[3,4] The use of these IOM/NAM criteria for an adequate gestational weight gain is widespread.

In 2019, the 'LifeCycle project - Maternal Obesity and Childhood Outcomes Study Group' (from here referred to as 'Lifecycle Study Group') estimated optimal gestational weight gain ranges using an Individual Participant Data analysis from 25 population-based cohorts from Europe, Australia and Canada.[5] Their optimal gestational weight gain ranges were based on odds ratios (ORs) for 'any adverse outcome'. This composite outcome included pre-eclampsia, gestational hypertension, gestational diabetes, caesarean section, preterm birth, small for gestational age, and large for gestational age.

The Lifecycle Study Group calculated odds ratios for 'any adverse outcome' for each 2-kg gestational weight gain range in comparison to all other 2-kg gestational weight gain ranges within the same BMI group (see e-Table 8 of this publication[5]). The optimal gestational weight gain range included all 2-kg gestational weight gain ranges associated with a statistically significant favourable outcome (OR < 1.00). However, if a 2-kg gestational weight gain range with a nonsignificant association was between two 2-kg gestational weight gain ranges with significant associations in the favourable direction, that range was also included in the optimal gestational weight gain range.

Table 1 shows that the optimal gestational weight gain ranges by the Lifecycle Study Group (2019)[5] differ from the adequate gestational weight gain ranges by IOM/NAM (2009)[3]. For women with pre-pregnancy underweight, the Lifecycle Study Group established an optimal gestational weight gain range which is narrower than, but within the adequate range defined by IOM/NAM (Lifecycle Study group: 14-15.9 kg; IOM/NAM: 12.7-18.1 kg). For normal weight women, the Lifecycle Study Group established an optimal gestational weight gain range broader than, but overlapping the adequate gestational weight gain range defined by IOM/NAM (Lifecycle Study group: 10.0-17.9 kg; IOM/NAM: 11.3-15.9 kg). The same applies to overweight women (Lifecycle Study group: 2.0-15.9 kg; IOM/NAM: 6.8-11.3 kg). The ranges for obese women established by the Lifecycle Study Group (2.0-5.9 kg, ≤3.9 kg and 0-5.9 kg for obesity grades 1, 2 and 3, respectively) are shifted towards lower values in comparison with

the adequate range defined by IOM/NAM (5.0-9.1 kg; IOM/NAM did not distinguish between grades of obesity).

The optimal gestational weight gain ranges by the Lifecycle Study Group were established based on a statistically significant association with a lower risk of 'any adverse outcome' (OR < 1.00). Table 2 shows the gestational weight gain ranges with a statistically significant association with a higher risk of 'any adverse outcome' (OR > 1.00). This was observed for underweight women at gestational weight gains below 10 kg, for normal weight women at weight gains either below 8 kg or above 20 kg, for overweight women and women with grade 1 obesity at weight gains above 20 kg, and for women with grade 2 or 3 obesity at weight gains above 16 kg. No statistically significant associations with a higher risk of 'any adverse outcome' were reported for underweight women with gestational weight gains above the optimal range, or for overweight and obese women with gestational weight gains below the optimal range. Had the optimal gestational weight gain ranges been based on statistically significant associations with a higher (instead of a lower) risk of 'any adverse outcome', they would have been broader and one-sided for underweight, overweight and obese women.

Table 1 Criteria for adequate or optimal gestational weight gain (GWG) for singleton pregnancies as established by IOM/NAM (2009)[3] and by the Lifecycle Study Group (2019).[5]

Pre-pregnancy BMI group (BMI-range)	IOM/NAM (2009)[3]: Adequate GWG	Lifecycle Study Group (2019)[5]: Optimal GWG [a]	Lifecycle Study Group (2019)[5]: ORs per 2-kg GWG range compared to all other 2-kg GWG ranges (95%CI) [b]
Underweight (< 18.5)	12.7-18.1 kg	14.0-15.9 kg	0.74 (0.65-0.84) for 14.0-15.9 kg
Normal weight (18.5-24.9)	11.3-15.9 kg	10.0-17.9 kg	0.96 (0.93-0.99) for 10.0-11.9 kg 0.88 (0.86-0.91) for 12.0-13.9 kg 0.87 (0.85-0.90) for 14.0-15.9 kg 0.91 (0.88-0.95) for 16.0-17.9 kg
Overweight (25.0-29.9)	6.8-11.3 kg	2.0-15.9 kg	0.81 (0.69-0.95) for 2.0-3.9 kg 0.90 (0.80-1.01) for 4.0-5.9 kg [d] 0.84 (0.77-0.92) for 6.0-7.9 kg 0.91 (0.85-0.98) for 8.0-9.9 kg 0.89 (0.83-0.94) for 10.0-11.9 kg 0.85 (0.80-0.90) for 12.0-13.9 kg 0.90 (0.85-0.96) for 14.0-15.9 kg
Obese grade 1 (30.0-34.9)	5.0-9.1 kg [c]	2.0-5.9 kg	0.76 (0.64-0.91) for 2.0-3.9 kg 0.73 (0.64-0.84) for 4.0-5.9 kg
Obese grade 2 (35-39.9)	5.0-9.1 kg [c]	≤3.9 kg	0.55 (0.39-0.78) for any weight loss 0.89 (0.70-1.13) for 0.0-1.9 kg [d] 0.67 (0.51-0.88) for 2.0-3.9 kg
Obese grade 3 (≥ 40.0)	5.0-9.1 kg [c]	0-5.9 kg	0.59 (0.41-0.85) for 0.0-1.9 kg 1.39 (0.81-2.39) for 2.0-3.9 kg [d] 0.62 (0.41-0.94) for 4.0-5.9 kg

[a] The optimal GWG ranges by the Lifecycle Study Group (2019[5]) comprised each 2-kg GWG range with a statistically significant protective association (OR < 1) for 'any adverse outcome' compared with all other 2-kg GWG ranges within the same BMI group, as well as GWG ranges with a nonsignificant association lying between two 2-kg GWG ranges with significant estimates and an OR < 1.

[b] OR (95%CI) = Odds Ratio (95% confidence interval) for 'any adverse outcome' per 2 kg range of GWG compared with all other 2-kg GWG ranges within the same BMI group. This table presents the ORs for the 2-kg GWG ranges within the optimal GWG ranges (other/all ORs can be found in e-Table 8 of the Lifecycle Study Group[5]).

[c] IOM/NAM (2009[3]) did not distinguish between grades of obesity.

[d] Although this OR value is not significantly different from 1.00, the Lifecycle Study Group does include the 2-kg GWG range in their optimal GWG range, because it is lying between two 2-kg GWG ranges with significant estimates and an OR < 1 (see footnote a).

Table 2 The optimal GWG range established by the Lifecycle Study Group 2019, along with the GWG ranges below and above the optimal range which show a statistically significant association with a higher risk of 'any adverse outcome' (OR > 1.00; p < 0.05).[a]

Pre-pregnancy BMI group	Lifecycle Study Group: Optimal GWG ranges, based on the association with a significantly lower risk of 'any adverse outcome' (OR < 1.00)[a]	Lifecycle Study Group: Lower GWG range associated with a significantly higher risk of 'any adverse outcome' (OR > 1.00)	Lifecycle Study Group: Higher GWG range associated with a significantly higher risk of 'any adverse outcome' (OR > 1.00)
Underweight (BMI < 18.5)	14.0-15.9 kg	<10 kg	None (NS [c])
Normal weight (BMI 18.5-24.9)	10.0-17.9 kg	<8 kg [b]	≥ 20 kg
Overweight (BMI 25.0-29.9)	2.0-15.9 kg	None (NS [c])	≥ 20 kg
Obese grade 1 (BMI 30.0-34.9)	2.0-5.9 kg	None (NS [c])	≥ 20 kg
Obese grade 2 (BMI 35-39.9)	≤3.9 kg	None (not applicable [d])	≥ 16 kg
Obese grade 3 (BMI ≥ 40.0)	0-5.9 kg	None (NS [c])	≥ 16 kg

[a] Based on e-Table 8 of the publication by the Lifecycle Study Group 2019. Odds ratios for 'any adverse outcome' were estimated for each 2-kg GWG range by comparison with all other 2-kg GWG ranges within the same BMI group. The optimal GWG ranges are also presented in Table 1.
[b] In normal weight women, a GWG between 8 and 9.9 kg was associated with a higher risk of 'any adverse outcome' reaching borderline statistical significance (OR > 1.00; p=0.05).
[c] NS = the ORs for all 2-kg GWG ranges lower/higher than the optimal GWG range showed no statistically significant difference from 0.00.
[d] Not applicable, because for obese grade 2, the Lifecycle Study Group procedure resulted in an optimal GWG range without a lower limit (≤3.9 kg).

Based on visual inspection, Figure 2 of the publication of the Lifecycle Study Group[5] provides some information on the nature of the risks associated with gestational weight gains outside the optimal range.

In underweight and normal weight women, gestational weight gains below the optimal range appear to be associated with:

- higher risks of SGA and preterm birth,
- lower risks of LGA.

In normal weight, overweight and obese women, gestational weight gains above the optimal range appear to be associated with:

- higher risks of LGA, gestational hypertension, pre-eclampsia, and caesarean section,
- lower risks of SGA and preterm birth.

Figure 2 of the publication of the Lifecycle Study Group[5] also shows that the absolute risk of 'any adverse outcome' increases gradually over the groups of women with increasing pre-pregnancy BMI categories.

2.3 Summary of findings from cohort studies

The findings in observational studies on the associations of gestational weight change with pregnancy complications may be influenced by *reversed causation*. However, it is clear that gestational weight gains within the optimal range are associated with lower risks of unfavourable outcomes and that the risks differ between categories of pre-pregnancy BMI. The specific unfavourable outcomes associated with gestational weight gains above the optimal range differ from those associated with gestational weight gains below the optimal range.

03
interventions for gestational weight gain management

In this chapter, the effects of interventions aiming at the prevention of excessive gestational weight gain on pregnancy outcomes are reviewed. The committee found no systematic review on the effects of interventions aiming at the prevention of low gestational weight gain.

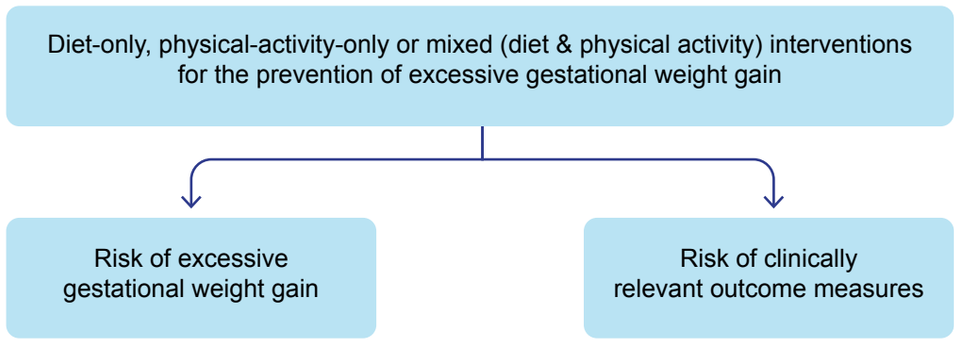
3.1 Specific considerations on the intervention research described in this background document

Conclusions on the effects of the interventions (not of gestational weight gain)

The advisory report and background documents focus on whether the diet offers possibilities to lower the risk of pregnancy complications and other undesirable outcomes. As observational studies have limitations, particularly regarding the “exposure” gestational weight change as a potential cause of pregnancy outcomes, this background document focuses on the findings of intervention studies. In general, RCTs study the direct effects of interventions on outcomes. However, the effect of gestational weight gain on outcomes cannot be studied in a direct way, as gestational weight gain is not an “exposure” which can be modified in a direct way. Gestational weight gain is, in fact, one of the outcomes of these intervention studies (Figure 1). Therefore, the conclusions in this chapter are not about the effects of gestational weight gain, but about the effects of the interventions.

Only studies with an effect on the risk of excessive (or low) gestational weight gain can provide insight on the importance of achieving an adequate/optimal gestational weight gain for the risk of pregnancy outcomes. Therefore, the committee describes not only the effects of interventions on clinically relevant outcomes, but also the effect on gestational weight gain.

Figure 1 Available research for evaluating the effect of gestational weight gain on outcomes, in relation to the causal pathway.



The advisory report addresses dietary recommendations, but this background document covers effects of physical-activity and mixed interventions as well

Interventions aiming to prevent excessive gestational weight gain are diet-only interventions[a], physical-activity-only interventions or mixed (diet & physical activity) interventions. The advisory report is specifically about dietary recommendations, not about recommendations on physical activity. However, if this chapter were restricted to dietary (caloric) interventions only, then the major part of the available research on "gestational weight gain interventions" would not be considered, and information with potential relevance to dietary recommendations could be missed. Therefore, the committee describes in this chapter not only the findings for dietary-only interventions but also the findings for physical-activity-only interventions and mixed (diet & physical activity). Conclusions are formulated separately for each of the three intervention types.

The committee considered that the findings from RCTs with mixed (diet & physical activity) interventions or even physical-activity-only interventions may be relevant for dietary recommendations if the effects appear to be similar across these different types of interventions. However, if there are too many inconsistencies between the conclusions for different intervention types, the committee will consider that the findings from RCTs with diet-only interventions are relevant for the formulation of dietary recommendations, whereas the findings from mixed (diet & physical activity) interventions and physical-activity-only interventions are not.

Selection of systematic reviews

As described in the background document on the working method for drawing up dietary recommendations for pregnant women[1], the committee's primary search was for meta-analyses of RCTs.

The committee found eight systematic reviews. The five oldest reviews[6-10] are not further described because all RCTs in these publications were considered (and either included or excluded) in the three more recent systematic reviews:

- The International Weight Management in Pregnancy Collaborative Group (i-WIP; 2017) published both pooled analyses of individual participant data (IPD analyses) and meta-analyses in which these data were combined with group-level data (IPD+non-IPD analyses); the IPD+non-IPD analyses combine RCTs providing IPD data with the RCTs not providing IPD data. The i-WIP Collaboration reported on a number of outcomes and their literature search included studies published until February 2017.[11]
- Muktabhant et al. (2015)[12] carried out meta-analyses of group-level data on a number of outcomes, based on studies published until November 2014.
- Bennett et al. (2018)[13] carried out meta-analyses of group-level data on

[a] Please note that the preventive effects of other nutritional interventions, i.e. interventions on diet quality instead of energy intake, are evaluated in the other background documents.

RCTs on the outcome gestational diabetes mellitus, based on RCTs published up to 2016.
- Syngelaki et al. (2019)[14] reviewed the outcome hypertensive disorders of pregnancy and included one RCT which had not been included by i-WIP.

These three systematic reviews state having specifically selected RCTs with interventions aiming at the prevention of excessive gestational weight gain.

i-WIP presented meta-analyses based on Individual Participant Data (IPD) and the combination of these IPD data with additional group-level data (IPD+non-IPD)

The i-WIP Collaboration[11] selected the largest number of RCTs. Their results are presented in the following paragraphs. The i-WIP publication presents meta-analyses of Individual Participant Data (IPD analyses) and meta-analyses of these IPD data combined with additional group-level data (IPD+non-IPD analyses). The committee describes the findings from both the IPD analyses and the IPD+non-IPD analyses. Although the adjustment for possible confounders is methodologically better in the IPD analyses, the number of included trials is (substantially) larger in the IPD+non-IPD analyses.

The primary outcomes by i-WIP were:
- gestational weight gain,
- the maternal composite outcome (this composite outcome comprised gestational diabetes mellitus, pre-eclampsia or pregnancy-induced hypertension, preterm delivery and caesarean section),
- the offspring (foetal and neonatal) composite outcome (this composite outcome comprised intrauterine death, small for gestational age, large for gestational age and admission to the neonatal intensive care unit).

The committee describes findings on specific outcomes; composite outcomes are not part of the committee's approach.[1] The findings on specific outcomes were secondary analyses by i-WIP. Information on sources of heterogeneity (sensitivity analyses, subgroup analyses) is only available for the outcome gestational weight gain but not for any of the other specific outcomes described in this background document because i-WIP investigated the sources of heterogeneity only for both composite outcomes. However, the i-WIP-authors do mention one thing on individual maternal and offspring outcomes: for all intervention types combined, they did not observe any differential effect according to baseline BMI.

Please note that the subgroup analyses presented by i-WIP for the primary outcomes generally relate to all intervention types combined and not the specific intervention types. These i-WIP subgroup analyses and sensitivity analyses for all interventions combined on both composite outcomes revealed no significant treatment-covariate interactions for baseline BMI, nor significant subgroup effects for age, parity, ethnicity, and underlying medical condition.

i-WIP mentioned that they observed significant evidence for small study effects (potential publication bias) for the maternal composite outcome but not for the offspring composite outcome.

Other meta-analyses were used to retrieve additional RCTs

The other meta-analyses were used to retrieve RCTs which had not been included in i-WIP. These additional RCTs are presented in paragraphs 3.2 to 3.9 only if the intervention lowered gestational weight gain by at least 0.5 kg (this cut-off point was arbitrarily chosen as an indication that the intervention had at least some effect on gestational weight gain).

Muktabhant et al. (2015)[12] reviewed diet-only interventions. They included RCTs on low-glycaemic-diets which had not been included by i-WIP. Furthermore, part of the RCTs with interventions classified by Muktabhant et al. as “other types of diet counselling” were not included in the i-WIP analyses either:

- Louie 2011 (diet-only intervention),
- Rhodes 2010 (diet-only intervention),
- ROLO 2012 (diet-only intervention),
- Jeffries 2009 (diet-only intervention),
- Quinlivan 2011 (diet-only intervention).

Bennett et al. (2018)[13] reviewed the outcome gestational diabetes mellitus and included five RCTs which had not been included by i-WIP[a]:

- Jiang 2015 (mixed intervention),
- Liao 2012 (diet-only intervention),
- Xiao 2015 (diet-only intervention),
- Zhang 2015 (mixed intervention).

Syngelaki et al. (2018)[14] reviewed the outcome hypertensive disorders of pregnancy and included one RCT which had not been included by i-WIP: Peccei 2017 (diet-only intervention).

The literature search by the committee resulted in one additional RCT, published after the i-WIP publication: the RCT by Bruno et al. (2017).[15] The intervention included caloric restriction and increased physical activity but did not lower gestational weight gain (the average gestational weight gain in the intervention group was 0.4 kg higher than in the control group; statistically not significant). Therefore, the RCT was considered not relevant for this background document on the effects of interventions aiming at lowering gestational weight gain.

[a] Zhang 2012 was excluded because the participants included in this RCT were pregnant women with gestational diabetes. The committee is interested in the effects of interventions on the risk of developing gestational diabetes in pregnant women without gestational diabetes at baseline.

3.2 Gestational weight gain

Summary: The effect on gestational weight gain of diet-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from four RCTs and one meta-analysis of IPD+non-IPD data from 12 RCTs.[11] Eight additional RCTs.
Heterogeneity	IPD analysis: No; IPD+non-IPD analysis: Yes.
Strength of the effect	IPD analysis: -0.72 kg (-1.48 to +0.04 kg); IPD+non-IPD analysis: -2.84 kg (-4.77 to -0.91 kg). Effect estimates of eight additional RCTs varied between -0.40 and -6.80 kg (three RCTs p>0.05; five RCTs p≤0.05).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

Diet-only interventions aiming at the prevention of excessive gestational weight gain reduce gestational weight gain.

Level of evidence: Strong.

Summary: The effect on gestational weight gain of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 13 RCTs and one meta-analysis of IPD+non-IPD data from 23 RCTs.[11]
Heterogeneity	No
Strength of the effect	IPD analysis: -0.73 kg (-1.11 to -0.34 kg); IPD+non-IPD analysis: -0.72 kg (-1.04 to -0.41 kg).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

Physical-activity-only interventions aiming at the prevention of excessive gestational weight gain reduce gestational weight gain by, on average, 0.7 kg (95% confidence interval -1.11 kg to -0.34 kg).

Level of evidence: Strong.

Summary: The effect on gestational weight gain of mixed interventions (diet and physical activity) to prevent excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 16 RCTs and one meta-analysis of IPD+non-IPD data from 36 RCTs.
Heterogeneity	IPD analysis: No; IPD+non-IPD analysis: Yes.
Strength of the effect	IPD analysis: -0.71 kg (-1.10 to -0.31 kg); IPD+non-IPD analysis: -1.00 kg (-1.39 to -0.61 kg). Effect estimates of two additional RCTs were -2.2 kg (p<0.05) and -1.7 kg (p>0.05).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

Mixed interventions aiming at the prevention of excessive gestational weight gain reduce gestational weight gain by, on average, 1 kg (95% confidence interval -1.39 kg to -0.61 kg).

Level of evidence: Strong.

Explanation

The results of the meta-analyses regarding the effects on gestational weight gain are summarised in Table 3. The committee notes that, despite the fact that the IPD analyses by i-WIP included only participants adhering to the protocol, ten of the 33 RCTs included in this IPD analysis showed a mean effect on gestational weight gain smaller than 0.5 kg. The i-WIP Collaboration did not provide analyses excluding RCTs in which the interventions did not result in a (significant) lowering on gestational weight gain.

The finding by i-WIP[11] on the effect of diet-only interventions aiming at the prevention of excessive gestational weight gain showed a significant reduction of gestational weight gain in the IPD+non-IPD analysis (12 RCTs), but not in the IPD analysis (four RCTs).

From other meta-analyses, eight additional RCTs were retrieved, comprising in total slightly more participants (n=2,284) than the IPD+non-IPD analysis by i-WIP (n=2,017). These eight RCTs all reported a lower gestational weight gain in the intervention group compared with the control group. The effect was statistically significant in five of the eight additional RCTs.

The number of RCTs (≥5) and participants (≥150) were sufficient for a strong evidence level. The committee considers that diet-only interventions aiming at the prevention of excessive gestational weight gain lower gestational weight gain. The (mean) differences and 95% confidence intervals varied substantially and heterogeneity was substantial in the IPD+non-IPD analysis. Furthermore, the IPD+non-IPD analysis and five additional RCTs showed a significant effect, but the IPD analysis and three additional RCTs did not. Therefore, the committee does not quantify the effect on gestational weight gain, despite the strong level of evidence.
The finding by i-WIP[11] on the effect of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain showed a significant reduction of gestational weight gain in both the IPD analysis (15 RCTs) and the IPD+non-IPD analysis (37 RCTs).

The number of RCTs (≥5) and participants (≥150) were sufficient for a strong evidence level. The mean differences between intervention and control groups were similar for the IPD analysis (-0.73 kg) and the IPD+non-IPD analysis (-0.72 kg). Therefore, the committee considers that physical-activity-only interventions aiming at the prevention of excessive gestational weight gain lower gestational weight gain by, on average, 0.7 kg (-1.1 to -0.3 kg).
The finding by i-WIP[11] on the effect of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain showed a significant reduction of gestational weight gain in the IPD analysis (15 RCTs) and in the IPD+non-IPD analysis (35 RCTs). From other meta-analyses, two additional RCTs were retrieved: one showed a signifi-

cant reduction of gestational weight gain and the other showed a reduction which was not significant.

The number of RCTs (≥5) and participants (≥150) were sufficient for a strong evidence level. The committee considers that mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain lower gestational weight gain, by, on average, 1 kg (-2.2 to -0.3 kg). The evidence level is strong.

Please note that i-WIP mentioned that they observed small study effects (potential publication bias) for both the IPD and the IPD+non-IPD analyses regarding the effect of all interventions combined on gestational weight gain. When studies with a high risk of bias were excluded from the analysis, there was no evidence for publication bias.

The reduction in gestational weight gain was consistently observed when the IPD analysis was restricted to studies with a low risk of bias (-0.67 kg; 95% confidence interval -0.95 to -0.38 kg; 15 studies, 5,585 women), women adherent to the intervention (-0.76 kg; 95% confidence interval -1.00 to -0.52 kg; 33 studies, 8,565 women), and women followed up until more than 37 weeks' gestation (-0.91 kg; 95% confidence interval -1.17 to -0.66 kg; 28 studies, 5,324 women).

i-WIP mentions the larger effect estimate in IPD+non-IPD analyses compared with IPD analyses, but does not elaborate on possible explanations for this finding.

i-WIP also described the results of subgroup analyses and sensitivity analyses for all interventions combined on gestational weight gain but not for the three specific intervention types separately. These analyses revealed no significant treatment-covariate interactions for baseline BMI, nor significant subgroup effects for age, parity, ethnicity, and underlying medical condition.

Table 3 The effect of interventions aiming at the prevention of excessive gestational weight gain on gestational weight gain in kilograms in the publication by the i-WIP Collaboration.[11]

Publication	Study type	Type of intervention	Number of RCTs (women)	Intervention group mean in kg (SD)	Control group mean in kg (SD)	Mean difference (kg)	95%CI	Heterogeneity I^2 (%)
i-WIP [11]	IPD	Diet only	4 (1,168)	10.2 (4.4)	11.0 (4.8)	-0.72	-1.48 to +0.04	0%
i-WIP [11]	IPD+non-IPD	Diet only	12 (2,017)	9.2 (n.a.)	11.7 (n.a.)	-2.84	-4.77 to -0.91	92%
Louie 2011 [b]	RCT	Diet-only	1 (87)	11.9 (4.6)	13.1 (5.9)	-1.20	-3.43 to +1.03	n.a.
Jeffries 2009 [b]	RCT	Diet-only	1 (236)	10.7 (4.2)	11.5 (4.0)	-0.80	-1.85 to +0.25	n.a.
Rhodes 2010 [b]	RCT	Diet-only	1 (38)	6.4 (4.5)	6.9 (4.2)	-0.50	-3.29 to +2.29	n.a.
ROLO 2012 [b]	RCT	Diet-only	1 (759)	12.2 (4.4)	13.7 (4.9)	-1.50	-2.16 to -0.84	n.a.
Quinlivan 2011 [b]	RCT	Diet-only	1 (124)	7.0 (5.2)	13.8 (5.2)	-6.80	-8.63 to -4.97	n.a.
Peccei 2017 [c]	RCT	Diet-only	1 (255)	11.0 (0.4)	12.2 (0.7)	-1.47	-1.97 to -0.97	n.a.
Liao 2012 [d]	RCT	Diet-only	1 (200)	13.2 (3.1)	15.6 (3.6)	-2.41	n.r. (p<0.05)	n.a.
Xiao 2015 [d]	RCT	Diet-only	1 (585)	14.9 (2.0)	15.3 (2.1)	-0.40	n.r. (p<0.05)	n.a.
i-WIP [11]	IPD	Physical-activity-only	15 (2,915)	9.8 (4.4)	10.8 (4.8)	-0.73	-1.11 to -0.34	0%
i-WIP [11]	IPD+non-IPD	Physical-activity-only	37 (7,355)	11.3 (n.a.)	11.9 (n.a.)	-0.72	-1.04 to -0.41	45%
i-WIP [11]	IPD	Mixed	15 (5,369)	10.2 (6.0)	10.6 (5.9)	-0.71	-1.10 to -0.31	35%
i-WIP [11]	IPD+non-IPD	Mixed	35 (8,448)	10.3 (n.a.)	11.0 (n.a.)	-1.00	-1.39 to -0.61	55%
Jiang 2015 [d]	RCT	Mixed	1 (200)	15.2 (1.9)	17.4 (2.1)	-2.2	n.r. (p<0.01)	n.a.
Zhang 2015 [d]	RCT	Mixed	1 (213)	12.5 (0.5)	14.2 (0.7)	-1.7	n.r. (p>0.05)	n.a.

CI: confidence interval; IPD: Individual Participant Data; i-WIP: International Weight Management in Pregnancy Collaborative Group; n.a.: not applicable; n.r.: not reported; RCT, randomised controlled trial; SD, standard deviation.

[a] The i-WIP IPD+non-IPD analyses are meta-analyses of group-level data, and include RCTs with and without IPD data.

[b] Additional RCT retrieved from the meta-analysis by Muktabhant et al. (2015).[1,2]

[c] Additional RCT retrieved from the meta-analysis by Syngelaki et al. (2018).[14]

[d] Additional RCT retrieved from the meta-analysis by Bennett et al. (2018).[13]

3.3 Foetal death (stillbirth)

Summary: The effect on the risk of stillbirth of interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One meta-analysis of Individual participant data (IPD) from two RCTs; one meta-analysis of IPD+non-IPD data from four RCTs.[11]
Heterogeneity	No
Strength of the effect	IPD meta-analysis: only two RCTs. IPD+non-IPD meta-analysis: RR = 0.85 (0.24 to 3.02). Too few cases in the intervention and control arms.
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

There is too little research to draw a conclusion on the effect of interventions aiming at the prevention of excessive gestational weight gain (all interventions combined) on the risk of stillbirth.

Explanation

The i-WIP Collaboration (2017)[11] presented findings on stillbirth for all interventions combined (Table 4).

The meta-analyses showed no effect and included too few (<60) cases both in the intervention and control arms (IPD and IPD+non-IPD analysis) to formulate a conclusion.

In addition, the IPD analysis comprised too few (≤2) RCTs. The committee considers that there is too little research to draw a conclusion on the effect of interventions aiming at the prevention of excessive gestational weight gain.

Table 4 The effect on the risk of stillbirth of interventions aiming at the prevention of excessive gestational weight gain. Overall analyses (effects for specific intervention types were not reported).

Publication	Study type	Number of RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2 (%)
i-WIP [11]	IPD	2	9 / 1,867	11 / 1,852	0.81	<0.01 to 256.69	0%
i-WIP [11]	IPD+non-IPD [a]	4	12 / 2,273	14 / 2,261	0.85	0.24 to 3.02	0%

CI: confidence interval; IPD: Individual Participant Data; i-WIP: International Weight Management in Pregnancy Collaborative Group; n / N: number of cases/total number of participants; RR: relative risk.
[a] The i-WIP IPD+non-IPD analyses are meta-analyses of group-level data and include RCTs with and without IPD data.

3.4 Preterm birth

Summary: The effect on the risk of preterm birth of diet-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from four RCTs and one meta-analysis of IPD+non-IPD data from seven RCTs.[11] Four additional RCTs.
Heterogeneity	No
Strength of the effect	IPD analysis: RR = 0.28 (0.08-0.96); IPD+non-IPD analysis: RR = 0.32 (0.14-0.70).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

Diet-only interventions aiming at the prevention of excessive gestational weight gain reduce the risk of preterm birth.

Level of evidence: Limited.

Summary: The effect on the risk of preterm birth of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 13 RCTs and one meta-analysis of IPD+non-IPD data from 23 RCTs.[11]
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 1.09 (0.90-1.85); IPD+non-IPD analysis: RR = 1.29 (0.84-1.41).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effect of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain on the risk of preterm birth are inconclusive.

Summary: The effect on the risk of preterm birth of mixed interventions (diet and physical activity) to prevent excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 16 RCTs and one meta-analysis of IPD+non-IPD data from 36 RCTs.
Heterogeneity	No.
Strength of the effect/ association	IPD analysis: RR = 0.91 (0.73-1.12); IPD+non-IPD analysis: RR = 0.92 (0.75-1.12).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effect of mixed interventions aiming at the prevention of excessive gestational weight gain on the risk of preterm birth are inconclusive.

Explanation

The results of the meta-analyses regarding the risk of preterm birth are summarised in Table 5, on page 22.

Diet-only interventions showed a statistically significant reduced risk of an effect on preterm birth and the risk estimates in the additional RCTs were below 1.00. In both the IPD and the IPD+non-IPD meta-analyses, heterogeneity was low and the number of RCTs was sufficient (≥3). However, in the IPD analysis the number of cases was not sufficient (<60 in both the intervention and the control arms).

The number of cases was not sufficient either in the IPD plus IPD+non-IPD analysis, but if the additional RCTs were added, all IPD+non-IPD control groups combined did comprise sufficient cases for formulating a conclusion (≥60 cases: 45+4+8+4+1=62 cases).

Therefore, the committee considers that diet-only interventions aiming at the prevention of excessive gestational weight gain reduce the risk of preterm birth. The level of evidence is limited, because the number of cases was larger than 60 but less than 100.

Physical-activity-only interventions showed no statistically significant effect on preterm birth, and heterogeneity was low. There were sufficient RCTs (≥5) and cases (≥100 in both the intervention arm and the control arm), but the risk estimates (1.29 and 1.09) were not close to 1.00. Therefore, the committee considers that the findings on the effect of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain on the risk of preterm birth are inconclusive.

Mixed (diet and physical activity) interventions showed no statistically significant effect on preterm birth, and heterogeneity was low to moderate. There were sufficient RCTs (≥5) and cases (≥100 in both the intervention arm and the control arm), but the risk estimates (0.91 and 0.92) were not close to 1.00.

Therefore, the committee considers that the findings on the effect of mixed interventions aiming at the prevention of excessive gestational weight gain on the risk of preterm birth are inconclusive.

Table 5 The effect on the risk of preterm birth of interventions aiming at the prevention of excessive gestational weight gain on the risk of preterm birth.

Publication	Study type	Type of intervention	Number of RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2 (%)
i-WIP [11]	IPD	Diet-only	4	9 / 656	35 / 688	0.28	0.08 to 0.96	0%
i-WIP [11]	IPD+non-IPD [a]	Diet-only	7	13 / 832	45 / 864	0.32	0.14 to 0.70	0%
Rhodes 2010 [b]	RCT	Diet-only	1	1 / 24	4 / 24	0.22	0.03 to 1.81	n.a.
ROLO 2012 [b]	RCT	Diet-only	1	3 / 372	8 / 387	0.39	0.10 to 1.46	n.a.
Jeffries 2009 [b]	RCT	Diet-only	1	3 / 124	4 / 111	0.67	0.15 to 2.93	n.a.
Quinlivan 2011 [b]	RCT	Diet-only	1	1 / 63	1 / 61	0.97	0.06 to 15.14	n.a.
i-WIP [11]	IPD	Physical-activity-only	13	95 / 1,636	73 / 1,613	1.29	0.90 to 1.85	0%
i-WIP [11]	IPD+non-IPD [a]	Physical-activity-only	23	160 / 2,591	148 / 2,558	1.09	0.84 to 1.41	0%
i-WIP [11]	IPD	Mixed	16	228 / 3,753	243 / 3,466	0.91	0.73 to 1.12	0%
i-WIP [11]	IPD+non-IPD [a]	Mixed	36	241 / 3,962	256 / 3,668	0.92	0.75 to 1.12	32%

CI: confidence interval; IPD: Individual Participant Data; i-WIP: International Weight Management in Pregnancy Collaborative Group; n / N: number of cases / total number of participants; RR: relative risk.

[a] The i-WIP IPD+non-IPD analyses are meta-analyses of group-level data, and include RCTs with and without IPD data.

[b] Data extracted from the meta-analysis by Muktabhant et al.[12]

3.5 Small for gestational age

Summary: The effect on the risk of a small for gestational age infant of diet-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from four RCTs and one meta-analysis of IPD+non-IPD data from seven RCTs.[11] Two additional RCTs.
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 0.92 (0.45-1.88); IPD+non-IPD analysis: RR = 1.05 (0.62-1.77).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

There is too little research for a conclusion on the effect of diet-only interventions aiming at the prevention of excessive gestational weight gain on the risk of a small for gestational age infant.

Summary: The effect on the risk of a small for gestational age infant of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 14 RCTs and one meta-analysis of IPD+non-IPD data from 21 RCTs.[11]
Heterogeneity	IPD analysis: No; IPD+non-IPD analysis: Yes.
Strength of the effect	IPD analysis: RR = 1.05 (0.84-1.34); IPD+non-IPD analysis: RR = 1.01 (0.83-1.24).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effect of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain on the risk of a small for gestational age infant are inconclusive.

Summary: The effect on the risk of a small for gestational age infant of mixed interventions (diet and physical activity) aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 16 RCTs and one meta-analysis of IPD+non-IPD data from 20 RCTs.
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 1.08 (0.92-1.28); IPD+non-IPD analysis: RR = 1.08 (0.93-1.27).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effect of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain on the risk of a small for gestational age infant are inconclusive.

Explanation

The results of the meta-analyses regarding the risk that the baby is small for gestational age (birth weight <10th centile for gestational age) are summarised in Table 6, on page 25.

Diet-only interventions showed no statistically significant effect on the risk of a small for gestational age infant. Heterogeneity was low, but the 95% confidence interval was relatively broad. The IPD+non-IPD analysis included six RCTs and – in addition - there were two extra RCTs, so that the total number of RCTs was eight (≥5). However, the number of cases per arm was less than 100. The risk estimates (0.92 and 1.05) were not close to 1.00 and were not statistically significant. Therefore, the committee concludes that there was too little research for a conclusion.

Physical-activity-only interventions showed no statistically significant effect on the risk of a small for gestational age infant. Heterogeneity was low in the IPD analysis, but substantial in the IPD+non-IPD analysis. The risk estimates (1.05 and 1.01) were close to 1.00 and there were sufficient RCTs (≥5) and cases (≥100 in both the intervention arm and the control arm). Because of the wide confidence interval in both IPD and non-IPD analyses and the substantial heterogeneity in the non-IPD analysis, the committee concludes that the effect of physical-activity-only interventions on the risk of a small for gestational age infant is inconclusive.

Mixed interventions (diet and physical activity) showed no statistically significant effect on the risk of a small for gestational age infant. Heterogeneity was low in both the IPD analysis and the IPD+non-IPD analysis. The number of cases was more than 100 in both arms, but the risk estimates (1.08 and 1.08) were neither close to 1.00, nor statistically significant. Therefore, the committee concludes that the findings are inconclusive.

Table 6 The effect of interventions aiming at the prevention of excessive gestational weight gain on the risk of a small for gestational age infant (birth weight < 10th centile).

Publication	Type of study	Type of intervention	Number of RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2 (%)
i-WIP [11]	IPD	Diet-only	4	41 / 651	47 / 686	0.92	0.45 to 1.88	0%
i-WIP [11]	IPD+non-IPD	Diet-only	6	56 / 802	55 / 826	1.05	0.62 to 1.77	0%
Louie 2011 [b]	RCT	Diet-only	1	5 / 47	4 / 45	1.20	0.34 to 4.18	n.a.
Jeffries 2009 [b]	RCT	Diet-only	1	1 / 124	1 / 111	0.90	0.06 to 14.14	n.a.
i-WIP [11]	IPD	Physical-activity-only	14	243 / 1,645	232 / 1,627	1.05	0.84 to 1.34	12%
i-WIP [11]	IPD+non-IPD	Physical-activity-only	21	274 / 2,014	271 / 1,941	1.01	0.83 to 1.24	52%
i-WIP [11]	IPD	Mixed	16	425 / 3,737	370 / 3,456	1.08	0.92 to 1.28	0%
i-WIP [11]	IPD+non-IPD	Mixed	20	443 / 3,975	386 / 3,695	1.08	0.93 to 1.27	0%

CI: confidence interval; IPD: Individual Participant Data; i-WIP: International Weight Management in Pregnancy Collaborative Group; n / N: number of cases / total number of participants; RR: relative risk.

[a] The i-WIP IPD+non-IPD analyses are meta-analyses of group-level data, and include RCTs with and without IPD data.

[b] Data extracted from the meta-analysis by Muktabhant et al.[12]

3.6 Large for gestational age

Summary: The effect on the risk of a large for gestational age infant of diet-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from four RCTs and one meta-analysis of IPD+non-IPD data from six RCTs.[11] Three additional RCTs.
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 0.91 (0.60-1.37); IPD+non-IPD analysis: RR = 0.82 (0.54-1.22).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effect of diet-only interventions aiming at the prevention of excessive gestational weight gain on the risk of a large for gestational age infant are inconclusive.

Summary: The effect on the risk of a large for gestational age infant of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 15 RCTs and one meta-analysis of IPD+non-IPD data from 21 RCTs.[11]
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 0.96 (0.59-1.54); IPD+non-IPD analysis: RR = 0.96 (0.67-1.37).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

An effect of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain on the risk of a large for gestational age infant is unlikely.

Summary: The effect on the risk of a large for gestational age infant of mixed interventions (diet and physical activity) aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 16 RCTs and one meta-analysis of IPD+non-IPD data from 21 RCTs.[11]
Heterogeneity	IPD analysis: Yes; IPD+non-IPD analysis: No.
Strength of the effect	IPD analysis: RR = 0.89 (0.67-1.17); IPD+non-IPD analysis: RR = 0.83 (0.83-1.10).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effects of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain on the risk of a large for gestational age infant are inconclusive.

Explanation

The results of the meta-analyses regarding the risk that the baby is large for gestational age (birth weight >90th centile for gestational age) are summarised in Table 7, on page 27.

Both diet-only and mixed (diet and physical activity) interventions showed no significant effect on the risk of a large for gestational age infant. In the IPD+non-IPD analyses there were sufficient RCTs (≥5) and cases (≥100 in the intervention and control arms), but the risk estimates were not close to 1.00. Because these risk estimates were not statistically significant, the committee considers that these findings are inconclusive.

Physical-activity only interventions showed no significant effect on the risk of a large for gestational age infant. These risk estimates were very close to 1.00, and there were sufficient numbers of RCTs (≥5) and cases (≥100 in both the intervention-arm and the control-arm). Therefore, the committee considers that it is unlikely that physical-activity-only interventions aiming at the prevention of excessive gestational weight gain have an effect on the risk of a large for gestational age infant.

Table 7 The effect of interventions aiming at the prevention of excessive gestational weight gain on the risk of a large for gestational age infant.

Publication	Type of study	Type of intervention	Number of RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2 (%)
i-WIP [11]	IPD	Diet-only	4	155 / 684	176 / 724	0.91	0.60 to 1.37	0%
i-WIP [11]	IPD+non-IPD	Diet-only	6	172 / 835	203 / 864	0.82	0.54 to 1.22	0%
Louie 2011 [b]	RCT	Diet-only	1	6 / 47	2 / 45	2.87	0.61 to 13.50	n.a.
Rhodes 2010 [b]	RCT	Diet-only	1	2 / 24	3 / 21	0.58	0.11 to 3.16	n.a.
Jeffries 2009 [b]	RCT	Diet-only	1	8 / 124	11 / 111	0.65	0.27 to 1.56	n.a.
i-WIP [11]	IPD	Physical-activity-only	15	121 / 1,678	124 / 1,652	0.96	0.59 to 1.54	34%
i-WIP [11]	IPD+non-IPD	Physical-activity-only	21	159 / 2,001	161 / 1,929	0.96	0.67 to 1.37	7%
i-WIP [11]	IPD	Mixed	16	468 / 3,874	481 / 3,576	0.89	0.67 to 1.17	51%
i-WIP [11]	IPD+non-IPD	Mixed	21	489 / 4,169	523 / 3,871	0.83	0.83 to 1.10	4%

CI: confidence interval; IPD: Individual Participant Data; i-WIP: International Weight Management in Pregnancy Collaborative Group; n.a.: not applicable; n / N: number of cases / total number of participants; RR: relative risk.

[a] The i-WIP IPD+non-IPD analyses are meta-analyses of group-level data, and include RCTs with and without IPD data.

[b] Data extracted from the meta-analysis by Muktabhant et al.[12]

3.7 Gestational diabetes mellitus

Summary: The effect on the risk of gestational diabetes of diet-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from four RCTs and one meta-analysis of IPD+non-IPD data from eight RCTs.[11] Three additional RCTs.
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 1.03 (0.30 to 3.61); IPD+non-IPD analysis: RR = 0.79 (0.37 to 1.69).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effect of diet-only interventions aiming at the prevention of excessive gestational weight gain on the risk of gestational diabetes are inconclusive.

Summary: The effect on the risk of gestational diabetes of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from ten RCTs and one meta-analysis of IPD+non-IPD data from 27 RCTs.[11]
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 0.67 (0.46 to 0.99); IPD+non-IPD analysis: RR = 0.66 (0.53 to 0.83).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

Physical-activity-only interventions aiming at the prevention of excessive gestational weight gain lead to a 33% (95% confidence interval -54% to -1%) lower risk of gestational diabetes.

Level of evidence: Strong.

Summary: The effect on the risk of gestational diabetes of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 14 RCTs and one meta-analysis of IPD+non-IPD data from 27 RCTs.[11] Two additional RCTs.
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 1.02 (0.79 to 1.32); IPD+non-IPD analysis: RR = 0.88 (0.72 to 1.07).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

The findings on the effect of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain on the risk of gestational diabetes are inconclusive.

Explanation

The results of the meta-analyses regarding the risk of gestational diabetes are summarised in Table 8, on page 30.

Diet-only interventions showed no significant effect on the risk of gestational diabetes, and in the IPD analysis, there were too few RCTs and cases (<5 and <100, respectively). In the IPD+non-IPD analysis, the number of RCTs was sufficient (≥5), but the number of cases per arm was too small (<100). However, the meta-analysis by Bennett et al.[13] resulted in two additional RCTs. The total number of cases in the control arms of the IPD+non-IPD analysis plus these additional RCTs was sufficient (≥100). The RR in the IPD+non-IPD analysis was 0.79 (95% confidence interval 0.37-1.69) and statistically not significant (low heterogeneity). The RRs in the additional RCTs were substantially lower (0.05 and 0.08) and (borderline) significant.

Based on the discrepancy between the risk estimates in the IPD and IPD+non-IPD analysis, and the large confidence interval in the IPD+non-IPD analysis, the committee considers that the findings on the effect of diet-only interventions aiming at the prevention of excessive gestational weight gain on the risk of gestational diabetes mellitus are inconclusive.

Physical-activity-only interventions significantly lowered the risk of gestational diabetes. Heterogeneity was low, and the risk estimates were similar in the IPD analysis and the IPD+non-IPD analyses (RR=0.67 and 0.66). There were more than 100 cases in the control arms of both analyses; therefore, the committee concludes that the level of evidence is strong. The committee rounds the findings to an RR of 0.7, and considers that physical-activity-only interventions aiming at the prevention of excessive gestational weight gain lead to a 33% (95% confidence interval -54% to -1%) lower risk of gestational diabetes.

Mixed (diet and physical activity) interventions showed no statistically significant effect on gestational diabetes. The IPD analysis had moderate heterogeneity, and the IPD+non-IPD analysis low heterogeneity. Both were based on sufficient RCTs (≥5) and cases (≥100 in both the intervention arm and the control arm). The risk estimate in the IPD analysis (RR=1.02) was close to 1.00, but the 95% confidence interval was broad (0.79 to 1.32). The risk estimate in the IPD+non-IPD analysis (RR=0.88; 95% confidence interval 0.72-1.07) was substantially lower than 1.00, and both additional RCTs from the publication by Bennett et al.[13] reported even lower risk estimates (RR=0.42 and 0.77). Based on the broad 95% confidence intervals and the discrepancy between the risk estimates in the IPD analysis and the estimate in the IPD+non-IPD analysis, the committee considers that the findings on the effect of mixed interventions on the risk of gestational diabetes are inconclusive.

Table 8 The effect of interventions aiming at the prevention of excessive gestational weight gain on the risk of gestational diabetes mellitus.

Publication	Type of study	Type of intervention	Number of RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2 (%)
i-WIP [11]	IPD	Diet-only	4	13 / 221	19 / 269	1.03	0.30 to 3.61	0%
i-WIP [11]	IPD+non-IPD	Diet-only	8	57 / 533	75 / 573	0.79	0.37 to 1.69	0%
Liao 2012 [b]	RCT	Diet-only	1	1 / 100	12 / 100	0.08	0.01 to 0.63	n.a.
Xiao 2015 [b]	RCT	Diet-only	1	11 / 286	18 / 299	0.05	0.25 to 1.01	n.a.
i-WIP [11]	IPD	Physical-activity-only	10	90 / 1390	121 / 1,310	0.67	0.46 to 0.99	0%
i-WIP [11]	IPD+non-IPD	Physical-activity-only	27	240 / 3,393	347 / 3,362	0.66	0.53 to 0.83	0%
i-WIP [11]	IPD	Mixed	14	481 / 3,306	441 / 3,049	1.02	0.79 to 1.32	35%
i-WIP [11]	IPD+non-IPD	Mixed	27	677 / 4,812	672 / 4,530	0.88	0.72 to 1.07	11%
Jiang 2015 [b]	RCT	Mixed	1	8 / 100	29 / 100	0.42	0.19 to 0.92	n.a.
Zhang 2015 [b]	RCT	Mixed	1	42 / 141	28 / 72	0.77	0.52 to 1.13	n.a.

CI: Confidence interval; IPD: pooled analysis or Individual Participant Data; i-WIP: International Weight Management in Pregnancy Collaborative Group; MA, meta-analysis of group-level data; n.a.: not applicable; n / N: number of cases/total number of participants; RR: relative risk.

[a] The i-WIP IPD+non-IPD analyses include RCTs with and without IPD data.

[b] Data extracted from the meta-analysis by Bennett et al., 2018[13]. Please note that Bennett et al. did not report the effect of the interventions on gestational weight gain.

3.8 Hypertensive disorders of pregnancy (pre-eclampsia or pregnancy-induced hypertension)

Summary: The effect on the risk of hypertensive disorders of pregnancy of diet-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from three RCTs and one meta-analysis of IPD+non-IPD data from five RCTs.[11] Two additional RCTs.
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 0.59 (0.07 to 4.65); IPD+non-IPD analysis: RR = 0.57 (0.18 to 1.79).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

There is too little research for a conclusion on the effect of diet-only interventions aiming at the prevention of excessive gestational weight gain on the risk of hypertensive disorders of pregnancy.

Summary: The effect on the risk of hypertensive disorders of pregnancy of physical-activity-only interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 13 RCTs and one meta-analysis of IPD+non-IPD data from 21 RCTs.[11]
Heterogeneity	No.
Strength of the effect	IPD analysis: RR = 0.74 (0.42 to 1.33); IPD+non-IPD analysis: RR = 0.68 (0.49 to 0.93).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

Physical-activity-only interventions aiming at the prevention of excessive gestational weight gain lower the risk of hypertensive disorders of pregnancy.

Level of evidence: Limited.

Summary: The effect on the risk of hypertensive disorders of pregnancy of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain.

Aspect	Explanation
Selected studies	One pooled analysis of individual participant data (IPD) from 13 RCTs and one meta-analysis of IPD+non-IPD data from 21 RCTs.[11]
Heterogeneity	No.
Strength of the effect/	IPD analysis: RR = 1.05 (0.86-1.28); IPD+non-IPD analysis: RR = 1.01 (0.87-1.17).
Study population	Healthy pregnant women, normal weight, overweight, and obese; no gestational diabetes at baseline.

Conclusion:

An effect of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain on the risk of hypertensive disorders of pregnancy is unlikely.

Explanation

The results of the meta-analyses regarding the risk of hypertensive disorders of pregnancy are summarised in Table 9, on page 33.

Diet-only interventions showed no significant effect on the risk of hypertensive disorders of pregnancy. The direction of the risk estimates in the i-WIP-analyses (<1) was opposite to the direction in the additional RCTs (>1). As the number of cases was lower than 60 in both the intervention arm and the control arm, the committee concludes that there is too little research for a conclusion.

Physical-activity-only interventions showed no significant effect on the risk of hypertensive disorders of pregnancy in the IPD analysis, but a significantly reduced risk in the IPD+non-IPD analysis. The data showed low heterogeneity, and the difference between the two risk estimates was small (0.74 and 0.68). The IPD+non-IPD findings were based on more than 100 cases per study arm. Based on the significant effect in the IPD+non-IPD analysis and the similarity of the risk estimate in the IPD analysis, the committee concludes that physical-activity-only interventions aiming at the prevention of excessive gestational weight gain lower the risk of hypertensive disorders of pregnancy. Because the IPD analysis showed no significant effect, the committee considers the level of evidence to be limited.

Mixed (diet and physical activity) interventions showed no significant effect on hypertensive disorders of pregnancy. Because the analyses included sufficient RCTs (≥5 RCTs) and cases (≥100 in both the intervention arm and the control arm), the risk estimates were close to 1.00, and heterogeneity was low, the committee considers that an effect was unlikely.

Table 9 The effect of interventions aiming at the prevention of excessive gestational weight gain on the risk of hypertensive disorders of pregnancy (pre-eclampsia or pregnancy-induced hypertension).

Publication	Type of study	Type of intervention	Number of RCTs	n / N intervention	n / N control	RR	95%CI	Heterogeneity I^2 (%)
i-WIP [11]	IPD	Diet-only	3	18 / 179	39 / 218	0.59	0.07 to 4.65	36%
i-WIP [11]	IPD+non-IPD	Diet-only	5	23 / 345	49 / 384	0.57	0.18 to 1.79	38%
Jeffries 2009 [b]	RCT	Diet-only	1	6 / 124	2 / 111	2.69	0.55 to 13.03	n.a.
Peccei 2017 [c]	RCT	Diet-only	1	4 / 186	0 / 87	4.69	0.26 to 86.06	n.a.
i-WIP [11]	IPD	Physical-activity-only	7	55 / 1,297	73 / 1,268	0.74	0.42 to 1.33	6%
i-WIP [11]	IPD+non-IPD	Physical-activity-only	20	106 / 2,619	147 / 2,506	0.68	0.49 to 0.93	0%
i-WIP [11]	IPD	Mixed	13	359 / 3,542	322 / 3,255	1.05	0.86 to 1.28	19%
i-WIP [11]	IPD+non-IPD	Mixed	21	430 / 4,725	407 / 4,411	1.01	0.87 to 1.17	16%

CI: Confidence interval; IPD: pooled analysis or Individual Participant Data; IPD+non-IPD: meta-analysis of group-level data; i-WIP: International Weight Management in Pregnancy Collaborative Group; n.a.: not applicable; n / N: number of cases/total number of participants; RR: relative risk.

[a] The i-WIP IPD+non-IPD analyses include RCTs with and without IPD data.

[b] Data extracted from the meta-analysis by Muktabhant et al.[12]

[c] Data extracted from the meta-analysis by Syngelaki et al.[14]

3.9 Summary of findings from RCTs

There is too little research from RCTs on the effect of interventions aiming at the prevention of excessive gestational weight gain on the risk of still-birth. For this outcome, all types of interventions were combined.

The following overview presents the conclusions of the committee based on RCTs aiming at the prevention of excessive gestational weight gain.

	Dietary interventions	Physical-activity interventions	Mixed (diet and physical-activity) interventions
Strong evidence	Based on RCTs, there is strong evidence that dietary interventions aiming at the prevention of excessive gestational weight gain: • lower gestational weight gain (the effect size could not be quantified).	Based on RCTs, there is strong evidence that physical-activity interventions aiming at the prevention of excessive gestational weight gain: • lower gestational weight gain by 0.7 kilogram, • lower the risk of gestational diabetes by 33%.	Based on RCTs, there is strong evidence that mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain: • lower gestational weight gain by 1.0 kilogram.
Limited evidence	Based on RCTs, there is limited evidence that dietary interventions aiming at the prevention of excessive gestational weight gain: • lower the risk of preterm birth.	Based on RCTs, there is limited evidence that physical-activity interventions aiming at the prevention of excessive gestational weight gain: • lower the risk of pre-eclampsia or gestational hypertension.	No conclusions with limited evidence.
Unlikely	No unlikely effects.	Based on RCTs, an effect is unlikely of physical-activity interventions aiming at the prevention of excessive gestational weight gain on: • the risk of large for gestational age.	Based on RCTs, an effect is unlikely of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain on: • the risk of pre-eclampsia or gestational hypertension.
Contra-dictory	No conclusions with contradictory evidence.	No conclusions with contradictory evidence.	No conclusions with contradictory evidence.
Too little research	There is too little research from RCTs on the effects of dietary interventions aiming at the prevention of excessive gestational weight gain on: • the risk of pre-eclampsia or gestational hypertension, • the risk of small for gestational age.	No conclusion that there is too little research.	No conclusion that there is too little research.
Inconclusive	Based on RCTs, the evidence is inconclusive on the effects of dietary interventions aiming at the prevention of excessive gestational weight gain on: • the risk of gestational diabetes, • the risk of large for gestational age.	Based on RCTs, the evidence is inconclusive on the effects of physical-activity interventions aiming at the prevention of excessive gestational weight gain on: • the risk of preterm birth, • the risk of small for gestational age.	Based on RCTs, the evidence is inconclusive on the effects of mixed (diet and physical activity) interventions aiming at the prevention of excessive gestational weight gain on: • the risk of preterm birth, • the risk of gestational diabetes, • the risk of small for gestational age, • the risk of large for gestational age.

3.10 Findings cited in the advisory report

The committee considers that the conclusions with strong or limited evidence from RCTs with dietary interventions and physical-activity interventions are not in line with the conclusion from the other intervention types:

- The RCTs with physical-activity interventions showed strong evidence for an effect on gestational diabetes, whereas the evidence from RCTs with dietary interventions and from RCTs with mixed (physical activity and dietary) interventions were both inconclusive for gestational diabetes.
- The RCTs with physical-activity interventions showed limited evidence for an effect on gestational hypertension and pre-eclampsia, whereas with mixed (physical activity and dietary) interventions, an effect was unlikely. (There was too little evidence from RCTs with dietary interventions.)
- The RCTs with dietary interventions showed limited evidence for an effect on preterm birth, whereas the evidence from RCTs with physical-activity interventions and from RCTs with mixed (physical activity and dietary) interventions were both inconclusive for preterm birth.

Because of the inconsistencies between findings from different types of interventions, the committee considers that the findings for the three types of interventions cannot be combined (see paragraph 3.1). This means that only the conclusions from RCTs with dietary interventions are considered relevant for the advisory report on dietary recommendations for pregnant women.

The committee based the recommendations in the advisory report primarily on the conclusions in the background documents with a strong evidence level. These are not available for dietary interventions aiming at the prevention of excessive gestational weight gain. The committee mentions in the advisory report:

- that the participants of these RCTs are mainly overweight and obese women;
- that there is limited evidence for an effect of dietary interventions aiming at the prevention of excessive gestational weight gain on preterm birth.

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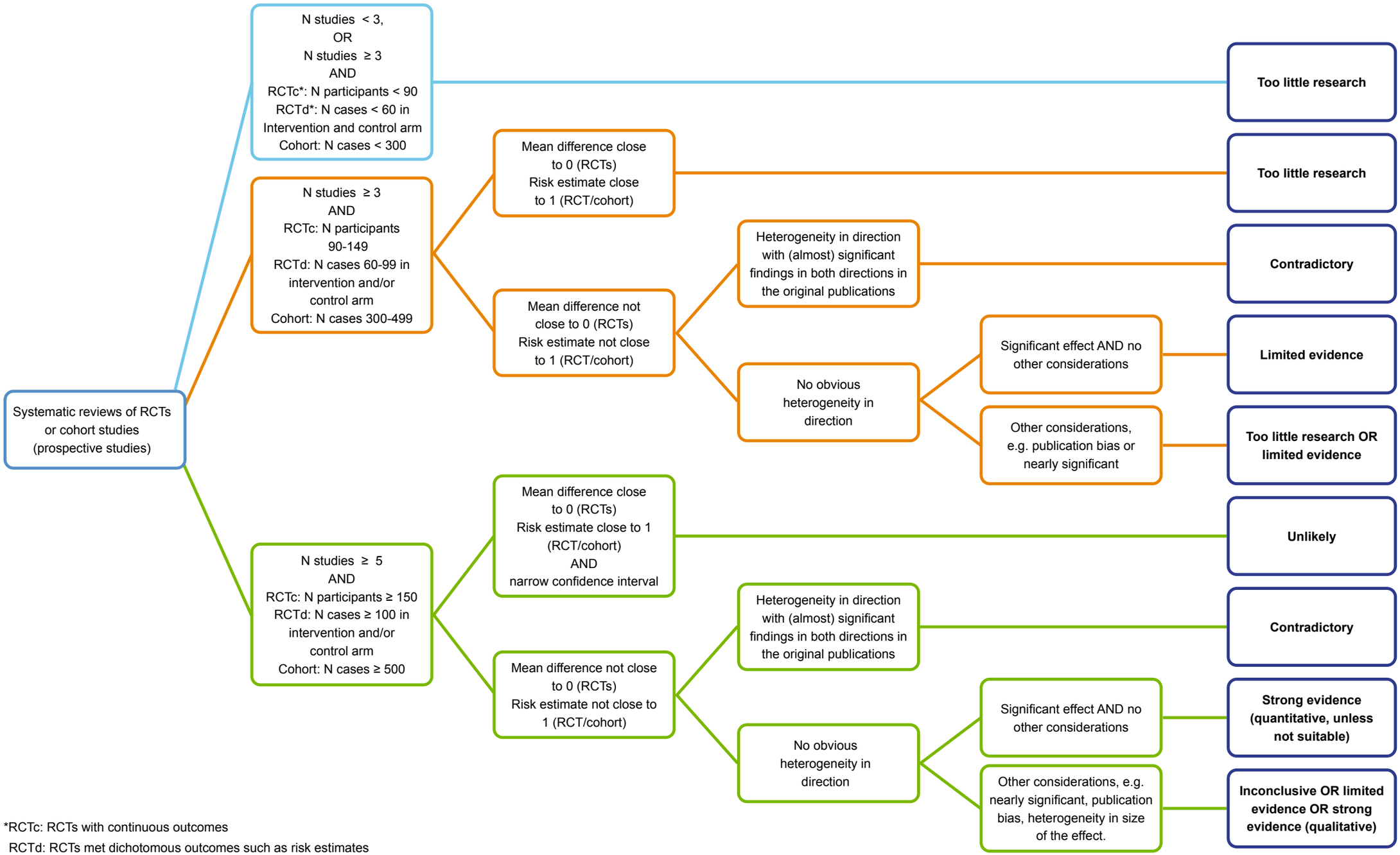
annexes

A decision tree



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

B literature search terms

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

Search in PubMed and Psychinfo until July 2018

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

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

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

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