10. Assessment of the data on type 1 diabetes mellitus in individuals born at term or mixed populations

10.1. Type 1 diabetes mellitus: final body of evidence

The 23 publications that were considered in the assessment in individuals born at term or mixed populations are given in Appendix B.7.

These publications reported on results from 18 studies:

- 7 prospective cohort studies and 1 nested case–control study (6 rated as Tier 1, 2 rated as Tier 2);
- 10 retrospective studies (all Tier 3).

In these studies, three different endpoints were investigated. Results of all the studies are given in Annex A as Microsoft Excel® file. In addition, for the main endpoints, results are summarised in the forest plots in Appendices A.42–A.45 of this Scientific Opinion.

With respect to the interpretation of the age at introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

10.2. Type 1 diabetes mellitus: endpoint and study selection

Studies were included if the diagnosis of T1DM in the studies was based on well-established criteria for diagnosing the disease at the time of the study (e.g. WHO (2006) or recommendations from the American Diabetes Association which are updated regularly).

With respect to the endpoint on islet autoimmunity, studies were included if the outcome assessment was based on the presence of elevated titres of at least one autoantibody in two consecutive samples. Chmiel et al. (2015) presented results for the hazard of having elevated titres for one and for two autoantibodies. In this case, the results related to the hazard of having an elevated titre of one autoantibody was considered in the analysis for comparability reasons.

No distinction was made in the assessment between study populations at risk of disease or not. The Panel decided to draw its conclusions from the disease-related endpoint, i.e. T1DM. Data on islet autoimmunity are used only as supportive evidence to the results from the studies on T1DM, as positive results are associated with a higher risk of developing T1DM but alone are not predictive of the disease.

10.3. Type 1 diabetes mellitus: summary of the evidence

10.3.1. Timing of introduction of CFs in general

Main line of evidence (4 studies)

From the meta-analysis of six age comparisons from four prospective cohort studies (Savilahti and Saarinen, 2009; Frederiksen et al., 2013; Lund-Blix et al., 2015; Hakola et al., 2018), there is no evidence for an association between various timings of introduction of CFs (ranging from < 3 months to < 5 months compared with thereafter) and the hazard of developing T1DM up to 15 years of age (Appendix A.42). Heterogeneity was substantial (I^2 = 65%).

> The Panel notes that, from the meta-analysis of four prospective cohort studies (Tiers 1 and 2) in the main line of evidence, there is no evidence for an association between various timings of introduction of CFs and the hazard of developing T1DM up to 15 years of age.

Supportive line of evidence

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

- **Retrospective studies (7 studies, Tier 3)**

From the meta-analysis of the six case–control studies (Kostraba et al., 1993; Meloni et al., 1997; EURODIAB Substudy 2 Study Group, 2002; Stene et al., 2003; Rosenbauer et al., 2008; Rabiei and Reza, 2012) in children with ages ranging from 2 to 18 years, there is no evidence for an association between various timings of introduction of CFs (ranging from < 3 months to < 6 months compared

with thereafter) and the odds of developing T1DM. Heterogeneity was substantial: I^2 = 79%, which cannot be explained (Appendix A.43).

In another case–control study that did not provide a point estimate (hence is not present in the forest plot), Visalli et al. (2003) did not find a significant association between the timing of introduction of CFs (< 3 vs > 3 months) and the odds of developing T1DM up to the age of 6-18 years.

- **Islet autoimmunity (2 studies)**

Neither the prospective cohort study by Hakola et al. (2018) nor that by Lund-Blix et al. (2015) (both Tier 1) found a statistically significant association between the timing of introduction of CFs (< 3 months and < 5 months vs thereafter, respectively) and the hazard of developing islet autoimmunity up to 15 years of age (Annex A as Microsoft Excel® file). Both studies also investigated T1DM and their results are consistent for the two endpoints investigated.

- **Difference in the timing of introduction of CFs in cases and controls (2 studies)**

The case–control study by Liese et al. (2012) did not find statistically significant differences between the timing of introduction of CFs in on average 15-year-old T1DM cases and controls, while in the case–control study by Perez-Bravo et al. (1996) (both Tier 3) on average 15-year-old cases were introduced to CFs earlier (mean difference: −1.01 (95% CI −1.83 to −0.2) months) (Annex A as Microsoft Excel® file). Both analyses were unadjusted and therefore are likely to overestimate the association.

The Panel notes that the findings of 10 out of 11 studies in the supportive line of evidence are consistent with the findings in the main line of evidence.

10.3.2. Timing of introduction of CFs in general and type 1 diabetes mellitus: conclusions and grading of the confidence in the evidence

Imprecision: There were no concerns with respect to imprecision.

Inconsistency: The results were consistent across populations and across lines of evidence (4 studies in the main line and 11 studies in the supportive line). For the meta-analysis conducted in the main line of evidence, I^2 was below 75%.

Generalisability: There were no concerns with respect to generalisability, as a variety of populations were studied.

Publication bias: Publication bias could not be evaluated, because of the insufficient number of studies available.

The Panel concludes from the four prospective cohort studies (Tiers 1 and 2) that there is no evidence for an association between the age of introduction of CFs and the hazard of developing T1DM up to 15 years of age (moderate confidence in the evidence).

The age of introduction investigated varied between studies, ranging from < 3 months of age to < 5 months of age for 'early' introduction, compared with thereafter.

10.3.3. Timing of introduction of gluten

Main line of evidence (5 studies)

From the meta-analysis of the five prospective cohort studies (Welander et al., 2010; Frederiksen et al., 2013; Chmiel et al., 2015; Lund-Blix et al., 2015; Hakola et al., 2018), there is no evidence for an association between various timings of introduction of gluten or gluten-containing foods (ranging from < 3 months to < 5 months compared with thereafter) and the hazard of developing T1DM up to 16 years of age (Appendix A.44). Heterogeneity was moderate (I^2 = 40%).

There were too few studies to assess whether gluten introduction < 4 months of age had a different effect than gluten introduction at 4–6 months of age, as purported by the Panel in its previous Scientific Opinion (EFSA NDA Panel, 2009).

There were also no data to evaluate a potential differential effect of continued breastfeeding while introducing gluten < 6 months of age. Considering breastfeeding while introducing gluten at any age, as done in two studies within the body of evidence (Welander et al., 2010; Frederiksen et al., 2013), is not part of the current mandate and was not considered further.

The Panel notes, from the meta-analysis of the five prospective cohort studies (Tiers 1 and 2) in the main line of evidence, that there is no evidence for an association between the timing of introduction of gluten or gluten-containing foods and the hazard of developing T1DM up to 16 years of age.

Supportive line of evidence

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

- **Islet autoimmunity (7 studies, Tiers 1 and 2)**

From the meta-analysis from seven prospective cohort studies (Norris et al., 2003; Wahlberg et al., 2006; Couper et al., 2009; Chmiel et al., 2015; Lund-Blix et al., 2015; Hakola et al., 2018; Uusitalo et al., 2018), there is no evidence for an association between various timings of introduction of gluten or gluten-containing foods (ranging from < 3 months to ≤ 6 months) and the hazard of developing islet autoimmunity up to 20 years of age (Appendix A.45). Heterogeneity was moderate to substantial (I^2 = 50%). All these studies (some with a different author name) were already included in the assessment of T1DM, except for Couper et al. (2009) and Uusitalo et al. (2018), and their findings with respect to islet autoimmunity are consistent with the results on T1DM.

Difference in the timing of introduction of gluten in cases and controls (1 study)

The case–control study in siblings by Bezzera Alves et al. (2012) did not find a statistically significant difference in the timing of introduction of gluten between on average 9-year-old cases with T1DM and controls.

10.3.4. Timing of introduction of gluten and type 1 diabetes mellitus: conclusions and grading of the confidence in the evidence

Imprecision: There were no concerns with respect to imprecision.
Inconsistency: The results were consistent across populations and across lines of evidence (five studies in the main line and eight studies in the supportive line). For the meta-analysis conducted in the main line of evidence, I^2 was below 75%.
Generalisability: There were no concerns with respect to generalisability, as a variety of populations were studied.
Publication bias: Publication bias could not be evaluated, because of the insufficient number of studies available.

The Panel concludes from the five prospective cohort studies (Tiers 1 and 2) that there is no evidence for an association between the age of introduction of gluten and the hazard of developing T1DM up to 16 years of age (moderate confidence in the evidence).

The age of introduction of gluten that was investigated varied between studies, ranging from < 3 months of age to < 5 months of age for 'early' introduction, compared with thereafter.

In its previous Scientific Opinion, the Panel considered that introduction of gluten < 4 months of age might increase the risk of T1DM, whereas introduction between 4 and 6 months of age while still breastfeeding might decrease the risk of T1DM. However, in the present assessment there were insufficient data to investigate whether the introduction of gluten < 4 months of age could have a different effect on the risk of developing T1DM than gluten introduction between 4 and 6 months of age. There were no data to evaluate whether gluten introduction < 6 months of age while still breastfeeding has a different effect than gluten introduction < 6 months of age while not breastfeeding.

11. Assessment of the data on risk factors for cardiovascular diseases in individuals born at term or mixed populations

11.1. Risk factors for cardiovascular diseases: final body of evidence

The eight publications that were considered in the assessment of risk factors for cardiovascular diseases in individuals born at term or mixed populations are given in Appendix B.8.

These publications reported on results from six studies:

- 4 prospective cohort studies (1 Tier 1, 3 Tier 2);
- 2 retrospective studies (all Tier 3).

For these outcomes, 15 different endpoints were investigated. Results of all the studies are given in Annex A as Microsoft Excel® file. In addition, for blood pressure, results are summarised in the forest plots in Appendices A.46 and A.47 of this Scientific Opinion.

With respect to the interpretation of the age at introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

11.2. Risk factors for cardiovascular diseases: endpoint and study selection

A sufficient number of studies was available to draw conclusions only for systolic and diastolic blood pressure expressed in mmHg. All other endpoints were generally studied in single studies and were not further considered.

11.3. Blood pressure: summary of the evidence

Main line of evidence (4 studies)

From the meta-analysis of four prospective cohort studies (Wilson et al., 1998; Martin et al., 2004; de Jonge et al., 2013; de Beer et al., 2016), there was a statistically significant association between earlier timings of introduction of CFs (< 3 to < 6 months, compared with thereafter) and higher systolic blood pressure at 5 to about 7 years of age (Appendix A.46). Heterogeneity was not important (I^2 = 0%). However, the Panel considers that the observed small mean difference of 0.6 mmHg (95% CI 0.2 to 1 mmHg) between the groups with earlier and later introduction of CFs is unlikely to affect the risk of cardiovascular diseases later in life.

The findings on diastolic blood pressure from the same cohort studies were similar (Appendix A.47). The mean difference that was observed between the groups with earlier and later introduction of CFs was 0.5 mmHg (95% CI 0.2 to 0.8 mmHg), which is again considered unlikely to affect the risk of cardiovascular diseases later in life.

> The Panel notes, from the four prospective cohort studies (Tiers 1 and 2) in the main line of evidence, that even though the statistical analysis of the association between the age of introduction of CFs (< 3 to < 6 months, compared with thereafter) and blood pressure was significant, the size of the effect was not biologically relevant.

11.4. Blood pressure: conclusions and grading of the confidence in the evidence

Imprecision: There were no concerns with respect to imprecision.

Inconsistency: Only studies in the main line of evidence were available. There was no inconsistency. For all the meta-analyses conducted in the main line of evidence, I^2 was below 75%.

Generalisability: There were no concerns with respect to generalisability, as a variety of populations were studied.

Publication bias: Publication bias could not be evaluated, because of the insufficient number of studies available.

> The Panel concludes from the four prospective cohort studies (Tiers 1 and 2) that even though the statistical analysis of the association between the age of introduction of CFs (< 3 to < 6 months, compared with thereafter) and blood pressure assessed up to 7 years of age was significant (moderate confidence in the evidence), the size of the effect was not biologically relevant.

12. Assessment of the data on infections in individuals born at term or mixed populations

12.1. Infections: final body of evidence

The 12 publications that were considered in the assessment of data on infections in individuals born at term or mixed populations are given in Appendix B.9.

These publications reported on results from 11 studies:

- 3 RCTs (3 rated as Tier 2);
- 7 prospective cohort studies (3 rated as Tier 1, 1 rated as Tier 2 and 3 rated as Tier 3);
- 1 retrospective study (Tier 3).

In these studies, 13 different endpoints were investigated. Results of all the studies are given in Annex A as Microsoft Excel® file.

With respect to the interpretation of the age at introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

12.2. Infections: endpoint and study selection

Endpoints considered were gastrointestinal infections, upper and lower respiratory tract infections and infections of all types.

In the RCT by Perkin et al. (2016), the endpoints designated as diarrhoea and vomiting were assessed as undesirable events and were not intended to comprise gastrointestinal infections only. Even though, it could be assumed that an infection would have been the most likely cause of diarrhoea and vomiting in infants, the different findings in relation to diarrhoea (i.e. no effect of the timing of introduction of CFs) and vomiting (i.e. earlier introduction of CFs related to a higher incidence of vomiting) in this study, indicate that at least vomiting cannot be interpreted as a symptom of an infection in this instance, as vomiting of infectious origin is usually accompanied by diarrhoea. Therefore, the results for vomiting in the study by Perkin et al. (2016) were not considered further.

Studies, in which the incidence of infections was assessed > 1 year of age only and which did not cover the period during which CFs were introduced were not considered in the assessment owing to the implausible association between the timing of introduction of CFs and infections that occur several months later (Section 1.6).

Studies conducted in low-income and lower-middle-income countries were excluded for this outcome, in line with the protocol for this review (EFSA, 2017b) owing to the difficulties of disentangling the effects on infections of poor food hygiene, suboptimal nutritional status and/or the nutritional inadequacy of CFs in these countries from the timing of introduction of CFs (Section 2.1.1.2). The Panel, however, decided to consider further two RCTs performed in Honduras (Cohen et al., 1994; Dewey et al., 1999), a lower-middle-income country, as the two studies were well controlled to exclude the interference of bad hygiene and nutritionally inadequate food, i.e. the CFs administered were provided by the investigators to the mothers of the study participants.

12.3. Gastrointestinal infections: summary of the evidence

Main line of evidence (5 studies)

Gastrointestinal infections were investigated during the time period of 4–6 months of age in exclusively breastfed infants in three RCTs (Cohen et al., 1994; Dewey et al., 1999; Perkin et al., 2016), all of which compared the introduction of CFs at 3-4 months with 6 months of age (Annex A as Microsoft Excel® file). Results of these trials are difficult to compare, as they used different outcome measures to assess gastrointestinal infections and reported the results in different metrics.

Dewey et al. (1999) found that the percentage of days with diarrhoea between 4 and 6 months was higher in exclusively breastfed infants than in those who had received CFs at 4 months of age (5.4 ± 8.5 vs 2.8 ± 5.4%, $p < 0.05$ using a (not further specified) non-parametric test). However, imprecision was serious. The Panel notes that the findings by Dewey et al. (1999) are contradictory to what is usually observed in assessment for the benefit of more prolonged exclusive breastfeeding (Kramer and Kakuma, 2012).

Cohen et al. (1994) and Perkin et al. (2016) did not find statistically significant differences in morbidity scores based on the number of days with diarrhoea (point estimate not reported; Cohen et al. (1994)) or absolute difference in number of days with diarrhoea (Perkin et al., 2016).

Two prospective cohort studies (Forsyth et al., 1993; Noppornlertwong and Tantibhaedhyangkul, 2016) were also available (Annex A as Microsoft Excel® file). Forsyth et al. (1993) did not find significant differences in the number of infants with one or more diarrhoea or vomiting episodes at 4–6, 6–9 and 9–12 months of age, comparing infants introduced to CFs < 2 months of age or between 2 and 3 months of age vs thereafter.

Noppornlertwong and Tantibhaedhyangkul (2016) (Tier 2) did not find a difference in gastrointestinal infections from 5 to 15 months of age in exclusively formula fed infants introduced to CFs at 4–6 months vs 6 months. However, this study in 41 infants is likely to have been underpowered for this outcome. Therefore, its non-statistically significant finding was not considered further by the Panel.

The Panel notes from the three RCTs and one prospective cohort study (Tiers 1 and 2) from which conclusions could be drawn in the main line of evidence that there is no evidence that the introduction of CFs at various ages < 6 months of age increases gastrointestinal infections.

Supportive line of evidence (4 studies)

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

- **Prospective cohort studies (2 studies, Tier 3)**

The pooled analysis by Morgan et al. (2004) found no evidence for an association between the timing of introduction of CFs (< vs > 3 months of age) and gastroenteritis assessed up to 18 months of age.

Wright et al. (2004) observed higher odds of diarrhoea during the time period of 1.5–4 months (aOR 1.65 (95% CI 1.09 to 2.50)) in infants introduced to CFs < 3 months of age compared with thereafter. The association between the timing of introduction of CFs and episodes of diarrhoea for which a medical doctor needed to be consulted was, however, not statistically significant (Annex A as Microsoft Excel® file).

- **Retrospective studies (1 study, Tier 3)**

In a cross-sectional analysis of baseline data of the Millennium Cohort Study (Quigley et al., 2009), the authors estimated the monthly risk of hospitalisation for diarrhoea between birth and 8 months of age, depending on whether or not CFs had been introduced in that month. They did not find an association between the introduction to CFs and the odds of the outcome (Annex A as Microsoft Excel® file).

- **Studies in which the timing of introduction of CF was used as a continuous variable in the analysis, irrespective of study design (1 study)**

The prospective cohort study by Lopez-Alarcon et al. (1997) (Tier 1) did not find an association between the timing of introduction of CFs and the odds of diarrhoea between birth and 6 months of age (Annex A as Microsoft Excel® file).

The Panel notes that the results of the four studies in the supportive line of evidence are mostly consistent with the findings in the main line of evidence. One study found the introduction of CFs < 3 months compared with thereafter to be associated with higher odds of diarrhoea between 1.5 and 4 months of age. However, there was no difference in this study in relation to more severe diarrhoea which required the consultation of a medical doctor.

12.4. Upper respiratory tract infections: summary of the evidence

Main line of evidence (5 studies)

Upper respiratory tract infections (URTIs) were investigated in the same RCTs in exclusively breastfed infants (Tier 2) and during the same time span (i.e. 4–6 months) as described above (Annex A as Microsoft Excel® file). Perkin et al. (2016) reported statistically significant increased odds of URTI at 5 and 6 months of age (OR 1.33 (95% CI 1.06 to 1.68) and 1.45 (1.15–1.83),[37]

[37] Calculation performed by EFSA based on data read from a graph.

respectively) in the group of infants introduced to CFs at 3–4 months of age compared with those introduced at 6 months of age. No statistically significant differences were observed at 4 months or at 7 months. Dewey et al. (1999) reported that nasal discharge, expressed in % of days, in the early introduction group was not statistically significantly different from that in the group introduced at 6 months of age. Cohen et al. (1994) reported no statistically significant difference in the incidence of URTI at 4–6 months in the group introduced to CFs at 4 months compared with the group that was introduced at 6 months of age.

The same two prospective cohort studies described above (Forsyth et al., 1993; Nopporlertwong and Tantibhaedhyangkul, 2016) (Tiers 1 and 2) also investigated URTI (Annex A as Microsoft Excel® file).

Forsyth et al. (1993) reported statistically significant differences in the number of infants with one or more episodes of URTI between 3 and 6 months of age, comparing infants with various background milk feedings introduced to CFs < 2 months of age (52% with URTI), at 2–3 months of age (46.9% with URTI) and thereafter (36.6% with URTI), after adjustment for confounders. There were no statistically significant differences in URTI in other time spans investigated, i.e. between 0 and 3, 6 and 9, and 9 and 12 months of age.

Nopporlertwong and Tantibhaedhyangkul (2016) did not find a difference in the number of respiratory tract infections (undefined) from 5 to 15 months of age in exclusively formula fed infants introduced to CFs between 4–6 months and 6 months. However, the study in 41 infants is likely to have been underpowered for this outcome. Therefore, its non-statistically significant finding was not considered further by the Panel.

No studies were available in the supportive line of evidence.

> The Panel notes that the results of the three RCTs and one prospective cohort study (Tiers 1 and 2) in the main line of evidence from which conclusions could be drawn in relation to URTI are inconsistent.
>
> In the two studies which observed an effect or association between the introduction of CFs (at 3–4 months of age compared with 6 months, and < 2 and 2–3 months of age compared with >3 months) and the endpoint, the difference in the incidence of URTI was limited to a time period of 2–3 months, considered transitory and of low biological significance by the Panel.

12.5. Lower respiratory tract infections: summary of the evidence

Main line of evidence (1 study)

The RCT by Perkin et al. (2016) did not find a statistically significant difference in the incidence of lower respiratory tract infections (LRTI) between the groups in which CFs were introduced at 3–4 months and that introduced at 6 months (Annex A as Microsoft Excel® file).

> The Panel notes that there is no evidence for an association between the timing of introduction of CFs and LRTI from the RCT in the main line of evidence.

Supportive line of evidence (3 studies)

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

- **Prospective cohort studies (2 studies, Tier 3)**

No association between the timing of introduction of CFs (< vs > 3 months) and the odds of developing LRTI was observed in the studies by Wright et al. (2004) and by Morgan et al. (2004) (Annex A as Microsoft Excel® file).

- **Retrospective studies (1 study, Tier 3)**

In a cross-sectional analysis of baseline data of the Millennium Cohort Study (Quigley et al., 2009), the authors estimated the monthly risk of hospitalisation for LRTI between birth and 8 months depending on whether or not CFs had been introduced in that month (Annex A as Microsoft Excel® file). They did not find an association between introduction to CFs and the odds of the outcome.

The Panel notes that the results of the studies in the supportive line of evidence (3 studies) are consistent with the main line.

12.6. Infections in general: summary of the evidence

Main line of evidence (1 study, Tier 1)

One prospective cohort study (Størdal et al., 2017) performed in Norway in a large population of 57,007 partially breastfed infants was available: the timing of introduction of CFs was unrelated to the risk of hospitalisation for infections in the time period 0–18 months (Annex A as Microsoft Excel® file).

The Panel notes that there is no evidence for an association between the timing of introduction of CFs and hospitalisation for infections in the study (Tier 1) in the main line of evidence from a large cohort.

Supportive line of evidence (1 study, Tier 3)

A prospective cohort study (Heinig et al., 1993), performed in a group of exclusively breastfed infants and in another group of exclusively formula fed infants, did not show statistically significant differences in the incidence of infections between infants introduced to CFs < and > 6 months of age in either group. No point estimate was provided. Infections in this study were defined as respiratory illness, diarrhoea, otitis media, unexplained fevers, vomiting, chicken pox and other non-respiratory and presumably viral infections.

The Panel notes that the findings of the study in the supportive line of evidence are consistent with the main line of evidence. This study investigated the incidence of infections in general, but not related to hospitalisation.

12.7. Infections: conclusions and grading of the confidence in the evidence

An overview of the considerations made with respect to the grading of the confidence in the evidence is given in Table 8. The lines of evidence are divided into:

- Main-A: RCTs
- Main-B: prospective cohort studies
- S-A: supportive line of evidence.

As the evidence in relation to URTI was inconsistent, the confidence in the evidence was not graded for this outcome.

Publication bias: Publication bias could not be evaluated, because of the insufficient number of studies available.

The Panel concludes from the three RCTs and the one prospective cohort study (Tiers 1 and 2) that there is no evidence for an effect or association between the introduction of CFs, ranging from < 3 months to 3–4 months compared with > 3 months and 6 months of age, and an increased risk of gastrointestinal infections (low level of confidence in the evidence).

The Panel concludes from one RCT (Tier 2) that there is no evidence for an effect of the introduction of CFs at 3–4 months compared with 6 months of age on LRTI (low level of confidence in the evidence).

The Panel concludes from one large prospective cohort study (Tier 1) that there is no evidence for an association between the odds of developing infections (in general) and the timing of introduction of CFs, ranging from 3–4 months to < 6 months compared with 6 months of age and thereafter (moderate level of confidence).

The Panel concludes that the evidence with respect to URTI is inconsistent.

The conclusions apply to settings with satisfactory hygiene conditions.[38]

[38] Studies in low-income and lower-middle-income countries that were conducted in poor hygiene conditions were excluded.

Table 8: Grading of the confidence in the evidence for infections and timing of introduction of CFs

Line of evidence and initial rating	Certainty assessment									Characteristics				Effect in the LoE	Certainty in the LoE	Certainty across LoE
	No studies	Design	RoB	Inconsistency	Generalisability	Imprecision	Magnitude	Dose response	Other	Comparator, population	Early CF	Late CF	Age	Relative		
Gastrointestinal infections																
1 (main-A) ++++	3	RCT	↔	↓	↓(d)	o	↔	o	↔	EBF	3-4 m	6 m	4–6 m	No evidence for increased risk	++	**++** (derived from RCTs)
2 (main-B) +++	1	PC	↔	o	↔	↔	↔	o	↔	Mixed	< 3 m	> 3 m	4–6 m	No evidence for effect	+++	
3 (S-A) +++	4	PC, CS(a)	↓	↓	↔	↔	↔	o	↔	Mixed	n/a	n/a	infancy	No evidence for effect	+	
Upper respiratory tract infections																
1 (main-A) ++++	3	RCT	n/a	n/a	n/a	n/a	n/a	n/a	n/a	EBF	3–4 m	6 m	4–6 m	Inconsistent	n/a	
2 (main-B) +++	1	PC	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Mixed	< 3 m	> 3 m	4–6 m	Inconsistent(b)	n/a	
Lower respiratory tract infections																
1 (main-A) ++++	1	RCT	↔	o	↓(d)	o	↔	o	↓(c)	EBF	3–4 m	6 m	4–6 m	No evidence for effect	++	**++**
2 (S-A) +++	2	PC	↓	↔	↔	↔	↔	o	↔	Mixed	< 3 m	> 3 m	infancy	No evidence for effect	++	
Undefined infections																
1 (main-A) ++++	1	RCT	↔	o	↓(d)	o	↔	o	↔	EBF	3–4 m	6 m	4–6 m	No evidence for effect	+++	**+++**
2 (main-B) +++	1	PC	↔	o	↔	↔	↔	o	↔	PBF	< 6 m	> 6 m	0–18 m	No evidence for effect	+++	
3 (S-A) +++	1	PC	↓	o	↓(d)	↔	↔	o	↔	EBF	< 6 m	> 6 m	4–6 m	No evidence for effect	+	

CS: cross-sectional; CF: complementary food; EBF: exclusively breastfed; LoE: line of evidence; m: months; n/a: not applicable; PBF: partially breastfed; PC: prospective cohort; RCT: randomised controlled trial; RoB: risk of bias; ↓: downgrade; ↑: upgrade; ↔: no concern/impact; o: not evaluable.
(a): Baseline data of the Millennium Cohort Study. (b): Only one time period out of many. (c): Limited evidence in the main line of evidence. (d): Studied on exclusively breastfed infants only.

13. Assessment of the data on sleep-related endpoints in individuals born at term or mixed populations

13.1. Sleep-related endpoints: final body of evidence

The five publications that were considered in the assessment of sleep-related endpoints in individuals born at term or mixed populations are given in Appendix B.10.

These publications reported on results from five studies:

- 2 RCTs (all Tier 2);
- 2 prospective cohort studies and 1 pooled analysis of prospective studies (all Tier 3).

In these studies, five different endpoints were investigated. Results of all the studies are given in Annex A as Microsoft Excel® file.

With respect to the interpretation of the age at introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

13.2. Sleep-related endpoints: endpoint selection

Included studies covered a variety of endpoints that are not directly comparable, i.e. night-time sleep duration, sleep time, 24-h sleep duration, night wakings and sleep problems. Thus, the findings were not represented in a forest plot and no pooled estimate was calculated.

13.3. Sleep-related endpoints: summary of the evidence

Main line of evidence (2 studies)

The RCT by Perkin et al. (2018) found a statistically significant effect of introduction of CFs at 3–4 months of age compared with 6 months of age on night time sleep duration assessed by a validated questionnaire (to assess sleep over the past week) in exclusively breastfed infants. Infants introduced to CFs at 3–4 months of age slept on average about 7 min longer during the night (95% CI: 2 to about 13 min) over the whole course of the study from birth to 3 years of age (adjusted FAS analysis). A peak was observed at 6 months of age at which infants introduced to CFs at 3–4 months of age slept on average about 17 min longer during the night (95% CI: about 8 to 25 min) than their counterparts introduced to CFs at 6 months of age.

In the same RCT, infants introduced to CFs at 3–4 months of age were also reported to have fewer night wakings (mean % difference: −9.1 (95% CI −4 to −14%), adjusted complete case analysis). The infants introduced to CFs at 3–4 months of age also showed lower odds of both 'very serious' and 'small' sleep problems (as perceived by the parents when answering the question 'do you consider your child's sleep as a problem?'), in comparison to infants introduced to CFs at 6 months of age (OR 0.83 (95% CI 0.71 to 0.95) and 0.55 (0.38–0.82), respectively, in an unadjusted FAS analyses).

The Panel notes that the observed differences in sleep duration or night wakings in the RCT by Perkin et al. (2016) were small in relation to an overall night time sleep duration of around 10–11 h at 6 months of age (Dias et al., 2018) and that the severity of sleep problems was based on the perception of the parents. The Panel considers that the results on these three endpoints are unlikely to be of biological relevance.

The RCT by Bainbridge et al. (1996), in which rice cereal was added to formula in the bottle in exclusively formula fed infants at 4 months vs 6 months of age, showed that infants receiving the rice cereal at 4 months slept on average 60 min longer during the night at 6 months of age (95% CI: −34 to 154 min). This was assessed as the time that had passed between the last bottle at night and the first in the morning. The result was not statistically significant. However, the study population included 38 infants only and thus the trial was most likely underpowered for this outcome. Therefore, the Panel did not consider further the non-statistically significant findings of this study.

> The Panel notes that from the RCT (Tier 2) from which conclusions could be drawn in the main line of evidence that even though the statistical analyses of the effect of the age of introduction of CFs (3–4 vs 6 months) on sleep-related endpoints was significant, the size of the effect was not biologically relevant.

Supportive line of evidence

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

- **Prospective cohort studies (3 studies, Tier 3)**

The prospective studies showed:

- either a longer night sleep duration (Morgan et al., 2004), i.e. on average 12 min at 9 and 18 months for those introduced to CFs at ≤ 3 vs > 3 months of age;
- or a shorter 24-h sleep duration (Nevarez et al., 2010), i.e. on average about 24 min at 1 year and 13 min at 2 years for those introduced to CFs at ≤ 4 vs > 4 months of age;
- or no association between the timing of introduction of CFs and 24-h sleep duration at 6 months of age (Nevarez et al., 2010) or with sleep time in breastfed infants at 9 months of age (Heinig et al., 1993).

The Panel notes that the findings in the supportive line of evidence are inconsistent.

13.4. Sleep-related endpoints: conclusions and grading of the confidence in the evidence

The non-statistically significant results of one of the two RCTs available were not further considered, as this RCT was likely underpowered for the assessment of sleep.

Imprecision: There were no concerns with respect to imprecision.
Inconsistency: There was only one study in the main line of evidence. The results of the studies in the supportive line of evidence were inconsistent within this line. For the decision with respect to downgrading, see 'other'.
Generalisability: The study population of the remaining RCT consisted of breastfed infants only. The Panel considers that the results of this study cannot be generalised to formula fed infants and thus to the whole population of infants living in Europe. Therefore, the Panel decided to downgrade the confidence in the evidence derived from this RCT.
Publication bias: Publication bias could not be evaluated, because of the insufficient number of studies available.
Other: The Panel downgraded the confidence in the evidence by one category, because of the limited number of studies that were available and because the results of the single RCT in the main line of evidence were not supported by the findings in the supportive line of evidence.

The Panel concludes from the RCT that even though the statistical analyses of the effect of the age of introduction of CFs (3–4 vs 6 months) on sleep-related endpoints was significant (low level of confidence in the evidence), the size of the effect is not biologically relevant.

14. Assessment of the data on infant and child development in individuals born at term or mixed populations

14.1. Infant and child development: final body of evidence

The three publications that were considered in the assessment of infant and child development in individuals born at term or mixed populations are given in Appendix B.11.

These publications reported on results of three studies:

- 1 RCT (Tier 1);
- 1 prospective cohort study (Tier 3);
- 1 retrospective study (Tier 3).

In these studies, 11 endpoints were investigated. Results of the studies are given in Annex A as Microsoft Excel® file.

With respect to the interpretation of the age of introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

14.2. Infant and child development: endpoint and study selection

The assessment of this outcome was based on studies that used validated tools for assessing infant and child development on the infant and child itself, i.e. Brigance Screens II by Jonsdottir et al. (2013) and the adapted, but validated, Kaufman Assessment Battery for Children II by Veena et al. (2010). Tools that evaluated parental concerns about the developmental status of their child, i.e. the Parent's Evaluation of Developmental Status (PEDS) (Jonsdottir et al., 2013) were not used.

Studies which only reported on the attainment of individual developmental milestones in months (Heinig et al., 1993; Michels et al., 2017) were not further considered in the assessment owing to the wide biological variability when infants achieve certain milestones (WHO Multicentre Growth Reference Study Group, 2006). Therefore, any potential effect of the timing of introduction of CFs is expected to be lower than the biological variability observed for this outcome.

Endpoints/constructs which were investigated in single studies only, i.e. fine and gross motor skills alone (Jonsdottir et al., 2013) and socio-emotional skills (Metwally et al., 2016) were not considered further as they cannot be used to determine an appropriate age range of introduction of CFs.

14.3. Infant and child development: summary of the evidence

Main line of evidence (1 study, Tier 1)

In the RCT by (Jonsdottir et al., 2013), there was no effect of introduction of CFs at 4 months of age compared with 6 months of age on the risk of developmental delay at about 3 years of age. Risk of developmental delay was defined based on the age-appropriate cut-off value of the total score of the Brigance Preschool Screens II. Skills that were assessed were: personal data response, identification of body parts, gross motor skills, identification of objects, repetition of sentences, visual motor skills, number concepts, building tower with blocks, matching colours, picture vocabulary and using plurals correctly.

> The Panel notes from the RCT in the main line of evidence that there is no evidence for an effect of the timing of introduction of CFs on child development.

Supportive line of evidence (1 study, Tier 3)

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

The prospective cohort study by Veena et al., 2010, in which the timing of introduction of CFs was analysed as a continuous variable, did not show an association between the timing of introduction of CFs and child development at 9.7 years of age. Child development in this study covered language development, learning ability, memory span, pattern reasoning, language production, visuospatial problem solving and visual-motor processing speed.

> The Panel notes that result of the prospective cohort study in the supportive line of evidence is consistent with the findings in the main line of evidence.

14.4. Infant and child development: conclusions and grading of the confidence in the evidence

Imprecision: There were no concerns with respect to imprecision.

Inconsistency: There was one study in the main line of evidence. The result of the study in the supportive line of evidence was consistent with the main line of evidence.

Generalisability: The study population of the RCT consisted of breastfed infants only. The Panel considers that the results of this study cannot be generalised to formula fed infants and thus to the whole population of infants living in Europe. Therefore, the Panel decided to downgrade by one category the confidence in the evidence derived from the RCT.

Publication bias: Publication bias could not be evaluated, because of the insufficient number of studies available.

Other: The Panel decided to downgrade by one category the confidence in the evidence, because of the limited evidence that was available.

The Panel concludes from the RCT that there is no evidence for an effect of the timing of introduction of CFs at 4 months vs 6 months of age on child development assessed at 3 years of age (low level of confidence in the evidence).

15. Assessment of the data on indicators of nutrient status in individuals born at term or mixed populations

15.1. Nutrient status: final body of evidence

The seven publications considered in the assessment of nutrient status in individuals born at term or mixed populations are given in Appendix B.12.

These publications reported on results from seven studies:

- 4 RCTs (1 rated as Tier 1, 3 rated as Tier 2);
- 2 prospective cohort studies (Tier 2);
- 1 retrospective study (Tier 3).

Results of all the studies are given in Annex A as Microsoft Excel® file. In addition, results are summarised in the forest plots in Appendix A.48 of this Scientific Opinion.

With respect to the interpretation of the age of introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

15.2. Nutrient status: endpoint and study selection

For the outcome on nutrient status, the Panel decided to limit the assessment to the nutrients which had been considered critical nutrients in infants and young children in Europe in a previous Scientific Opinion (EFSA NDA Panel, 2013), i.e. iron, vitamin D, iodine (in some subpopulations), docosahexaenoic acid (DHA) and alpha-linolenic acid (ALA). The Panel also considered that vitamin D status is more influenced by vitamin D supplementation (programmes) and sunlight exposure than by the timing of introduction of CFs. Therefore, vitamin D was not considered further.

In addition, to evaluate nutrient status, reliable biomarkers of status of the respective nutrients need to be available. Pertinent studies were those which investigated whether the timing of introduction of CFs influences the proportion of subjects that are below a certain cut-off for nutrient sufficiency. Studies comparing mean blood concentrations of biomarkers are difficult to interpret and have, therefore, not been considered in this section.

Finally, studies pertinent for this assessment were only available for iron status. All studies in the main line of evidence assessed iron depletion, defined in all the studies as serum ferritin (SF) < 12 μg/L. Therefore, the Panel concentrated in the following on the assessment of iron depletion. The proportion of children with anaemia or iron-deficiency anaemia will be reported for each study whenever this information is available. Study populations receiving iron supplements in addition to CFs were not considered pertinent for the assessment, as term infants living in Europe are not routinely supplemented with iron. Therefore, the aim of the assessment is to investigate the effect of the timing of introduction of CFs *per se* and not concomitant with iron supplementation. For considerations of the Panel regarding the inclusion of RCTs performed in Honduras discussed further below, please see also Section 12.2.

Studies or time points in studies in which nutrient status was assessed after the age of 1 year only were not considered in the assessment owing to the implausible association between the timing of introduction of CFs and nutrient status after the complementary feeding period. Within this first year of life, results for the first and second half-year are discussed separately in the following sections.

15.3. Iron status: summary of the evidence

Main line of evidence (5 studies)

- **Iron status at 6 months of age in exclusively breastfed infants (3 studies)**

Three RCTs (Dewey et al., 1998; Dewey et al., 2004; Jonsdottir et al., 2012) were available that investigated the effect of introduction of CFs at 4 months compared with exclusive breastfeeding up to 6 months of age on iron depletion.

Two RCTs were conducted in Honduras (Dewey et al., 1998; Dewey et al., 2004) and their study population consisted of term infants that were SGA (Dewey et al., 2004) and a mixture of term infants born SGA and AGA (Dewey et al., 1998). In these two studies, infants consumed commercial baby foods provided by the investigators. Iron depletion occurred in around 23% of SGA infants introduced to CFs at 6 months of age versus around 8% of those introduced at 4 months in the study by Dewey et al. (2004). Hb concentrations < 100 g/L were observed in 21% and 2% of these infants, respectively. In the population of term infants that were a mixture of SGA and AGA, iron depletion occurred in 16% of infants introduced to CFs at 6 months of age compared with 7% of those introduced at 4 months of age (Dewey et al., 1998). Hb concentrations < 110 g/L and < 103 g/L were observed in 66% and 32% of infants introduced to CFs at 6 months of age and in 55% and 25% of infants introduced to CFs at 4 months of age.

The third RCT that was available was conducted in Iceland on healthy term infants (Jonsdottir et al., 2012). In this study, 10% of infants exclusively breastfed for 6 months were iron depleted at 6 months of age, versus 4% of those introduced to CFs at 4 months of age. Iron-deficiency, defined by the authors as mean corpuscular volume (MCV) 74 fl and SF < 12 μg/L, occurred in 8% vs 4% of infants and iron-deficiency anaemia (defined by the authors as Hb < 105 g/L, MCV 74 fl and SF < 12 μg/L) in 2% of infants in each group. However, this study was performed before recommendations for delaying umbilical cord clamping (that increases iron stores of the infant at birth, see Section 1.4.1.2) were routinely implemented in Iceland (Thorsdottir, personal communication).

Individually, these studies did not show a statistically significant effect of the timing of introduction of CFs on iron depletion. However, in the meta-analysis (Appendix A.48), a statistically significant reduction of risk of iron depletion at 6 months of age was observed in the group of exclusively breastfed infants who had been introduced to CFs at 4 months of age, i.e. RR 0.38 (95% CI: 0.18 to 0.80).[39] The 95% prediction interval crossed the line of the 'null' effect. Heterogeneity was not important (I^2 = 0%). The Panel notes that the study population of the three RCTs consisted of infants who were to some degree at risk of iron depletion, either because they were SGA or because delayed umbilical cord clamping was not routine practice or both.

> The Panel notes, from three RCTs (Tiers 1 and 2) in the main line of evidence, that introduction of CFs at 4 months of age compared with 6 months of age in exclusively breastfed infants to some degree at risk of iron depletion reduces the risk of iron depletion at 6 months of age.

- **Iron status in the second half of the first year of life (between 7 and 12 months of age) (2 studies)**

One RCT (Kattelmann et al., 2001) in exclusively formula fed infants did not show an effect of introduction of CFs at 3-4 months vs 6 months of age on iron depletion (12% and 9% in the early and late introduction groups, respectively) or anaemia (defined by the authors as Hb < 110 g/L; 10.5% vs 11%) at 1 year of age.

The prospective cohort study (Libuda et al., 2016) in a population of breastfed and formula fed infants did not show an association between the timing of introduction of CFs < vs > 5 months of age and iron status at 10 months of age (assessed by the authors using the odds of having a concentration of SF < 12 μg/L and odds of having Hb < 105 g/L and SF < 12 μg/L).

[39] Calculated using the DerSimonian and Laird approach without the Hartung and Knapp modification (see Section 2.2.3 for reasons).

The Panel notes that, from the RCT and the prospective cohort study (both Tier 2) in the main line of evidence, that there is no evidence for an effect or association between the timing of introduction of CFs and iron depletion at 10-12 months of age in formula fed infants and infants with a variety of background 'milk' feedings.

Supportive line of evidence (2 studies): iron status in the second half of the first year of life (between 7 and 12 months of age)

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

- **Retrospective studies (1 study, Tier 3)**

The cross-sectional study by Hong et al. (2017), in a population of infants breastfed or formula fed, showed lower odds of iron-deficiency (defined by the authors as SF < 12 μg/L, MCV < 70 fl and transferrin saturation (TfS) < 10%) at around 12 months of age in those infants introduced to CFs before 6 months of age compared with thereafter (OR 0.49 (95% CI 0.33 to 0.72)) (Annex A as Microsoft Excel® file). This analysis was unadjusted and therefore is likely to overestimate the association.

- **Studies in which the timing of introduction of CFs was used as a continuous variable in the analysis, irrespective of the study design (1 study, Tier 2)**

The prospective cohort study by Meinzen-Derr et al. (2006) in breastfed infants did not show an association between introduction of CFs and iron status at 9 months of age (assessed by the authors as the odds of Hb < 100 g/L) (Annex A as Microsoft Excel® file).

The Panel notes that the results of studies in the supportive line of evidence are not directly comparable, because different biomarkers have been used. Therefore, they cannot be evaluated with respect to their consistency with the main line of evidence.

15.4. Iron status: conclusions and grading of the confidence in the evidence

Magnitude of the effect and imprecision: The magnitude of the effect was large (see Section 2.2.3.3). There were no concerns with respect to imprecision. For the meta-analysis of the three RCTs in exclusively breastfed infants that assessed the risk of developing iron depletion at 6 months of age, the 95% prediction interval crossed the line of 'null' effect. However, given the uncertainty that is associated with the estimation of the prediction interval when only three studies are available, the Panel decided that this finding was not sufficient to downgrade the confidence in the evidence.

Inconsistency: There was no inconsistency in the main line of evidence for studies that assessed the risk of developing iron depletion at 6 months of age (exclusively breastfed infants) and those in the second half of the first year of life (7–12 months of age) (formula fed and mixed fed infants). Studies in the supportive line of evidence cannot be interpreted with respect to their consistency as different biomarkers were used.

Generalisability: All RCTs that investigated iron status at 6 months of age were conducted in exclusively breastfed infants who were to some degree at risk of iron depletion, i.e. because infants were SGA, or because delayed umbilical cord clamping was not routine practice or both. The Panel considers that the results of the meta-analysis on these studies can be generalised to the whole population of infants at risk of iron depletion living in Europe (i.e. exclusively breastfed infants born to mothers with a low iron status, or with early umbilical cord clamping (< 1 min after birth), or born preterm, or born SGA, or with a high growth velocity). They cannot be used to establish an effect of the timing of introduction of CFs on iron status in formula fed infants.

Similarly, results obtained in exclusively formula fed or mixed fed populations cannot be used to establish an effect on iron status in exclusively breastfed infants. Therefore, the two studies investigating iron status in the second half of the first year of life (between 7 and 12 months of age) that were performed in formula fed infants or infants with a variety of background milk feedings cannot be used to draw conclusions on how the risk of iron depletion in exclusively breastfed infants evolves after the age of 6 months.

Publication bias: Publication bias could not be evaluated, because of the insufficient number of studies available.

The Panel concludes from three RCTs (Tiers 1 and 2) that introduction of CFs at 4 months of age compared with introduction at 6 months of age reduces the risk of iron depletion (SF < 12 μg/L) at 6 months of age in exclusively breastfed infants at risk of iron depletion (high level of confidence in the evidence).

The Panel notes that the effect on iron depletion is not an effect of introduction of CFs *per se*, but an effect of introduction of CFs that are a source of iron. Infants that may benefit from an early introduction of CFs that are a source of iron are exclusively breastfed infants born to mothers with a low iron status, or with early umbilical cord clamping (< 1 min after birth), or born preterm, or born SGA, or with a high growth velocity. The Panel also notes that iron depletion is a risk factor for iron-deficiency anaemia which is associated with deleterious effects (e.g. delayed attention, poor recognition memory, long-lasting poor cognitive and behavioural performance) (Section 1.4.2).

The Panel concludes, from one RCT and one prospective cohort study (both Tier 2), that there is no evidence for an effect or association between the timing of introduction of CFs (at 3–4 months of age and < 5 months of age vs 6 months and >5 months of age, respectively) and iron depletion at 10-12 months of age in formula and mixed fed infants (high level of confidence in the evidence).

16. Assessment of the data on food preferences and eating behaviours in individuals born at term or mixed populations

16.1. Food preferences and eating behaviours: final body of evidence

The 17 publications considered in the assessment of food preferences and eating behaviours in individuals born at term or mixed populations are given in Appendix B.13. These included two publications that reported on the same four studies (de Lauzon-Guillain et al., 2013; Jones et al., 2015).

These publications reported on results from 18 studies:

- 1 RCT (Tier 3);
- 13 prospective cohort studies (2 rated as Tier 1, 8 rated as Tier 2 and 4 rated as Tier 3; 1 study was allocated two different Tiers depending on the endpoint that was assessed);
- 4 retrospective studies (all Tier 3).

In these studies, 19 different endpoints were investigated. Results of the studies are given in Annex A as Microsoft Excel® file.

With respect to the interpretation of the age at introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

16.2. Food preferences and eating behaviours: endpoint and study selection

A variety of endpoints was investigated in the included studies, which were not directly comparable. Thus, the results could not be represented in forest plots. However, studies that investigated similar concepts of eating behaviours were clustered together, i.e.:

- Food approach,[40] covering the following endpoints that were assessed in the studies: food responsiveness[41] and enjoyment of food.
- Food avoidance,[42] covering the following endpoints that were assessed in the studies: satiety responsiveness, slowness in eating and food fussiness. The latter covers also the following related endpoints: composite food acceptance scores, picky eating behaviour, acceptance of new foods, food neophobia and feeding difficulties.
- Eating patterns, covering the following endpoints that were assessed in the studies: positive eating pattern, food diversity of 'healthy' foods, number of food groups consumed per day and proportion of daily energy intake from ultra-processed foods.
- Vegetable and fruit intake assessed either in absolute terms or as frequency of their consumption or as odds of consuming less than one serving per day.

[40] In practical terms, higher scores are indicative of children who like eating.
[41] The desire of the child to eat in response to food stimuli regardless of how hungry it is.
[42] In practical terms, higher scores are indicative of children who do not like eating.

The following endpoints were considered in single studies only and were not considered further: 'food intake at the midday meal' (Cohen et al., 1995b).

In the following Sections, the timing of introduction of CFs (in general) is discussed first followed by the timing of introduction of vegetables and fruit.

16.3. Food preferences and eating behaviours: summary of evidence

16.3.1. Timing of introduction of CFs in general

Main line of evidence (4 studies)

- **Measures of food approach**

In the prospective cohort study by Möller et al. (2013), no association between the timing of introduction of CFs < 4 months of age compared with 6 months of age and food responsiveness and enjoyment of food assessed at 5 years of age was observed (Annex A as Microsoft Excel® file).

- **Measures of food avoidance**

In two prospective cohort studies, no association between the introduction of CFs < 4 months of age as compared with introduction at 6 months of age or thereafter on food fussiness (de Barse et al., 2017) and slowness in eating (Möller et al., 2013) assessed at 4 and 5 years of age, respectively, was observed (Annex A as Microsoft Excel® file).

Möller et al. (2013) found a lower satiety responsiveness at 5 years of age to be associated with introduction of CFs < 4 months of age as compared with introduction at 6 months. Hollis et al. (2016), in a prospective cohort study, reported higher feeding difficulties (undefined) to be associated with introduction of CFs at 4–6 months of age compared with ≥ 6 months of age.

- **Eating patterns**

In the prospective cohort study by Abraham et al. (2012), 1.5- to 2-year-old children introduced to CFs < 3 months compared with those introduced at 4–5 months and compared with those introduced > 6 months were less likely to show a positive eating pattern (Annex A as Microsoft Excel® file).

- **Vegetable and fruit intake**

Introduction of CFs < 4 months compared with 6 months of age was associated with a statistically significantly higher fruit intake (on average 16 g difference), but not vegetable intake, at 5 years of age (Möller et al., 2013). The Panel notes that the difference in fruit intake observed at 5 years of age (i.e. 16 g/day) is small and unlikely to be of biological relevance.

> The Panel notes from the four prospective cohort studies (Tier 2) in the main line of evidence that introduction of CFs below 3 or 4 months of age compared with 6 months of age and thereafter is associated with some less desirable eating behaviours (i.e. lower satiety responsiveness, higher feeding difficulties and lower likelihood to have a positive eating pattern), while other, potentially also less desirable,[43] eating behaviours (i.e. food responsiveness, enjoyment of food, food fussiness and slowness in eating) are not associated with the timing of introduction of CFs.
>
> The Panel notes from the one prospective cohort study (Tier 2) in the main line of evidence that even though introduction of CFs < 3 months of age (compared with 4–5 and > 6 months of age) was statistically significantly associated with a higher fruit intake at 5 years of age, the observed difference is not biologically relevant. The Panel also notes from this study that there is no association between the timing of introduction of CFs and vegetable intake.

Supportive line of evidence (7 studies)

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

[43] Depending on the direction of the association.

- **Measures of food approach**

In the prospective cohort study (Tier 1) that used the timing of introduction of CFs as a continuous variable in the analysis (Brown and Lee, 2012) earlier introduction of CFs was not associated with food responsiveness at 1.5–2 years of age.

- **Measures of food avoidance**

There was no association between the timing of introduction of CFs with food fussiness (defined in different ways, see Section 16.2) in the following studies:

- the RCT (Tier 3) by Cohen et al. (1995b) at 9 and 12 months of age comparing CF introduction at 4 with 6 months of age;
- the prospective cohort study (Tier 3) by Emmett et al. (2018) at 3 years of age comparing CF introduction < 3 with > 5 months of age;
- the prospective cohort study (Tier 2) that used the timing of introduction of CFs as continuous variable in the analysis (Lange et al., 2013). In this study, the outcome was assessed two months after each infant had started complementary feeding;
- the cross-sectional study (Tier 3) by Bell LK et al. (2018) at 2–3 years of age comparing CF introduction < 3 with 4–5 and ≥ 6 months of age (Annex A as Microsoft Excel® file).

The only study that found an association between the introduction of CFs and food fussiness was the cross-sectional analysis of baseline data of a prospective cohort study by Shim et al. (2011), in which the introduction of CFs < 6 months compared with thereafter was associated with higher odds of developing food fussiness (in particular of not readily accepting new foods and consuming a limited variety of foods) at 2–3 years of age.

With respect to satiety responsiveness, the prospective cohort study (Tier 1) that used the timing of introduction of CFs as continuous variable in the analysis (Brown and Lee, 2012) found that earlier introduction of CFs was associated with a lower satiety responsiveness at 1.5–2 years of age.

- **Eating patterns**

A prospective cohort study (Tier 3) (Bielemann et al., 2018) found that the proportion of daily energy intake from ultra-processed foods was higher in around 7-year-old children when they had been introduced to CFs < 3 months of age as compared with thereafter (Annex A as Microsoft Excel® file).

- **Vegetable and fruit intake**

In the cross-sectional analysis of baseline data of a prospective cohort study (Tier 3), Okubo et al. (2016) did not observe an association between the introduction of CFs < 5 months of age compared with thereafter on the frequency of vegetable and fruit consumption at 1.5–2 years of age.

The Panel notes that consistent with the main line of evidence, in the supportive line of evidence, there is no association between the timing of introduction of CFs and food responsiveness, and the frequency of vegetable and fruit consumption. This is also true for four of the five studies that investigated food fussiness; one study found introduction of CFs < 6 months of age to be associated with higher odds of developing food fussiness. Finally, the study that assessed eating patterns found in line with the main line of evidence a less favourable eating pattern (i.e. a higher proportion of daily energy intake from ultra-processed foods) to be associated with introduction of CFs < 3 months of age compared with thereafter.

16.3.2. Timing of introduction of vegetables and fruit

Main line of evidence (5 studies, Tiers 1 and 2)

- **Measures of food avoidance**

The prospective cohort study by de Barse et al. (2017) found lower food fussiness at 4 years of age to be associated with introduction of vegetables at 4–5 months of age compared with ≥ 6 months. A similar point estimate was found for the comparison of introduction of CFs < 4 months of age with ≥ 6 months, but this comparison did not reach statistical significance. The Panel notes that this last comparison may, however, have been underpowered to detect significant differences. Timing of introduction of fruit was not associated with food fussiness in this study.

- **Eating patterns**

Jones et al. (2015) reported on two prospective cohort studies rated as Tier 2 (i.e. ALSPAC and EDEN). For the ALSPAC study, vegetable introduction at 4–5 months of age compared with ≥ 6 months of age was associated with higher 'healthy plate variety scores' at 4 years of age (adjusted mean difference 0.09 (95% CI 0.04 to 0.14)). The Panel notes that considering that the 'healthy plate variety scores' used in this publication had a maximum score of 5, the observed differences are unlikely to be of biological relevance. In the EDEN study, in which the latest age at outcome assessment was 3 years, no association between the timing of introduction of vegetables and the 'healthy plate variety score' was observed. Also, there was no association between the timing of introduction of fruit and the 'healthy plate variety score'.

- **Vegetable and fruit intake**

In four prospective cohort studies reported in three papers ((Burnier et al., 2011; Grimm et al., 2014) and de Lauzon-Guillain et al. (2013) for the studies ALSPAC and EDEN), there was no association between the timing of introduction of vegetables, comparing various ages of introduction, and the frequency of vegetable consumption. The latest age at outcome assessment was 13 years.

In three of these studies ((Grimm et al., 2014) and de Lauzon-Guillain et al. (2013) for the studies ALSPAC and EDEN), the timing of introduction of fruit was investigated. There were no statistically significant associations between the timing of introduction of fruit and the frequency of fruit consumption.

> The Panel notes from one prospective cohort study (Tier 2) in the main line of evidence that there is an association between the timing of introduction of vegetables, but not fruit, < 6 months of age compared with thereafter and a lower food fussiness at 4 years of age.
>
> The Panel also notes that in the main line of evidence there is no biologically relevant association between the timing of introduction of vegetables and fruit and eating patterns (2 prospective cohort studies, Tier 2) and the frequency of consumption of vegetables and fruit (4 and 3 prospective cohort studies, respectively, Tiers 1 and 2).

Supportive line of evidence (4 studies)

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

- **Measures of food approach**

In the prospective cohort study in which the timing of introduction of CFs was used as a continuous variable in the analysis (Lange et al., 2013) (Tier 2), earlier introduction of vegetables was associated with a lower food fussiness as indicated by a higher acceptance of new vegetables, but earlier introduction of fruit was not related to a higher acceptance of new fruit. The outcome was assessed two months after each infant had been introduced to the food groups.

- **Eating patterns**

Jones et al. (2015) reported for the prospective cohort studies rated as Tier 3 (i.e. Generation XXI and Greek EuroPrevall) that there was no association between the timing of introduction of vegetables or fruit at 4–5 months compared with 5–6 and >6 months of age and 'healthy plate variety scores' at 4 and 3 years of age, respectively.

- **Vegetable and fruit intake**

In the studies Generation XXI and Greek EuroPrevall (Tier 3) reported in de Lauzon-Guillain et al. (2013), there was no association between the timing of introduction of vegetables or fruit (< 5 months compared with 5–6 and > 6 months) and the frequency of vegetable and fruit consumption at 4 and 2 years, respectively.

In the cross-sectional study by Cooke et al. (2004) in which the timing of introduction of CFs was used as a continuous variable in the analysis, it was reported that earlier fruit introduction was associated with a higher frequency of fruit consumption at 2–6 years of age. No association was found for vegetables.

The Panel notes that the results with respect to food fussiness (i.e. earlier introduction of vegetables associated with lower food fussiness, no association for fruit) are consistent with the findings in main line of evidence, as are the results with respect to eating patterns. The results related to the association between the introduction of vegetables and fruit and the frequency of vegetable and fruit consumption are inconsistent within the supportive line of evidence.

16.4. Food preferences and eating behaviours: conclusions

The Panel considers that the evidence in relation to the outcome on food preference and eating behaviours is inconsistent. Therefore, the confidence in the evidence was not graded.

17. Assessment of the data on other health outcomes

Other outcomes that were investigated in the studies retrieved in the systematic review were non-alcoholic fatty liver disease (Ayonrinde et al., 2017), juvenile idiopathic arthritis (Ellis et al., 2012; Kindgren et al., 2017) (investigating the timing of introduction of CFs and gluten, respectively), dental caries (Tanaka et al., 2013), thyroid disease (Fort et al., 1990) and Crohn's disease and ulcerative colitis (Strisciuglio et al., 2017). These outcomes were investigated in single studies only. Therefore, they were not considered further.

18. Assessment of the data on the timing of introduction of CFs in individuals born preterm

18.1. Developmental readiness of the preterm infant to consume CFs

Available developmental data on the introduction of CFs in term infants (Section 3) cannot be directly translated to preterm infants. These represent a more heterogeneous population than infants born at term as they vary in the stage of development at birth (gestational age ranging from 23 to 36 weeks), their postnatal course (illness, nutrient intake and mode/type of feeding) and sequelae. All these factors may influence their developmental readiness to consume CFs, and also their nutritional requirements.

18.1.1. Gastrointestinal function

The human gut is anatomically mature by around 25 weeks gestation and enteral feeding appears to play a part in triggering the maturation of gastric and pancreatic enzymes (WHO, 1989) and gut motility (Berseth, 1992).

Intestinal permeability, a biomarker of the gastrointestinal barrier function, measured using sugar absorption tests in 116 preterm infants (gestational age 26–36 weeks) and 16 term infants was not related to gestational age or birthweight but was higher during the first two days of life than 3–6 days later (van Elburg et al., 2003). It was higher in preterm infants than in healthy term infants only if measured within two days of birth, suggesting rapid postnatal adaptation of the small intestine in preterm infants.

The Panel considers that the available data suggest that gastrointestinal function is not a limiting factor with respect to the timing of introduction of CFs once the preterm infant has the necessary neuromotor skills and the infant has developed an apparent interest in non-milk foods and feeding.

18.1.2. Renal function

While renal glomerular and tubular function are influenced by gestational age, there is a high capacity for postnatal maturation, regardless of the degree of prematurity (Gubhaju et al., 2014).

D'Souza et al. (1985) measured serum electrolytes and osmolality at term equivalent and 4 months post-term in 50 infants born at 28–32 weeks gestation with birthweight < 1,501 g. All infants received formula, and 26 infants received CFs between 2 weeks and 4 months post-term. There were no significant differences in serum electrolytes or serum osmolality between those receiving formula alone or formula with CFs, suggesting that renal function was sufficient to process the protein load imposed by CFs combined with formula.

The Panel considers that the available data suggest that renal function is not a limiting factor with respect to the timing of introduction of CFs once the preterm infant has the necessary neuromotor skills and the infant has developed an apparent interest in non-milk foods and feeding.

18.1.3. Neuromuscular coordination and neurodevelopment

The skills necessary for an infant to coordinate efficient suckling, swallowing and respiration, which are essential for safe oral milk feeding, start to appear from around 32 to 34 weeks of gestation (Mizuno and Ueda, 2003), but this will vary depending on the degree of prematurity and related illness.

A prospective study (Törölä et al., 2012), comparing the feeding development (assessed by video recording in regular intervals from 37 weeks post-conceptional age onwards until chewing skills appeared) of 19 preterm infants (birthweight 670–1,020 g, gestational age ranging from 23 to 30 weeks) and 11 term infants, concluded that most of the preterm infants showed a disorganised sucking pattern as long as suckling was present, and still used the sucking pattern for 1–3 months following introduction of CFs before they started to munch. Therefore, preterm infants were considered to have more feeding problems than term infants, as feeding was prolonged and messy. However, these infants were introduced to CFs considerably earlier than term infants (1–4 months post-term age vs 4–7 months).

Emerging chewing skills (i.e. lateral and diagonal jaw movements and lateral tongue movements), emerged at 2.5–7 months post-term age in preterm infants. Chewing skills (i.e. diagonal rotatory and circular rotatory jaw movements) appeared at 5–10 months post-term age. There were no statistically significant differences in the attainment of these skills in preterm and term infants. However, munching was learned earlier in preterm infants (median 3 months post-term age (range 1.5–5) vs 5 months (4–8) in the term infants).

Also, the age at which preterm infants attain gross motor developmental milestones may be delayed compared to term infants, even when accounting for the degree of prematurity (van Haastert et al., 2006). This is also likely to vary according to the severity of illness experienced during the neonatal period and any sequelae.

These findings suggest that there is a wide range of ages at which preterm infants develop the necessary neuromotor skills for progressing from a liquid to a solid diet.

The Panel considers that the available data do not suggest a precise age at which CFs should be introduced to preterm infants from the perspective of neuromuscular development. The skills necessary to consume small amounts of pureed foods will differ from those required to consume more textured, lumpy or finger foods. It has been suggested that, as a guide, most preterm infants may be developmentally ready to receive pureed CFs at 3 months (13 weeks, post-term), having gained sufficient head control (that is a prerequisite for improved jaw control, see Section 3). However, this must be adapted for individual infants (Palmer and Makrides, 2012).

18.2. Preterm infants: final body of evidence

The four publications considered in the assessment of outcomes in preterm infants are given in Appendix B.15.

These publications reported results from four studies:

- 1 RCT (Tier 1);
- 1 prospective cohort study and 1 pooled analysis of prospective studies (both Tier 3);
- 1 retrospective study (Tier 3).

Results of the studies are given in Annex A as an Microsoft Excel® file. Available data was insufficient to present in forest plots.

With respect to the interpretation of the age at introduction of CFs as reported in the following, please refer to Section 2.2.3.3.

18.3. Preterm infants: endpoint selection

Endpoints already investigated in individuals born at term or mixed populations were considered for preterm infants (Appendix B.15). Results for infections (diarrhoea, LRTI and hospital admission) reported in Gupta et al. (2017) were not considered as this study was conducted in a lower-middle-income country (according to the criterion explained in Section 2.1.1.2). There was insufficient data on

endpoints investigated in preterm infants to create forest plots. Owing to the low number of studies available for the assessment, all studies were evaluated, even if an outcome was addressed in a single study only. Contrary to term infants, study populations of preterm infants receiving iron supplementation were considered pertinent for the endpoint 'iron status', as recommendations in Europe exist to provide preterm infants with supplemental iron from 2 to 6 weeks of life onwards (Agostoni et al., 2010).

BMC measurements not adjusted for bone area were not considered as an outcome for this assessment, owing to the lack of comparability in growing children that are of different size.

The four studies considered were conducted in preterm infants with the following gestational ages and birthweights:

- The RCT by Gupta et al. (2017) included infants < 34 weeks of gestation, of which the average gestational age was 31.7 (SD 1.4) weeks and the birthweight 1,479 (SD 308) g among infants in the early introduction group (4 months) and 31.5 (SD 1.7) weeks and 1492 (SD 344) g among infants in the late introduction group (6 months). In the two groups, 28.4% and 27.4%, respectively, were SGA.
- The pooled analysis by Morgan et al. (2004) included infants < 37 weeks of gestation with a birthweight < 2,000 g.
- The prospective cohort study by Spiegler et al. (2015) included infants at 22 + 0 to 36 + 6 weeks of gestation with a birthweight < 1,500 g.
- The retrospective study by Yrjänä et al. (2018) included infants born below 37 weeks of gestation with a birthweight between 440 and 4,915 g.

All time points that are reported in the following subsections are post-term ages of infants.

18.4. Preterm infants: summary of the evidence

18.4.1. Body weight, body length/height, head circumference, and BMI-related endpoints

Main line of evidence (1 study, Tier 1)

In the RCT (Gupta et al., 2017), there was no statistically significant difference in WAZ, attained body weight, L(H)AZ, attained body length, HCZ, attained HC, BMIZ and attained BMI at 12 months of age comparing an introduction of CFs at 4 months of age vs introduction at 6 months (Annex A as Microsoft Excel® file).

Supportive line of evidence (2 studies, Tier 3)

The reasoning behind the use of the data comprised in the supportive line of evidence is explained in Section 2.2.3.3.

The results of the pooled analysis of prospective studies by Morgan et al. (2004) did not find a significant association between the timing of introduction of CFs and attained body weight and attained body length at 18 months of age and body weight gain, body length gain and HC gain between 3 and 9 months of age, comparing introduction of CFs before with after 3 months of age (Annex A as Microsoft Excel® file).

The other prospective cohort study by Spiegler et al. (2015) used the age of introduction of CFs as a continuous variable in the analysis and found earlier introduction of CFs to be significantly associated with higher body weight (WAZ or attained body weight) and height (L(H)AZ or attained height) at 2 years of age.

18.4.2. Body composition

Main line of evidence (1 study, Tier 1)

Gupta et al. (2017) did not find an effect of the timing of introduction of CFs (at 4 months vs 6 months of age) on fat mass endpoints, i.e. fat mass and % fat mass, and on lean mass endpoints (i.e. lean mass plus BMC), and on BMD (Annex A as Microsoft Excel® file).

Supportive line of evidence (1 study, Tier 3)

Fat mass endpoints or BMD were not investigated in the supportive line of evidence. In the pooled analysis by Morgan et al. (2004), subscapular SFT gain and triceps SFT gain between 3 and 9 months

of age were not associated with the timing of introduction of CFs (comparing introduction of CFs before with after 3 months of age) (Annex A as Microsoft Excel® file).

18.4.3. Atopic diseases (asthma-like symptoms, eczema and symptomatic food allergy)

No study was available for this outcome in the main line of evidence.

Supportive line of evidence (2 studies, Tier 3)

Both studies that were available assessed atopic-diseases in children in the general population (i.e. no at-risk population).

Morgan et al. (2004) found no evidence for an association between the timing of introduction of CFs before vs after 3 months of age and the odds of developing asthma-like symptoms and eczema up to 18 months of age (Annex A as Microsoft Excel® file).

In a case–control study (Yrjänä et al., 2018), 2-year-old children who had developed symptomatic food allergy had been introduced to CFs significantly later compared with controls (median age of 2.3 vs 1.4 months post-term). This was not the case for children who had developed eczema, compared with controls.

18.4.4. Risk factors for cardiovascular diseases

Main line of evidence (1 study, Tier 1)

No significant difference between complementary feeding groups (i.e. introduced at 4 months vs 6 months) was shown in the RCT by Gupta et al. (2017) in relation to concentrations of total cholesterol, high-density lipoprotein (HDL)-, low-density lipoprotein (LDL)- and very-low-density lipoprotein (VLDL) cholesterol, and triglycerides, as well as systolic and diastolic blood pressure (Annex A as Microsoft Excel® file).

No study was available for this outcome in the supportive line of evidence.

18.4.5. Infant and child development

Main line of evidence (1 study, Tier 1)

The RCT (Gupta et al., 2017) did not show differences in the risk of delay with respect to motor development or mental development (using the Developmental Assessment Scale for Indian Infants, a validated adaptation of the Bayley-II scales) between the group introduced to CFs at 4 months of age and the one introduced at 6 months.

18.4.6. Infections

No study was available for this outcome in the main line of evidence.

Supportive line of evidence (1 study, Tier 3)

Morgan et al. (2004) did not find an association between the timing of introduction of CFs before vs after 3 months of age and the odds of developing gastrointestinal infections and LRTI (Annex A as Microsoft Excel® file).

18.4.7. Sleep

No study was available for this outcome in the main line of evidence.

Supportive line of evidence (1 study, Tier 3)

In Morgan et al. (2004), there was no difference in night time sleep duration at 9 and 18 months of age comparing introduction of CFs before with after 3 months of age (Annex A as Microsoft Excel® file).

18.4.8. Nutrient status (iron status)

Main line of evidence (1 study, Tier 1)

The RCT (Gupta et al., 2017) did not show any difference in the odds of developing iron depletion (SF < 12 μg/L), concomitant with iron supplementation, assessed at 12 months of age between the

group introduced to CFs at 4 months of age and the one introduced at 6 months (91.4% in the 'early' introduction group vs 88.9% in the 'late' group were supplemented with iron).

18.5. Timing of introduction of CFs in preterm infants: conclusions

Only one study was available in the main line of evidence. This was an RCT (Tier 1) that was performed in India (Gupta et al., 2017). The study population consisted mostly of infants on vegetarian diets. The mortality rate in the population was high, i.e. 34% died before hospital discharge and another 10% died before the age of 4 months. Surviving infants showed severe growth failure and the prevalence of iron depletion was high, despite the recommended use of iron supplements (Embleton and Fewtrell, 2017). The Panel considers that taken together the generalisability of the findings of this study to the whole population of preterm infants born in Europe is uncertain.

Only for body weight, body length and HC enough studies were available to grade the confidence in the evidence. There was no imprecision in the results of the RCT in the main line of evidence. The results of the studies in the supportive line of evidence were inconsistent. Therefore, the Panel downgraded by one category the confidence in the evidence. As explained above, generalisability of the RCT to the European setting is uncertain. Therefore, the evidence was downgraded by another category.

The Panel concludes from the RCT, that there is no evidence for an effect in preterm infants of introduction of CFs at 4 months of age post-term compared with 6 months of age post-term on body weight, body length and HC assessed at 1 year of age (low level of confidence in the evidence).

The Panel considers that no conclusions can be drawn for the other endpoints (i.e. BMI, fat mass, lean mass, SFT, BMD, asthma-like symptoms, eczema, food allergy, concentrations of blood lipids, blood pressure, infant and child development, infections, sleep and iron depletion) that were assessed in the available studies, because endpoints were either investigated in single studies only or only in studies in the supportive line of evidence.

19. Integration of results

Complementary feeding has been defined, for this assessment, as the period when CFs are given together with either breast milk or formula or both. CFs comprise foods other than breast milk, formula, water or vitamins that are given to infants and can be beverages, spoon-fed pureed foods, spoon-fed lumpy foods or finger foods, either prepared at home or produced commercially. Therefore, the definition of complementary feeding in this Scientific Opinion does not include formula (Section 1.3) and the assessment has been made irrespective of whether infants had been breastfed or formula fed (Section 2.1.1). Subgroup analyses on exclusively breastfed or formula fed infants were made, in order to explore if the background milk feeding could have an influence on the results of the studies, but the number of available studies and assessed endpoints in such analyses was limited (Section 2.2.3.2 and Appendix A). The Panel wishes to emphasise that, from a scientific point of view, an assessment of the appropriate age range of introduction of CFs (which is the subject of this mandate) is not an assessment of the optimal duration of exclusive breastfeeding (Section 1.3).

The Panel wishes to clarify that, in this Scientific Opinion, introduction of CFs was defined as 'early' or 'delayed' when it occurred before or after 6 months of age, respectively. The rationale for this was that, for most healthy infants born at term to healthy well-nourished mothers, breast milk alone will provide sufficient nutrients up to 6 months of age (Section 1.4.1). Owing to this definition of 'early' introduction of CFs, some studies, including some well-known RCTs, in particular on the introduction of allergenic foods (e.g. introduction of fish, egg or peanut) and of gluten, that have been used by other bodies in their assessment on a similar topic, did not meet the inclusion criteria for this Scientific Opinion (Section 2.1.1.2).

In the context of complementary feeding, the appropriate age of introduction of CFs is influenced not only by nutritional considerations, but also by effects on health outcomes and by infant development.

As indicated in the interpretation of the Terms of Reference, the questions that the Panel set out to answer were:

1) Are there any developmental factors relevant for the introduction of CFs, based on an extensive literature review?

2) Are there any adverse health effects associated with the introduction of CFs before 6 months of age, based on a systematic literature review?
3) Are there any benefits associated with the introduction of CFs before 6 months of age, based on a systematic literature review?

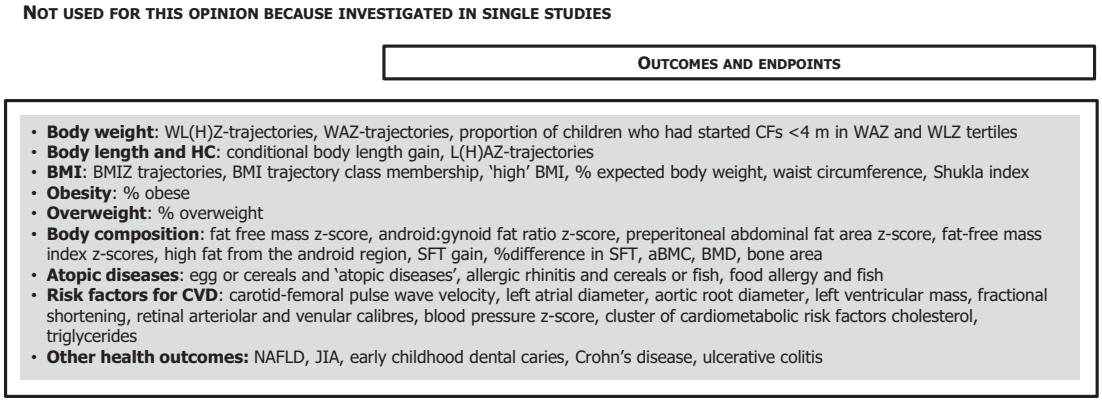
In the systematic literature review undertaken for the (health) outcomes investigated, the Panel created forest plots and undertook meta-analyses (whenever possible), identified main and supportive lines of evidence and graded the confidence in the evidence (Section 2). An overview is presented in Figure 6.

MAIN LINE OF EVIDENCE

	OUTCOMES AND ENDPOINTS
RCTs and prospective observational studies (Tiers 1 and 2): age of introduction of CFs as **categorical** variable	
Forest plots if >2 studies with PE on the same endpoint	• **Body weight**: WAZ, attained body weight, related sub-group analyses, WL(H)Z • **Body length and HC**: L(H)AZ, attained body length/height, related sub-group analyses, attained HC • **BMI**: BMIZ and related subgroup analysis, attained BMI • **Obesity**: odds of being obese, • **Overweight**: odds of being (at least) overweight • **Body composition**: fat mass, fat-mass z-score, SFT • **Atopic diseases**: asthma and CFs (general and at-risk pop.), asthma and cereals or fish (general pop.), eczema and CFs (general and at-risk pop.), eczema and egg (general and at-risk pop.), eczema and cereals or fish (general pop.), allergic rhinitis and CFs (general pop.), food allergy and CFs (general pop.), food allergy and egg (at-risk pop.) • **CD**: CD and gluten • **T1DM:** T1DM and CFs, T1DM and gluten • **Risk factors for CVD**: SBP, DBP • **Iron depletion** at 6 months in EBF infants
No forest plots	• **Body weight**: conditional body weight gain, absolute body weight gain, rapid body weight gain, WAZ gain • **Body length and HC:** absolute body length gain, HCZ, HC gain • **Body composition**: % fat mass, high fat mass • **Atopic diseases:** 'outcome cluster of atopic diseases' and CFs, asthma and egg, asthma and cereals or fish (at-risk pop.), eczema and cereals or fish (at-risk pop.), allergic rhinitis and CFs (at-risk pop.), food allergy and CFs (at-risk pop.), food allergy and egg (general pop.), food allergy and cereals, food allergy and peanuts • **Infections** (gastrointestinal, upper and lower respiratory tract, infections in general) • **Sleep** • **Infant/child development** • **Food preferences/eating behaviours** • **Outcomes in preterm** infants

SUPPORTIVE LINE OF EVIDENCE

	OUTCOMES AND ENDPOINTS
Type of supportive evidence	**Forest plots** if > 2 studies with PE on the same endpoint.
Prospective observational studies in Tier 3	In most of the forest plots mentioned above
Retrospective studies	• Obesity • Overweight • Eczema and CFs • T1DM and CFs
Studies analysing the timing of introduction of CFs as a **continuous variable – Not in a forest plot**	
Sensitisation, CD autoimmunity, islet autoimmunity	• **Sensitisation** and CFs (general and at-risk pop.), sensitisation and egg (general and at-risk pop.), sensitisation and fish (general pop.) • **CD autoimmunity** and gluten (prosp) • **CD autoimmunity** and gluten (retro) • **Islet autoimmunity** and gluten (prosp)
Studies on the difference in timing of introduction of CFs between cases and controls – **Not in a forest plot**	



aBMC: areal bone mineral content; BMD: bone mineral density; BMI: body mass index; BMIZ: body mass index-for-age z-score; CD: coeliac disease; CF: complementary food; CVD: cardiovascular disease; DBP: diastolic blood pressure; EBF: exclusively breastfed; HC: head circumference; HCZ: head circumference-for-age z-score; JIA: juvenile idiopathic arthritis; L(H)AZ: length(height)-for-age z-score; m: months; NAFLD: non-alcoholic fatty liver disease; PE: point estimate; RCT: randomised controlled trial; SBP: systolic blood pressure; SFT: skinfold thickness; T1DM: type 1 diabetes mellitus; WAZ: weight-for-age z-score; WLZ: weight length z-score WL(H)Z: weight-length (height)-for-age z-score.

Figure 6: Overview of the endpoints considered in main and supportive lines of evidence and those that could not be used for this assessment

Developmental readiness of the infant to consume CFs

Developmental readiness can be defined as the physiological maturation necessary for an infant to metabolise 'non-milk foods', i.e. other than breast milk or formula, and the neurodevelopmental changes necessary for safe and effective progression from suckling to spoon- and self-feeding, including the infant's apparent emerging interest in non-milk foods and feeding (Section 3). Gastrointestinal and renal functions are not limiting factors with respect to the timing of introduction of CFs once the infant has the necessary neuromotor skills and has developed an apparent interest in non-milk foods and feeding.

A number of changes are required for progressing from a liquid to a semi-solid and solid diet:

- anatomical changes in the oral cavity,
- the disappearance or diminishing of reflexes present at birth that coordinate suckling, swallowing and respiration and protect the infant from aspiration and choking (i.e. the extrusion reflex of the tongue), in favour of more voluntary movements,
- and the development of gross motor skills (head and trunk control to allow an improved movement of the jaw) and fine motor skills (lip, tongue and jaw movements).

Developmental skills necessary to consume CFs will differ depending on the texture of the food. The skills needed for spoon-feeding of pureed foods will appear earlier than the ones required for self-feeding and therefore, will be used to define the lower bound of the age range of developmental readiness.

The age range at which infants attain developmental milestones shows considerable variation within and between populations, presumably reflecting the infant's innate developmental trajectory combined with the opportunities and experiences provided by the carer.

The infant's ability of holding the head in midline when in supine position and to control its head well when pulled to sitting or at aided sitting are considered by the Panel as the earliest gross motor skills that are indicative of an infant's developmental readiness to consume spoon-fed pureed CFs. These earliest skills can be observed between 3 and 4 months of age. At this age, it can be assumed that the rooting and the extrusion reflexes may have also diminished in some infants. The skills needed for consuming self-fed finger foods (i.e. sitting without support) can be observed in some infants at 4 months, but more commonly between 5 and 7 months of age. In preterm infants, the necessary developmental milestones for feeding are also reached around the same age range (post-term), depending on the severity of illness experienced during the neonatal period, the degree of prematurity and any sequelae.

Most infants do not need CFs for nutritional reasons up to around 6 months of age, with the exception of some infants at risk of iron depletion who may benefit from earlier introduction of CFs that are a source of iron. From this systematic review, the Panel concludes that there is high confidence in the evidence that an introduction of CFs at 4 months of age compared with 6 months reduces the risk of iron depletion at 6 months of age in exclusively breastfed infants at risk of iron depletion. However, the effect on iron depletion is not an effect of introducing CFs *per se*, but an effect of introducing CFs that are a source of iron. Infants that may benefit from an early introduction of CFs that are a source of iron are exclusively breastfed infants born to mothers with a low iron status, or with early umbilical cord clamping (< 1 min after birth), or born preterm, or born SGA, or with a high growth velocity.

Summary of the conclusions on adverse health effects or benefits associated with the introduction of CFs before 6 months of age

Term infants

In the systematic review (undertaken according to the criteria described in Section 2), the Panel has assessed 283 studies that reported on the relationship between the timing of introduction of CFs (or of specific foods, for some outcomes) and (health) outcomes. These were: (1) body weight and growth, including BMI, risk of developing overweight and obesity, as well as body composition, (2) risk of developing atopic diseases or symptoms of atopic diseases, such as asthma-like symptoms, eczema, allergic rhinitis and symptomatic food allergy, (3) risk of developing coeliac disease and type 1 diabetes mellitus, (4) blood pressure, (5) infections, (6) sleep, (7) infant and child development, (8) nutrient status (i.e. iron) and (9) food preferences and eating behaviours in later life.

The Panel applied a weight of evidence approach to derive its conclusions and grade the confidence in the evidence (Section 2.2.3.3). The Panel concludes that there is no convincing evidence for adverse health effects of introducing CFs at any of the ages that were studied. In the studies rated as Tiers 1 and 2, these ages ranged from < 1 month to < 6 months for 'early' introduction and, mostly, thereafter for 'late' introduction.

Table 9 gives an overview about the conclusions of the Panel and the confidence in the evidence upon which these conclusions are based. For the same outcome, the conclusions in relation to the confidence in the evidence may be different for the different age ranges of introduction of CFs that were studied in RCTs or prospective observational studies.[44]

Table 9: Level of confidence in the evidence (per outcome and study design) and related conclusions

Confidence in the evidence	Outcome	'Early' introduction'	'Late' introduction	Conclusions[(a)]
Term infants				
High	Body weight	3–4 m	6 m	No effect
	Body length/height	3–4 m	6 m	No effect
	Head circumference	3–4 m	6 m	No effect
	BMI	3–4 m	6 m	No effect
	Body composition	3–4 m	6 m	No effect
	Coeliac disease and gluten (hazard)	4 m	6 m	No effect
	Iron depletion 6 m (EBF infants)	4 m	6 m	Reduction of the risk of iron depletion
	Iron depletion 7-12 m[(b)] (mixed feeding)	3–4 m	6 m	No evidence for an effect or association
Moderate	Body weight	< 2 to < 6 m	Thereafter	No evidence for association
	Body length/height	2–3 to < 6 m	Thereafter	No evidence for association
	BMI	≤ 2 to ≤ 5 m	Thereafter	No evidence for association

[44] Confidence in evidence derived from RCTs is generally higher than the one derived from prospective observational studies.

Confidence in the evidence	Outcome	'Early' introduction'	'Late' introduction	Conclusions[a]
	Overweight	≤ 2 to < 4 m	> 2 to > 6 m	No evidence for association
	Obesity	< 1 to < 4 m	≥ 3 to ≥ 6 m	No evidence for association
	Body composition	< 4 m	≥ 4 to > 6 m	No evidence for association
	Atopic diseases	3–4 m	6 m	No evidence for effect
	Asthma-like symptoms and CFs	3–4 m	6 m	No evidence for effect
	Asthma-like symptoms and cereals	< 3.75 to ≤ 5.5 m	Thereafter	No evidence for association
	Asthma-like symptoms and fish	< 5.25 to ≤ 6 m	> 5.25 to > 8.5 m	No evidence for association
	Eczema and CFs	< 3 to ≤ 6 m	Thereafter	No evidence for association
	Allergic rhinitis and CFs	3–4 m	6 m	No evidence for effect
	Symptomatic food allergy and CFs	3–4 m	6 m	No evidence for effect
	Coeliac disease and gluten (hazard)	≤3 to ≤4 m	Thereafter	No evidence for association
	T1DM and CFs	< 3 to < 5 m	Thereafter	No evidence for association
	T1DM and gluten	< 3 to < 5 m	Thereafter	No evidence for association
	Blood pressure	< 3 to < 5 m	Thereafter	Size of the effect not biologically relevant
	Infections in general	3–4 and < 6 m	6 and > 6 m	No evidence for association
Low to moderate	Egg allergy and egg	3–4 m	6 m	Reduction of the risk of egg allergy
Low	Atopic diseases	< 3 m	> 3 m	No evidence for association
	Asthma-like symptoms and CFs	≤ 3 to < 6 m	Thereafter	No evidence for association
	Asthma-like symptoms and egg	< 5 and 4–6.5 m	≥ 5 and ≥ 10 m	No evidence for effect
	Asthma-like symptoms and egg	< 5 m	Thereafter	No evidence for association
	Eczema and egg	≤ 4 to ≤ 6 m	Thereafter	No evidence for association
	Eczema and cereal	≤ 4 m	Thereafter	No evidence for association
	Eczema and fish	≤ 5–6 m	Thereafter	No evidence for association
	Allergic rhinitis and CF	≤ 4 m	Thereafter	No evidence for association
	Symptomatic food allergy and CFs	≤ 3–4 m	Thereafter	No evidence for association
	Wheat allergy and cereals	3–4 m	6 m	No evidence for effect
	GI infections	< 3 and 3–4 m	> 3 m and 6 m	No evidence for association
	LRT infections	< 3 and 3–4 m	> 3 m and 6 m	No evidence for association
	Sleep	3–4 m	6 m	Size of the effect not biologically relevant
	Infant and child development	4 m	6 m	No evidence for effect
Very low	Eczema and egg	4–6 m	8-10 m	No evidence for effect
n/a[c]	Peanut allergy and peanut	≤ 6 m	> 6 m	Insufficient evidence to conclude
	URT infections	< 3 and 3–4 m	> 3 and 6 m	Insufficient evidence to conclude
	Food preferences and eating behaviours and CFs/fruit/vegetables	Multitude of ages investigated		Insufficient evidence to conclude
Preterm infants				
Low	Weight	4 m	6 m	No evidence for effect
	Length	4 m	6 m	No evidence for effect
	Head circumference	4 m	6 m	No evidence for effect

Confidence in the evidence	Outcome	'Early' introduction'	'Late' introduction	Conclusions[a]
n/a[c]	BMI, fat mass, lean mass, SFT, bone mineral density, asthma-like symptoms, eczema, symptomatic food allergy, concentrations of blood lipids, blood pressure, infant and child development, infections, sleep and iron depletion	n/a	n/a	Insufficient evidence to conclude

BMI: body mass index; CF: complementary food; EBF: exclusively breastfed; GI: gastrointestinal; LRT: lower respiratory tract; m: months; SFT: skinfold thickness; T1DM: type-1 diabetes mellitus; URT: upper respiratory tract.
(a): Conclusions were derived as follows: 'no effect': high confidence in the evidence derived from (an) RCT(s); 'no evidence for an effect': moderate, low or very low confidence in the evidence derived from (an) RCT(s); 'no evidence for an association': evidence derived from observational studies (see Section 2.2.3.3).
(b): second half of the first year of life (7–12 months).
(c): not graded because the evidence was insufficient to conclude.

In relation to the delayed introduction of allergenic foods into an infant's diet, the Panel finds no evidence to support postponing the introduction of potentially allergenic foods to a later age than the introduction of other CFs. The Panel also finds no evidence that the introduction of gluten < 6 months of age compared with thereafter increases the risk of developing coeliac disease or T1DM. As far as the risk of developing coeliac disease or type 1 diabetes mellitus is concerned, gluten can be introduced to an infant's diet when other CFs are introduced. Time to onset of coeliac disease or T1DM in relation to the timing of introduction of CFs was not considered.

Even though there is no convincing evidence for a harmful effect of CF introduction at any age studied on the selected health outcomes, it needs to be emphasised that foods that are given to infants should be presented in an age-appropriate texture (to prevent choking), are nutritionally appropriate and are prepared according to good hygiene practices. Also, the fact that, based on the available evidence, CFs could be introduced at an early age does not mean that this is necessary or desirable.

Preterm infants

For preterm infants, as a specific subpopulation of the general population, one RCT (Tier 1) (Gupta et al., 2017) was available in the main line of evidence. However, given the specific population of preterm infants that was studied, i.e. mostly infants on a vegetarian diet, a population with a high mortality rate, severe growth failure and high prevalence of iron depletion (despite recommendations for use of iron supplements), the Panel considers that generalisability of the findings of this study to the general population of preterm infants born in Europe is uncertain. Based on this RCT, the Panel concludes that there is no effect of the introduction of CFs at 4 vs 6 months of post-term age on body weight, body length and HC (low level of confidence in the evidence). No conclusions could be drawn on the other endpoints that were assessed in the available studies, as these were investigated only in single studies or in studies in the supportive line of evidence.

Main reasons for the conclusions of the Panel (see above) for selected outcomes

- **Hen's egg and egg allergy**[45]

The Panel concludes that introduction of hen's egg at around 3–4 months compared with 6 months of age may reduce the risk of egg allergy. However, given that all included studies have limitations, the confidence in the evidence is low to moderate and is, therefore, insufficient to support introducing egg at around 3–4 months of age in all infants for the prevention of egg allergy.

This conclusion is based on the following evidence:

There is only one RCT performed in Europe in the general population (Perkin et al., 2016) (EAT study) that compared introduction of cooked egg at 3–4 months of age to exclusively breastfed infants with introduction at 6 months of age. The FAS analysis in this study did not show a statistically

[45] The RCT by Bellach et al. (2017) (HEAP) study was not used in the integration of the evidence, as its specific study design did not address the question to be answered in this opinion. The study by Tham et al. (2017) was also not used further, because of the high likelihood that this study was underpowered for this outcome. (see Section 8.7.3).

significant difference in the risk of egg allergy at 1 or 3 years of age, while the PP analysis found an average of 75% (95% CI 18 to 92%) reduced risk of egg allergy. However, more than 50% of children were excluded from the intervention group, compared with only around 7% in the control group, which may have violated the principle of randomisation. Given that the authors of the study presented results comparing the prevalence of egg allergy in the non-compliant intervention group with that in the control group, and that the prevalence was not different, the Panel considers that the findings in the PP analysis were unlikely caused by reverse causality (i.e. by excluding egg allergic children or those becoming allergic who cannot consume the food). The findings of this study are strengthened by the fact that there was limited evidence for a dose–response relationship when considering the amount of egg that was consumed by infants. The Panel has, however, reservations in relation to the generalisability of the results of the study to the whole population of infants living in Europe as the study population consisted of exclusively breastfed infants. It is unknown whether breastfeeding could be an effect modifier and whether effects could be different in formula or mixed fed infants.

In at-risk populations, three RCTs were available, which were conducted by two research groups in Australia (Palmer et al., 2013; Palmer et al., 2017; Tan et al., 2017) (STAR, STEP and BEAT studies), a country with a high prevalence of egg allergy. Even though two of them were underpowered for the outcome and the third one was powered for sensitisation, the meta-analysis of the three trials performed by the Panel showed a statistically significantly reduced risk of egg allergy (on average 31% (95% CI 7 to 49%)) associated with introduction of egg in a pasteurised raw form between around 4 and 6 months of age, compared with after 8–10 months of age. The comparison group continued the usual diet until egg was introduced, therefore, combining a variety of possible feeding modes, not only breast milk or formula feeding. The Panel considers that the generalisability to the whole population of infants living in Europe is hampered (1) because of the form of the egg that was used (i.e. pasteurised raw egg powder) that is not the form that would be used in the normal diet of an infant and (2) because the studies were conducted in at-risk populations in a country with a prevalence of egg allergy that is higher than in Europe which cannot be explained. Finally, there was a cross-sectional analysis of baseline data of an Australian population-based cohort study (HealthNuts study (Koplin et al., 2010; Koplin et al., 2012)) available in the supportive line of evidence, whose results were consistent with the findings of the RCTs in Australia.

In addition, regarding safety, there were some anaphylactic reactions associated with the consumption of pasteurised raw egg powders as intervention products. In the trial in which cooked egg was given to infants, no such reactions were observed.

- **Peanut and peanut allergy**

There is evidence from an RCT (Du et al., 2015) (LEAP study) conducted in an at-risk population that the introduction of peanut between 4 and 10 months compared with peanut avoidance up to 5 years of age reduces the risk of developing peanut allergy.

The same RCT that investigated the effect of early egg introduction on egg allergy (Perkin et al., 2016) (EAT study) also assessed the effect of introducing peanut at 3–4 months of age compared with introduction at 6 months of age. Like the results for egg, the FAS analysis for peanut did not show an effect of early peanut introduction on the outcome, while in the PP analysis a statistically significant reduction of the risk of peanut allergy was observed.

A re-analysis of data from the LEAP study performed by EFSA, based on the publication by Lawson et al. (2017), compared those infants who were introduced to peanut $\leq$ 6 months of age with those who avoided peanut up to the age of 5 years. This analysis found that those introduced to peanut $\leq$ 6 months of age had a reduced risk of peanut allergy compared with those who avoided peanut up to 5 years. However, there were no statistically significant differences in the risk of peanut allergy between those introduced to peanut $\leq$ 6 months and those introduced between 7 and 10 months of age. This observational re-analysis was not based on the original randomised groups.

The Panel considers that there is evidence that peanut introduction during the first year of life (either at 4–10 months or at 4–6 months) compared with peanut avoidance up to 5 years of age reduces the risk of peanut allergy. However, the evidence is insufficient to conclude whether, when comparing infants introduced to peanut $\leq$ 6 months of age with those introduced $>$ 6 months (but still within the first year of life, which is the subject of this mandate), a similar effect occurs. Therefore, the confidence in the evidence was not graded.

- **Overweight and obesity**

There is no evidence that the timing of introduction of CFs is associated with higher risk of developing overweight and obesity (moderate confidence in the evidence). This finding is supported by the available data on weight, BMI and fat mass (moderate to high confidence in the evidence, depending on the outcome).

- **Coeliac disease and type 1 diabetes mellitus**

In its previous Scientific Opinion (EFSA NDA Panel, 2009), the Panel considered that introduction of gluten before 4 months of age might increase the risk of coeliac disease and T1DM, whereas introduction between 4 and 6 months of age while still breastfeeding might decrease the risk of coeliac disease and T1DM.

  - **Coeliac disease**

Based on the findings of an RCT conducted in seven EU Member States plus Israel (Vriezinga et al., 2014) (PreventCD study) and a meta-analysis of four prospective cohort studies rated as Tiers 1 and 2 performed by the Panel, there is no evidence for an effect or association between the timing of introduction of gluten and the risk of developing coeliac disease (moderate to high level of confidence in the evidence, depending on the age of introduction of CFs investigated). This is true overall and when the analysis was stratified by age of introduction, comparing early introduction (mostly < 4 months of age) with a middle age category (4 to 6 months) and the middle age category with late introduction (mostly > 6 months of age).

The previous conclusion (EFSA NDA Panel, 2009), that (any) continued breastfeeding could modify the effect of gluten introduction < 6 months of age, is not confirmed in an observational analysis of the RCT (Vriezinga et al. (2014) reported in Szajewska et al. (2015)) and a large prospective cohort study (Størdal et al., 2013) (Section 9).

  - **Type 1 diabetes mellitus**

For T1DM, the meta-analysis of the four prospective cohort studies rated as Tiers 1 and 2 did not show an association between the age of introduction of CFs or gluten ranging from < 3 to < 5 months of age compared with thereafter and the outcome assessed (moderate confidence in the evidence).

There were insufficient data to investigate whether the introduction of gluten < 4 months of age could have different effects on the risk of developing T1DM than gluten introduction between 4 and 6 months of age as purported by the Panel in its previous Scientific Opinion (EFSA NDA Panel, 2009). There were no data to evaluate whether gluten introduction < 6 months of age while still breastfeeding has a different effect than gluten introduction < 6 months of age in infants not breastfed at the time of this introduction.

- **Infections**

There is no evidence that, when hygiene conditions are satisfactory,[46] the introduction of CFs < 6 months of age compared with thereafter is associated with an increased risk of (1) gastrointestinal infections (low level of confidence in the evidence), (2) LRTI (moderate level of confidence in the evidence) or (3) infections in general (including hospital admissions for infections; moderate level of confidence in the evidence). The evidence for URTI is inconsistent and insufficient to draw conclusions. Therefore, the confidence in the evidence was not graded. It should, however, be noted that URTI are less severe than gastrointestinal infections, LRTI or infections requiring hospital admissions. In addition, the Panel considers that the criteria for diagnosis of URTI are less reliable and less specific than for other infections, which introduces considerable uncertainty into the assessment of the outcome. Also, the difference in the incidence of URTI was transitory and limited to a time period of 2–3 months.

- **Sleep-related endpoints**

Two RCTs (Tiers 1 and 2) were available, including one (Bainbridge et al., 1996) most likely underpowered for this outcome and with non-statistically significant results. This RCT was therefore not considered further by the Panel. The other (Perkin et al., 2016) (EAT study) provided findings considered by the Panel of no biological relevance: the difference of on average 7 min in night time

[46] Studies in low-income and lower-middle-income countries that were conducted in poor hygiene conditions were excluded.

sleep over the duration of the study (peaking at on average about 17 min at 6 months of age) is small compared to the average night time sleep at that age (around 10 h). The confidence in the evidence was low.

- **Food preferences and eating behaviours**

The evidence for an association between the timing of introduction of CFs and food preferences and eating behaviours is inconsistent. Therefore, the confidence in the evidence was not graded. While earlier introduction of CFs is associated with less desirable eating behaviours (i.e. lower satiety responsiveness, higher feeding difficulties and lower likelihood to have a positive eating pattern), there is no relationship between the timing of introduction of CFs with other (potentially also less desirable) aspects of eating behaviours (i.e. food responsiveness, enjoyment of food, food fussiness and slowness in eating, vegetable or fruit intake).

This inconsistency is also observed for the assessment of the timing of introduction of vegetables and fruit for which an association between the introduction of vegetables, but not fruit, < 6 months of age and a lower food fussiness was observed. No biologically relevant association between the timing of introduction of vegetables and fruit and eating patterns as well as the frequency of consumption of vegetables and fruit were observed.

Uncertainties in the body of evidence

The following sources of uncertainties in the body of evidence were identified. Some of them were addressed in the appraisal of the RoB.

- **Classification into exposure groups**

The classification into exposure groups may be influenced by recall bias, which increases with time elapsed since the exposure and depends on whether the information was interviewer-elicited or not. This was discussed during the appraisal of the RoB (Section 2.2.2 and Appendix C).

The classification into exposure groups may also be affected by the lack of a definition provided to caregivers about what the 'introduction' of CFs means, e.g. first tastes vs regular consumption, and what to be considered as 'CFs' or 'solids'.

It can be assumed that the timing of introduction of CFs in general may be remembered more precisely by caregivers than the introduction of more specific food items, especially when asked at more distant time points.

In addition, residual uncertainty remains on how the age of introduction of CFs was defined in the individual publications, unless the age was reported in weeks. For example, an introduction at 5 months of age could mean that the infant is introduced during the fifth month of life or in the month following the 5-month birthday (i.e. the sixth month of life) (see also Section 2.2.3.3.). In some publications, introduction of CFs is reported as before or after a certain cut-off (e.g. < vs > 3 months) without information to which group infants introduced at the precise age of the cut-off (e.g. infants introduced to CFs at 3 months of age) were attributed. In addition, the same cut-offs used in the studies may have been expressed in different ways (e.g. < 4 months equivalent to ≤ 3 months). However, given the uncertainties around the classification into age groups of introduction of CFs, no efforts of harmonisation (in the text of this Scientific Opinion and related Annexes) have been made by the Panel. Age groups reported in this Scientific Opinion are those provided in the individual papers.

- **Lack of information on the diet of children between the introduction of CFs and the outcome measurement**

There is a general lack of information on the diet of children between the introduction of CFs and the outcome assessment. The lack of such information is of particular importance for (health) outcomes for which the evidence was solely available from observational studies.

It is difficult to judge whether any differences observed in the outcomes may be attributed solely to the age at which CFs were introduced or whether other influencing factors, such as the composition of the diet, may have contributed to the effect (that could not be accounted for by adjusting the analysis for confounders). This was discussed during the appraisal of the RoB (Section 2.2.2. and Appendix C).

- **Generalisability**

The available data originate mainly from large prospective cohort studies that were initially representative of the population to be studied. However, in many studies, a substantial number of

subjects had missing data on the exposure and/or the outcome. This resulted in a selective subgroup of the original populations that could be included in the analyses.

When comparisons between the characteristics of the included and excluded children are available, the caregivers of included children generally had a higher education or socioeconomic status and breastfed for longer compared to those not included in the analyses. In addition, subjects that agree to take part in a study tend to have a higher socioeconomic status than those who do not participate.

Whether the loss of subjects or the exclusion of subjects could have influenced the internal validity of the study was discussed during the appraisal of the RoB (Section 2.2.2. and Appendix C).

Whether or not results could be generalised to the whole population of infants living in Europe was considered in the grading of the confidence in the evidence.

20. Conclusions

General considerations

- The conclusions are intended for infants living in Europe.
- Complementary feeding in this Scientific Opinion means the period when CFs are given together with either breast milk or formula or both. CFs comprise, therefore, foods other than breast milk, formula, water or vitamins that are given to infants and can be beverages, spoon-fed pureed foods, spoon-fed lumpy foods or finger foods, either prepared at home or produced commercially.
- This Scientific Opinion is a scientific assessment of the available evidence and should not be interpreted as providing public health recommendations for the timing of introduction of CFs. This task is outside the remit of EFSA but it is within the remit of public health authorities in Member States.
- From a scientific point of view, the assessment of the appropriate age range of introduction of CFs (which is the subject of this mandate) is not an assessment of the optimal duration of exclusive breastfeeding.
- The appropriate age range of introduction of CFs was evaluated in this Scientific Opinion by considering developmental, nutritional, and health outcomes. Other aspects of complementary feeding that were not part of this assessment may need to be considered when discussing an appropriate age range of introduction of CFs, for example social interactions and the cultural context.
- Most infants do not need CFs for nutritional reasons up to around 6 months of age, with the exception of some infants at risk of iron depletion who may benefit from earlier introduction of CFs that are a source of iron. Infants at risk of iron depletion are exclusively breastfed infants born to mothers with a low iron status, or with early umbilical cord clamping (< 1 min after birth), or born preterm, or born SGA, or with a high growth velocity.
- The earliest skills considered relevant for the consumption of spoon-fed pureed CFs (i.e. holding the head in midline when in supine position and good head control when pulled to sitting or at aided sitting together with a diminishing in the rooting and extrusion reflexes) can be observed between 3 and 4 months of age. Skills necessary for the consumption of self-fed finger foods (i.e. sitting without support) can be observed in some infants at 4 months, but more commonly between 5 and 7 months of age.
- There is no convincing evidence for adverse health effects of introduction of CFs in term infants at any of the ages investigated by the studies assessed in this Scientific Opinion, as long as the foods are given in an age-appropriate texture, are nutritionally appropriate and prepared according to good hygiene practices. Equally, there is no convincing evidence for any benefit of introducing CFs < 6 months of age, except for infants at risk of iron depletion. In the studies that were assessed, the age group for 'early' CF introduction ranged from < 1 month of age to < 6 months of age but was in most instances defined as either < 3 or < 4 months of age[47] without precise information on the earliest age of introduction. The outcomes that have been studied in relation to CFs were body weight, body length, HC, BMI, risk of developing overweight or obesity, body composition, risk of developing atopic diseases, including asthma-like symptoms, eczema, allergic rhinitis, and symptomatic food allergy, risk of developing coeliac disease or T1DM, blood pressure, infections, sleep, infant and child development, iron status and food preferences and eating behaviours.

[47] For observational studies, the exact ages that were covered in the investigated age categories were in most instances not well defined (see Section 19). Therefore, there is uncertainty around the classification into age categories of introduction of CFs as defined in the included papers.

- Once the infant has the necessary neuromotor skills and has developed an apparent interest in non-milk foods and feeding, allergenic foods can be introduced in the same way as other CFs.
- The evidence for preterm infants in relation to introduction of CFs is limited. From the available data, there is no evidence for an effect of introduction of CFs at 4 months (post-term) compared with 6 months (post-term) on body weight, body length and head circumference.

Specific considerations

- There is some evidence that the introduction of hen's egg at around 3–4 months of age compared with 6 months of age may reduce the risk of developing egg allergy. However, the Panel notes that the confidence in the evidence is insufficient to support introducing egg at around 3–4 months of age in all infants for the prevention of egg allergy. In the available studies, no serious adverse reactions occurred with consumption of cooked egg, while anaphylactic reactions were observed when the intervention consisted of pasteurised raw egg powder. As far as the risk of developing allergy is concerned, cooked egg can be introduced into the diet of infants when other CFs are introduced.
- There is evidence that peanut introduction during the first year of life (either at 4–10 months or at 4–6 months) compared with peanut avoidance up to 5 years of age reduces the risk of peanut allergy. However, the evidence is insufficient to conclude whether, when comparing infants introduced to peanut $\leq$ 6 months of age with those introduced > 6 months (but still within the first year of life, which is the subject of this mandate), a similar effect occurs. As far as the risk of developing allergy is concerned, peanut can be introduced into the diet of infants when other CFs are introduced.
- There is no evidence for an association between various timings of introduction of gluten or gluten-containing foods and the risk of developing coeliac disease. Regarding the risk of coeliac disease, gluten can be introduced to an infant's diet when other CFs are introduced.
- The evidence suggests that, when hygiene conditions are satisfactory,[48] there is no evidence for an adverse effect of introduction of CFs before 6 months of age on gastrointestinal infections, LRTI and infections in general (including hospital admission for infections). The evidence with respect to URTI is insufficient.

Overall conclusions

The appropriate age range of introduction of CFs has been evaluated taking into account effects on health outcomes, nutritional considerations and infant development.

- The available data do not allow the determination of a single age for the introduction of CFs for infants living in Europe. The appropriate age range depends on the individual's characteristics and development, even more so if the infant was born preterm.
- As long as the foods are given in an age-appropriate texture, are nutritionally appropriate and prepared according to good hygiene practices, there is no convincing evidence that the introduction of CFs is associated with either adverse or beneficial health effects (except for infants at risk of iron depletion) at any age investigated in the included studies (< 1 months to < 6 months for earlier introduction).
- For nutritional reasons, the majority of infants need CFs from around 6 months of age. For preterm infants, this refers to post-term age.
- Infants at risk of iron depletion (exclusively breastfed infants born to mothers with low iron status, or with early umbilical cord clamping (< 1 min after birth), or born preterm, or born SGA or with high growth velocity) may benefit from introduction of CFs that are a source of iron before 6 months of age.
- The earliest developmental skills relevant for the consumption of spoon-fed pureed CFs can be observed between 3 and 4 months of age. Skills necessary for consuming self-fed finger foods can be observed in some infants at 4 months, but more commonly between 5 and 7 months of age. For preterm infants, this refers to post-term age.
- The fact that an infant may be ready from a neurodevelopmental point of view to progress from a liquid to a more diversified diet before 6 months of age does not imply that there is a need to introduce CFs.

[48] Studies in low-income and lower-middle-income countries that were conducted in poor hygiene conditions were excluded.

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Glossary

Conditional weight gain	difference between the actual weight z-scores and the ones predicted by weight at an earlier time point, adjusted for regression to the mean.
FAS analysis	the analysis set that contains all children with at least one outcome measurement irrespective of whether they had consumed the food under investigation in the pre-specified amounts or not. This type of analysis is more indicative of results that could be obtained in the whole population where the adherence pattern might be similar (e.g. the proportion of infants who have difficulty consuming the food at an early age could be assumed to be similar in the whole population and the study population).
Shukla index	(actual weight/actual height)/(50th percentile weight-for-age/50th percentile height-for-age) × 100
Percentage expected weight-for-age	(actual weight of the child/50th percentile weight at the age when the child's height was on the 50th percentile of reference standards) × 100
PP analysis	the analysis set that includes only those children who had followed the protocol, i.e. complied with the *a priori* assumption of the amount and settings in which the food is assumed to show an effect and provided a full data set with respect to outcome measurements and compliance measurements. This analysis is more indicative of whether the food has an effect under the assumptions that had been made *a priori*.
Vital gluten	are a by-product of starch isolation obtained during wet milling, in which flour is separated into starch and proteins (including gluten).

Abbreviations

AAP	American Academy of Pediatrics
ABCD (study)	Amsterdam born children and their development (study)
aBMC	areal bone mineral content
ABIS (study)	alla barn i sydöstra sverige (study) [all babies in Southeast Sweden]
ACF	age at complementary feeding
ADA	American Diabetes Association
ADJ	adjusted
AGA	appropriate-for-gestational age
ALA	alpha-linolenic acid
ALSPAC (study)	Avon longitudinal study of parents and children (study)
AM	Armenia
aOR	adjusted odds ratio
at-risk pop	at-risk population
AU	Australia
BE	Belgium
BEAT (study)	beating egg allergy trial (study)
BF	breastfed
BIA	bioelectrical impedance analysis
BioIC	automated microfluidic-based immunoassay system

BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BMIZ	body mass index-for-age z-score
BR	Brazil
CA	Canada
CAPS (study)	childhood asthma prevention study
CBGS (study)	Cambridge baby growth study
CC	case–control study
CD	coeliac disease
CDC	US Centers for Disease Control and Prevention
CF	complementary food
CH	Switzerland
CHILD (study)	Canadian healthy infant longitudinal development (study)
CI	confidence interval
CLARITY (study)	childhood arthritis risk factor identification study
CLG	conditional length gain
CN	China
COT	UK Committee on Toxicity of Chemicals in Food, Consumer products and the environment
CS	cross-sectional study
CSA	cross-sectional analysis
CV	continuous variable
CVD	cardiovascular disease
CWG	conditional weight gain
DAISY (study)	diabetes autoimmunity study in the young (study)
DARLING (study)	Davis area research on lactation, infant nutrition and growth (study)
DBP	diastolic blood pressure
DBH (study)	dampness in building and health (study)
DE	Germany
DHA	docosahexaenoic acid
DIPP (study)	type 1 diabetes prediction and prevention (study)
DK	Denmark
DNBC (study)	Danish national birth cohort (study)
DXA	dual-energy X-ray absorptiometry
EAT (study)	enquiring about tolerance (study)
EBF	exclusively breastfed
ECLS-B (study)	early childhood longitudinal study-birth cohort (study)
EDEN (study)	étude des déterminants pré et postnatals précoces du développement et de la santé de l'enfant (study) [study on the pre- and early postnatal determinants of child health and development]
EFHL (study)	environments for healthy living (study)
ENID (study)	early nutrition and immune development (study)
ES	Spain
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FAIR (study)	food allergy and intolerance research (study)
FAS	full analysis set
FC	food challenge
FF	formula fed
FI	Finland
FR	France
gen pop	general population
GH	Ghana
GINI (study)	German infant nutritional intervention program (study)
GNN (study)	German neonatal network (study)
GM	Gambia
GR	Greece

GUS (study)	growing up in Scotland (study)
GUSTO (study)	growing up in Singapore towards healthy outcomes (study)
Hb	haemoglobin
HC	head circumference
HCZ	head circumference-for-age z-score
HDL	high-density lipoprotein
HEAP (study)	hen's egg allergy prevention (study)
HLA	human leucocyte antigen
HN	Honduras
HR	Croatia
HR	hazard ratio
HU	Hungary
ID	identification
IDEFICS (study)	identification and prevention of dietary- and lifestyle- induced health effects in children and infants (study)
IE	Ireland
IFPS (study)	infant feeding practices study
Ig	immunoglobulin
IL	Israel
IN	India
InFANT (study)	Melbourne infant feeding, activity and nutrition trial (study)
IOTF	International Obesity Task Force
IQR	interquartile range
IR	Iran
IS	Iceland
IT	Italy
ITT	intention-to-treat (analysis)
IOTF	international obesity task force
JIA	juvenile idiopathic arthritis
JP	Japan
KNHANES (study)	Korea national health and nutrition examination survey (study)
KOALA (study)	kind, ouders en gezondheid: aandacht voor leefstijl en aanleg (study)
KR	South Korea
kU_A	kilounits of allergen(-specific IgE)
LDL	low-density lipoprotein
LEAP (study)	learning early about peanut allergy (study)
L(H)AZ	length-(height)-for-age z-score
LISA (study)	Einfluss von Lebensbedingungen und Verhaltensweisen auf die Entwicklung von Immunsystem und Allergien (study) [influences of lifestyle related factors on the human immune system and development of allergies in childhood]
LoE	line of evidence
LRTI	lower respiratory tract infection
LSAC (study)	longitudinal study of Australian children
LT	Lithuania
LU	Luxembourg
LV	Latvia
m	Months
MACS (study)	Melbourne atopy cohort study
MAS (study)	multicenter allergy study
MCS (study)	millennium cohort study
MCV	mean corpuscular volume
MD	mean difference
MIDIA (study)	miljøårsaker til type 1-diabetes (study) [environmental causes of type 1 diabetes]
mmHg	millimetre mercury
MoBa (study)	den norske mor og barn-undersøkelsen (study) [the Norwegian mother and child cohort]

mOsm	Milliosmole
MW	Malawi
MX	Mexico
n/a	not applicable
NAFLD	non-alcoholic fatty liver disease
NHANES (study)	US national health and nutrition examination survey
NL	the Netherlands
NO	Norway
NOURISH (study)	nourishing our understanding of role modelling to improve support and health (study)
NTIS	National Technical Information Service
NTP	US National Toxicology Program
NZ	New Zealand
OHAT	US Office of Health Assessment and Translation
OM	Oman
OMCHS (study)	Osaka maternal and child health study
OPALINE (study)	observatory of food preferences in infants and children (study)
OR	odds ratio
PA	pooled analysis
PARIS (study)	pollution and asthma risk: an infant study
PASTURE (study)	protection against allergy–study in rural environments (study)
PATCH (study)	prediction of allergies in Taiwanese children (study)
PBF	partially breastfed
PC	prospective cohort study
PE	point estimate
PE (in forest plots)	pooled estimate
PEDS	Parent's Evaluation of Developmental Status
PI	prediction interval
PIAMA (study)	prevention and incidence of asthma and mite allergy (study)
PIFA (study)	prevalence of infant food allergy study
PINGU (study)	polyunsaturated fatty acids in child nutrition - a German multimodal optimisation study
PIPA (study)	prebiotics in prevention of atopy (study)
PIPO (study)	prospective cohort on the influence of perinatal factors on the occurrence of asthma and allergies (study)
PreventCD (study)	prevent coeliac disease (study)
PP	per protocol (analysis)
PRPD	parents' report of physician's diagnosis
PRS	parents' report of symptoms
PT	Portugal
QLSCD (study)	Québec longitudinal study of child development
RC	retrospective cohort study
RCT	randomised controlled trial
RETRO	retrospective study
RoB	risk of bias
RR	risk ratio
SACN	UK Scientific Advisory Committee on Nutrition
SACN (study)	study of children's activity and nutrition
SBP	systolic blood pressure
SCC	sibling case–control study
SCORAD	scoring atopic dermatitis
SD	standard deviation
SE	Sweden
SEARCH CC (study)	search for diabetes in youth case–control (study)
SEATON (study)	study of eczema and asthma to observe the influence of nutrition
SF	serum ferritin
SFT	skinfold thickness

SG	Singapore
SGA	small-for-gestational age
sIg	specific immunoglobulin
SKOT (study)	smabørns kost og trivsel (study) [small children's diet and well-being]
SMILE (study)	study of mothers and infants' life events affecting oral health
SPT	skin prick test
STAR (study)	solids timing for allergy research (study)
STEP (study)	starting time of egg protein (study)
STEPS (study)	steps to healthy development (study)
STRONG Kids (study)	synergistic theory and research on obesity and nutrition group kids (study)
SWS (study)	Southampton women's survey (study)
T	Term
T1DM	type 1 diabetes mellitus
TBCS (study)	Taiwan birth cohort study
TEDDY (study)	the environmental determinants of diabetes in the young (study)
TfS	transferrin saturation
TH	Thailand
TR	Turkey
tTG (=TGC=TGM2)	tissue transglutaminase
tTGA	tTG autoantibodies
TW	Taiwan
UK	United Kingdom
URECA (study)	urban environment and childhood asthma (study)
URTI	upper respiratory tract infection
US	United States
USDA	United States Department of Agriculture
VLDL	very-low-density lipoprotein
WAZ	weight-for-age z-score
WHEALS (study)	Wayne county health, environment, allergy and asthma longitudinal study
WG	working group
WHO	World Health Organization
WL	weight-for-length
WL(H)Z	weight-for-length(height) z-score
y	year(s)
Y6FU	year 6 follow-up (of the infant feeding practices study IFPS II)

Appendix A – Data analysis and synthesis in forest-plots

Interpretation of the graphical representation:

In the following appendices (and in line with the explanations given in Section 2.2.3.2), results are presented in forest-plots, i.e. graphical representations in which:

- the point estimate, i.e. the mean difference/odds ratio (OR)/risk ratio (RR)/hazard ratio (HR), of each comparison from each study is represented by a small black dot;
- the 95% confidence interval (CI) around this point estimate is represented by a horizontal line;
- the vertical line is the line of the 'null effect';
- the size of a grey square represents the weight given to the related individual study estimate (indicated in the last column), when calculating a pooled estimate over several studies;
- the pooled estimate is shown as a diamond, and the width of each diamond represents its 95% CI calculated based on the DerSimonian and Laird approach with the Hartung and Knapp modification (with some exceptions; see below);
- below each pooled estimate and 95% CI, whenever more than two comparisons were available, the 95% prediction interval based on a t-distribution with k-2 degrees of freedom is depicted by a black line;
- the heterogeneity index I^2 is shown together with its 95% CI, the latter only whenever more than two comparisons were available; the p-value provided is related to the χ^2 test of heterogeneity.

Different possible sources of heterogeneity are indicated in the plots in addition to the age of introduction to complementary feeding, i.e. the specific study population, age at outcome assessment, reference data (e.g. reference population used to calculate z-scores, cut-off for the definition of binary endpoints of interest), the main confounders for the outcome of interest (identified by the Panel) or whether the analysis was unadjusted.

Structure of this appendix

The following plots are organised following the order in the core text of the opinion.

Below eight forest plots[49] results of the meta-analysis performed using the DerSimonian and Laird approach without the Hartung and Knapp modification are shown for some subgroups. The forest plot on 'iron depletion in exclusively breastfed infants at 6 months of age' is as a whole based on the DerSimonian and Laird approach without the Hartung and Knapp modification. This has been done following the sensitivity analysis performed by the Panel that indicated that the Hartung and Knapp modification did not perform well in those cases (see Section 2.2.3.2). Therefore, the Panel considered the results without the modification to be more reliable.

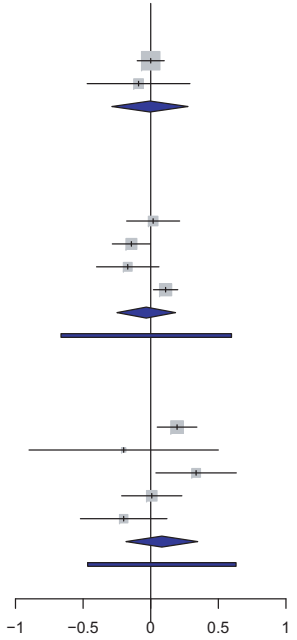
[49] (1) Attained body weight: subgroups of RCTs in Tiers 1 and 2 and prospective cohort studies in Tiers 1 and 2; (2) attained body length/height: subgroups of RCTs in Tiers 1 and 2, and prospective cohort studies in Tiers 1 and 2; (3) attained body length/height by feeding mode: subgroup of formula fed infants; (4) attained HC: subgroups of RCTs in Tiers 1 and 2; (5) odds of developing (at least) overweight: subgroup of prospective cohort studies in Tier 3; (6) asthma-like symptoms and fish – general population: subgroup of prospective cohort studies in Tiers 1 and 2; (7) eczema and fish – general population: subgroup of prospective cohort studies in Tiers 1 and 2; (8) risk of iron depletion at 6 months of age in exclusively breastfed infants.

A.1. WAZ comparing early introduction with later introduction of CFs

Weight−for−age z−score (WAZ)

Sorted by Study Design and Tier

Author	Tier	Country	Age	ACF1	ACF2	Specific group	Reference data or cut−offs	A	B	C	D	ADJ	MD (z−score)	95% CI	Weights (%)	Note
Subgroup = 1_RCT Tier 1+2																
Perkin et al., 2016	1	UK	3 y	3−4 m	6 m	BF	WHO 2006						0.00	[−0.10; 0.10]	78.5	
Dewey et al., 1999	2	HN	12 m	4 m	6 m	BF, SGA, T	CDC 1977						−0.09	[−0.47; 0.29]	21.5	
RMA PE [95%CI]													**−0.01**	**[−0.29; 0.28]**	**100.0**	
PI (95%)															--	
Heterogeneity: I^2 = 0%, p = 0.65																
Subgroup = 2_PC Tier 1+2																
Grote et al., 2011	1	5 EU	2 y	<=3 m	>3 m	FF, T	WHO 2006	c	n	i	c		0.02	[−0.18; 0.21]	21.0	&
Eriksen et al., 2017	1	GM	2 y	<6 m	>6 m	BF	WHO 2006	i	n	i	i		−0.14	[−0.28; 0.00]	27.4	
Haschke and van't Hof, 2000	2	12 EU	3 y	<4 m	>4 m	BF, T	internal	i	n	n	n		−0.17	[−0.40; 0.06]	17.7	*
Wilson et al., 1998	2	UK	7.2 y	<3.5 m	>= 3.5 m	T	UK 1995 BMI	n	c	i	n		0.11	[0.02; 0.20]	34.0	
RMA PE [95%CI]													**−0.03**	**[−0.25; 0.18]**	**100.0**	
PI (95%)														**[−0.66; 0.60]**	--	
Heterogeneity: I^2 = 74% [28%; 91%], p < 0.01																
Subgroup = 3_PC Tier 3																
Gaffney et al., 2012	3	US	12 m	<4 m	>=4 m		CDC 2000	i	i	n	i		0.19	[0.05; 0.34]	36.7	*&
Heinig et al., 1993	3	US	18 m	<6 m	>6 m	BF, T	CDC 1977	n	n	n	n	N	−0.20	[−0.90; 0.50]	4.3	
Huh et al., 2011	3	US	3 y	<4 m	>=4 m	FF	CDC 2000	n	n	n	n	N	0.34	[0.04; 0.63]	17.7	&
Huh et al., 2011	3	US	3 y	<4 m	>=4 m	BF	CDC 2000	n	n	n	n	N	0.01	[−0.21; 0.23]	25.3	&
Kalanda et al., 2007	3	MW	12 m	<3 m	> 3 m	BF	CDC 2000	n	n	n	n	N	−0.20	[−0.52; 0.12]	16.0	
RMA PE [95%CI]													**0.08**	**[−0.18; 0.35]**	**100.0**	
PI (95%)														**[−0.47; 0.63]**	--	
Heterogeneity: I^2 = 54% [0%; 83%], p = 0.07																



* Imputed standard deviation, & Combined estimates across study ACF groups adjusted for correlation.

Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass Index (BMI).

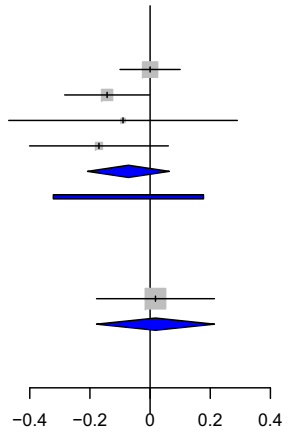
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, BMI = Body Mass Index, c = considered, CDC = Centers for Disease Control and Prevention, CI = confidence interval, EU = European Union, FF = formula fed, GM = Gambia, HN = Honduras, i = included, m = months, MD = mean difference, MW = Malawi, n = not considered, N = unadjusted, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, SGA = small for gestational age, T = term infants, UK = United Kingdom, US = United States, WHO = World Health Organization, y = years.

A.2. WAZ by feeding mode (exclusive breastfeeding or formula feeding) for studies rated as Tiers 1 and 2 comparing early introduction with later introduction of CFs

Weight−for−age z−score (WAZ) by feeding mode
(exclusive breastfeeding or formula feeding)

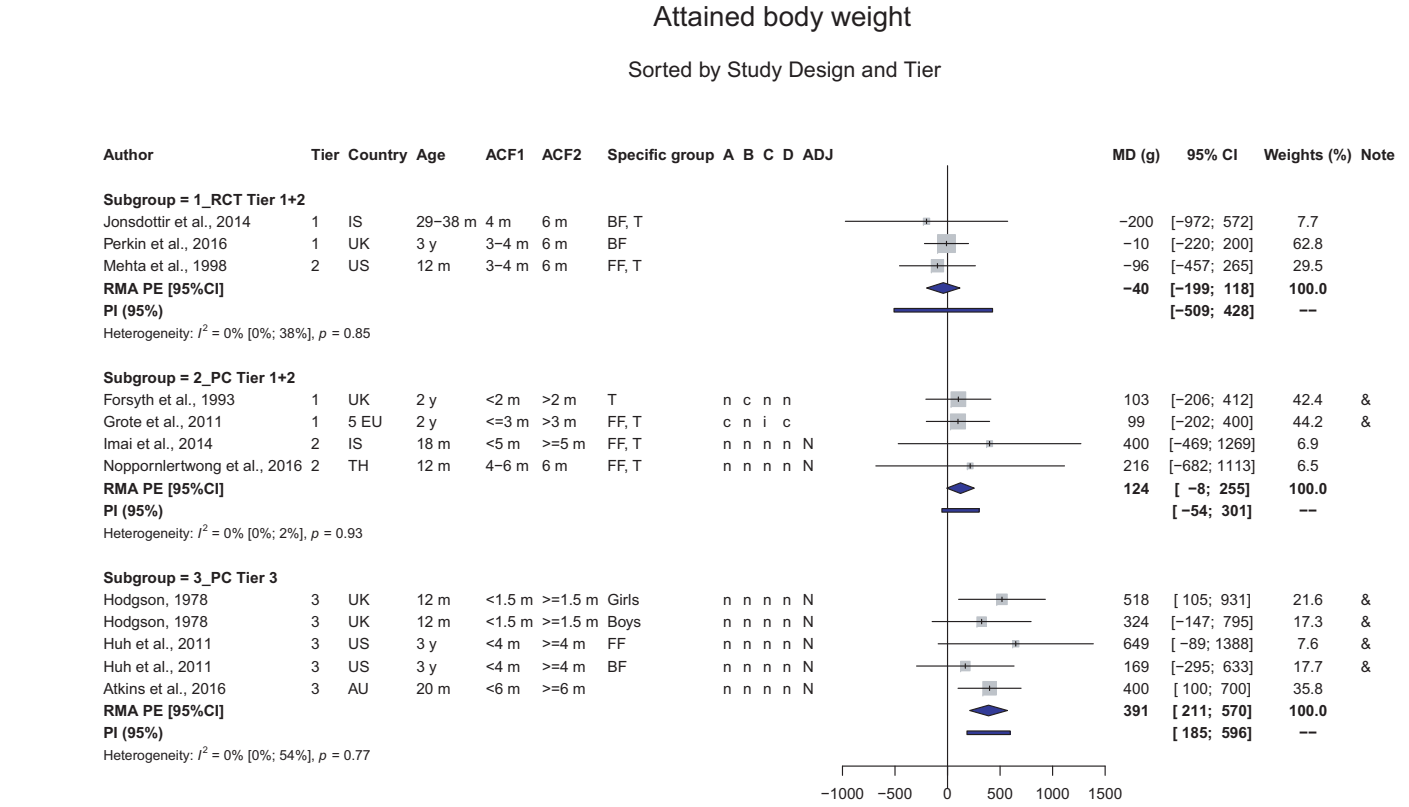
Sorted by Feeding Mode and Tier

Author	Tier	Study design	Country	Age	ACF1	ACF2	Reference data or cut−offs	A	B	C	D	MD (z−score)	95% CI	Weights (%)	Note
Subgroup = BF															
Perkin et al., 2016	1	RCT	UK	3 y	3−4 m	6 m	WHO 2006					0.00	[−0.10; 0.10]	55.0	
Eriksen et al., 2017	1	PC	GM	2 y	<6 m	>6 m	WHO 2006	i	n	i	i	−0.14	[−0.28; 0.00]	29.3	
Dewey et al., 1999	2	RCT	HN	12 m	4 m	6 m	CDC 1977					−0.09	[−0.47; 0.29]	4.3	
Haschke and van't Hof, 2000	2	PC	12 EU	3 y	<4 m	>4 m	internal	i	n	n	n	−0.17	[−0.40; 0.06]	11.4	*
RMA PE [95%CI]												**−0.07**	**[−0.21; 0.06]**	**100.0**	
PI (95%)													**[−0.32; 0.18]**	**--**	
Heterogeneity: I^2 = 17% [0%; 87%], p = 0.31															
Subgroup = FF															
Grote et al., 2011	1	PC	5 EU	2 y	<=3 m	>3 m	WHO 2006	c	n	i	c	0.02	[−0.18; 0.21]	100.0	&
RMA PE [95%CI]												**0.02**	**[−0.18; 0.21]**	**100.0**	
PI (95%)														**--**	
Heterogeneity: not applicable															



* Imputed standard deviation; & Combined estimates across study ACF groups adjusted for correlation.
Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass Index (BMI).
ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, c = considered, CDC = Centers for Disease Control and Prevention, CI = confidence interval, EU = European Union, FF = formula fed, HN = Honduras, GM = Gambia, i = included, m = months, MD = mean difference, n = not considered, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, WHO = World Health Organization, y = years.

A.3. Attained body weight comparing early introduction with later introduction of CFs



& Combined estimates across study ACF groups adjusted for correlation.
Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass Index (BMI).
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, AU = Australia, BF = breastfed, c = considered, CI = confidence interval, EU = European Union, FF = formula fed, i = included, IS = Iceland, m = months, MD = mean difference, n = not considered, N = unadjusted, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, T = term infants, TH = Thailand, UK = United Kingdom, US = United States, y = years.

Random effects meta-analysis calculated using the DerSimonian and Laird approach without the Hartung and Knapp modification:

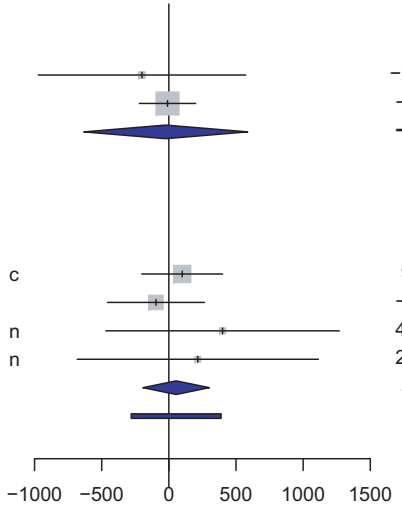
- subgroup of RCTs rated as Tiers 1 and 2: PE = −40; 95% CI [−217; 136]
- subgroup of prospective cohort studies rated as Tiers 1 and 2: PE = 124; 95% CI [−80; 327]

A.4. Attained body weight by feeding mode (exclusive breastfeeding or formula feeding) for studies rated as Tiers 1 and 2 comparing early introduction with later introduction of CFs

Attained body weight by feeding mode
(exclusive breastfeeding or formula feeding)

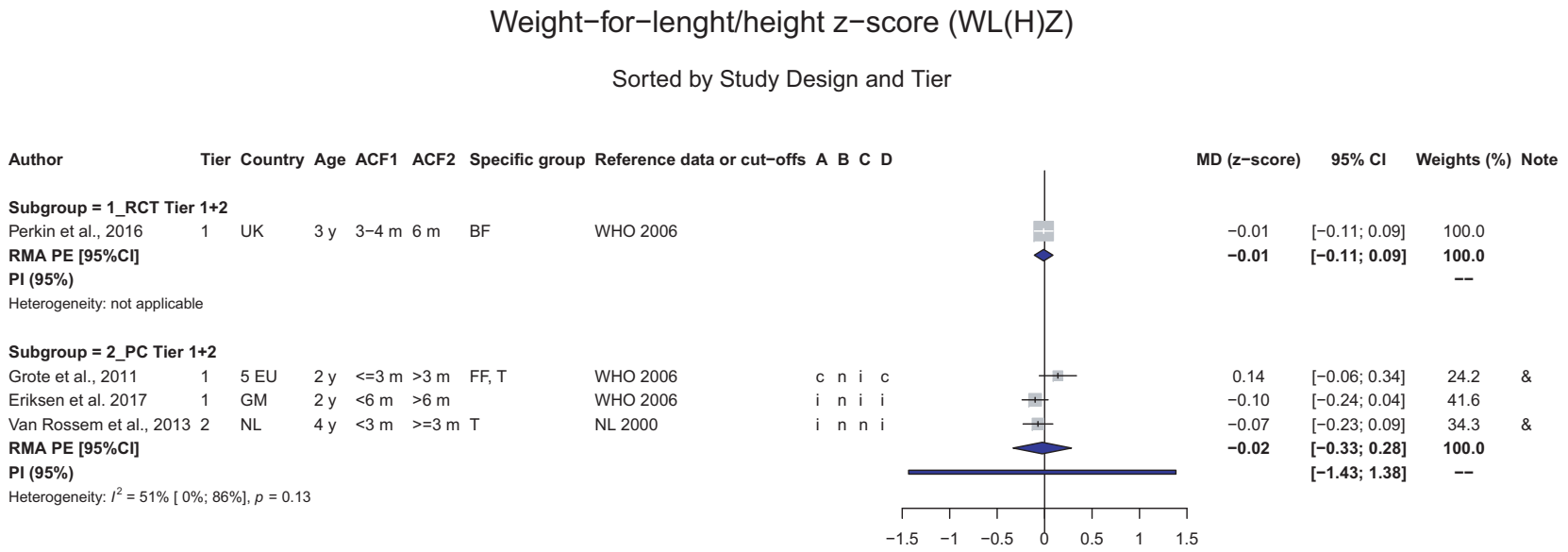
Sorted by Feeding Mode and Tier

Author	Tier	Study design	Country	Age	ACF1	ACF2	A	B	C	D	MD (g)	95% CI	Weights (%)	Note
Subgroup = BF														
Jonsdottir et al., 2014	1	RCT	IS	29−38 m	4 m	6 m					−200	[−972; 572]	6.9	
Perkin et al., 2016	1	RCT	UK	3 y	3−4 m	6 m					−10	[−220; 200]	93.1	
RMA PE [95%CI]											**−23**	**[−633; 587]**	**100.0**	
PI (95%)													**--**	
Heterogeneity: I^2 = 0%, p = 0.64														
Subgroup = FF														
Grote et al., 2011	1	PC	5 EU	2 y	<=3 m	>3 m	c	n	i	c	99	[−202; 400]	51.9	&
Mehta et al., 1998	1	RCT	US	12 m	3−4 m	6 m					−96	[−457; 265]	36.1	
Imai et al., 2014	2	PC	IS	18 m	<5 m	>=5 m	n	n	n	n	400	[−469; 1269]	6.2	
Noppornlertwong et al., 2016	2	PC	TH	12 m	4−6 m	6 m	n	n	n	n	216	[−682; 1113]	5.8	
RMA PE [95%CI]											**54**	**[−193; 302]**	**100.0**	
PI (95%)												**[−280; 389]**	**--**	
Heterogeneity: I^2 = 0% [0%; 69%], p = 0.69														



& Combined estimates across study ACF groups adjusted for correlation.
Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass Index (BMI).
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, c = considered, CI = confidence interval, EU = European Union, FF = formula fed, i = included, IS = Iceland, m = months, MD = mean difference, n = not considered, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, TH = Thailand, UK = United Kingdom, US = United States, y = years.

A.5. WL(H)Z comparing early introduction with later introduction of CFs



& Combined estimates across study ACF groups adjusted for correlation

Confounders: A = Education of the caregivers, B = socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass Index (BMI)

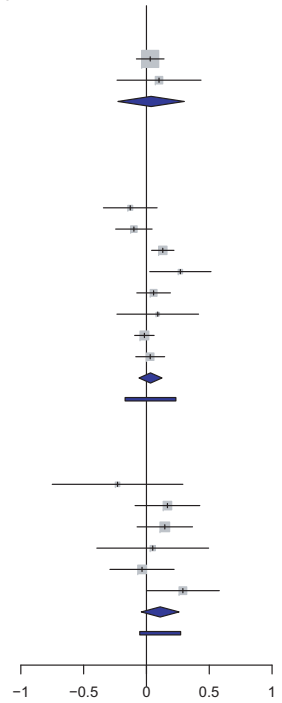
Abbreviations: ACF = age at complmentary feeding, ADJ = adjusted, BF = breastfed, c = considered, CI = confidence interval, EU = European Union, FF = formula fed, GM = Gambia, i = included, MD = mean difference, m = months, n = not considered, NL = Netherlands, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, T = term infants, UK = United Kingdom, WHO = World Health Organization, y = years.

A.6. L(H)AZ comparing early introduction with later introduction of CFs

Length/height−for−age z−score (L(H)AZ)

Sorted by Study Design and Tier

Author	Tier	Country	Age	ACF1	ACF2	Specific group	Reference data or cut−offs	C	E	ADJ	MD (z−score)	95% CI	Weights (%)	Note
Subgroup = 1_RCT Tier 1+2														
Perkin et al., 2016	1	UK	3 y	3−4 m	6 m	BF	WHO 2006				0.03	[−0.08; 0.14]	84.0	
Dewey et al., 1999	2	HN	12 m	4 m	6 m	BF, SGA, T	CDC 1977				0.10	[−0.23; 0.43]	16.0	*
RMA PE [95%CI]											**0.04**	**[−0.23; 0.30]**	**100.0**	
PI (95%)													**--**	
Heterogeneity: I^2 = 0%, p = 0.70														
Subgroup = 2_PC Tier 1+2														
Grote et al., 2011	1	5 EU	2 y	<=3 m	>3 m	FF, T	WHO 2006	i	n		−0.13	[−0.34; 0.08]	6.9	&
Eriksen et al., 2017	1	GM	2 y	<6 m	>6 m		WHO 2006	n	i		−0.10	[−0.25; 0.05]	12.1	
de Beer et al., 2015	2	NL	5−6 y	<4 m	>=4 m	T	internal	i	i		0.13	[0.04; 0.22]	20.3	&
Haschke and van't Hof, 2000	2	12 EU	3 y	<4 m	>4 m	BF	internal	n	i		0.27	[0.03; 0.51]	5.5	*
Moschonis et al., 2017	2	FR	5 y	<5 m	5−6 m			n	n		0.06	[−0.08; 0.19]	13.4	&
Moschonis et al., 2017	2	FR	5 y	5−6 m	>=6 m			n	n		0.09	[−0.23; 0.41]	3.4	
Moschonis et al., 2017	2	UK	9 y	<5 m	5−6 m			n	n		−0.02	[−0.09; 0.06]	22.5	&
Moschonis et al., 2017	2	UK	9 y	5−6 m	>=6 m			n	n		0.03	[−0.08; 0.14]	15.9	
RMA PE [95%CI]											**0.03**	**[−0.06; 0.12]**	**100.0**	
PI (95%)												**[−0.17; 0.23]**	**--**	
Heterogeneity: I^2 = 55% [0%; 80%], p = 0.03														
Subgroup = 3_PC Tier 3														
Heinig et al., 1993	3	US	18 m	<6 m	>6 m	BF, T	CDC 1977	n	n	N	−0.23	[−0.75; 0.29]	5.8	
Huh et al., 2011	3	US	3 y	<4 m	>=4 m	FF	CDC 2000	n	n	N	0.17	[−0.09; 0.42]	21.0	&
Huh et al., 2011	3	US	3 y	<4 m	>=4 m	BF	CDC 2000	n	n	N	0.15	[−0.07; 0.37]	27.1	&
Moschonis et al., 2017	3	GR	4 y	5−6 m	>=6 m			n	n		0.05	[−0.39; 0.49]	7.8	
Moschonis et al., 2017	3	PT	4 y	<5 m	5−6 m			n	n		−0.04	[−0.29; 0.22]	21.3	&
Moschonis et al., 2017	3	PT	4 y	5−6 m	>=6 m			n	n		0.29	[0.00; 0.58]	17.1	
RMA PE [95%CI]											**0.11**	**[−0.04; 0.26]**	**100.0**	
PI (95%)												**[−0.05; 0.27]**	**--**	
Heterogeneity: I^2 = 0% [0%; 73%], p = 0.45														



* Imputed standard deviation; & Combined estimates across study ACF groups adjusted for correlation.

Confounders: C = Previous measurements, E = Parental height.

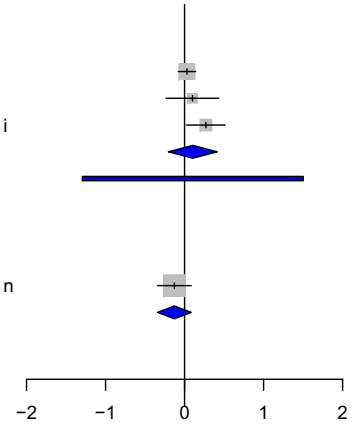
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, CDC = Centers for Disease Control and Prevention, CI = confidence interval, EU = European Union, FF = formula fed, FR = France, GR = Greece, GM = Gambia, HN = Honduras, i = included, m = months, MD = mean difference, n = not considered, N = unadjusted, NL = Netherlands, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, PT = Portugal, RCT = randomised controlled trial, RMA = random effects meta−analysis, SGA = small for gestational age, T = term infants, UK = United Kingdom, US = United States, WHO = World Health Organization, y = years.

A.7. L(H)AZ by feeding mode (exclusive breastfeeding or formula feeding) for studies rated as Tiers 1 and 2 comparing early introduction with later introduction of CFs

Length/height−for−age z−score (L(H)AZ) by feeding mode
(exclusive breastfeeding or formula feeding)

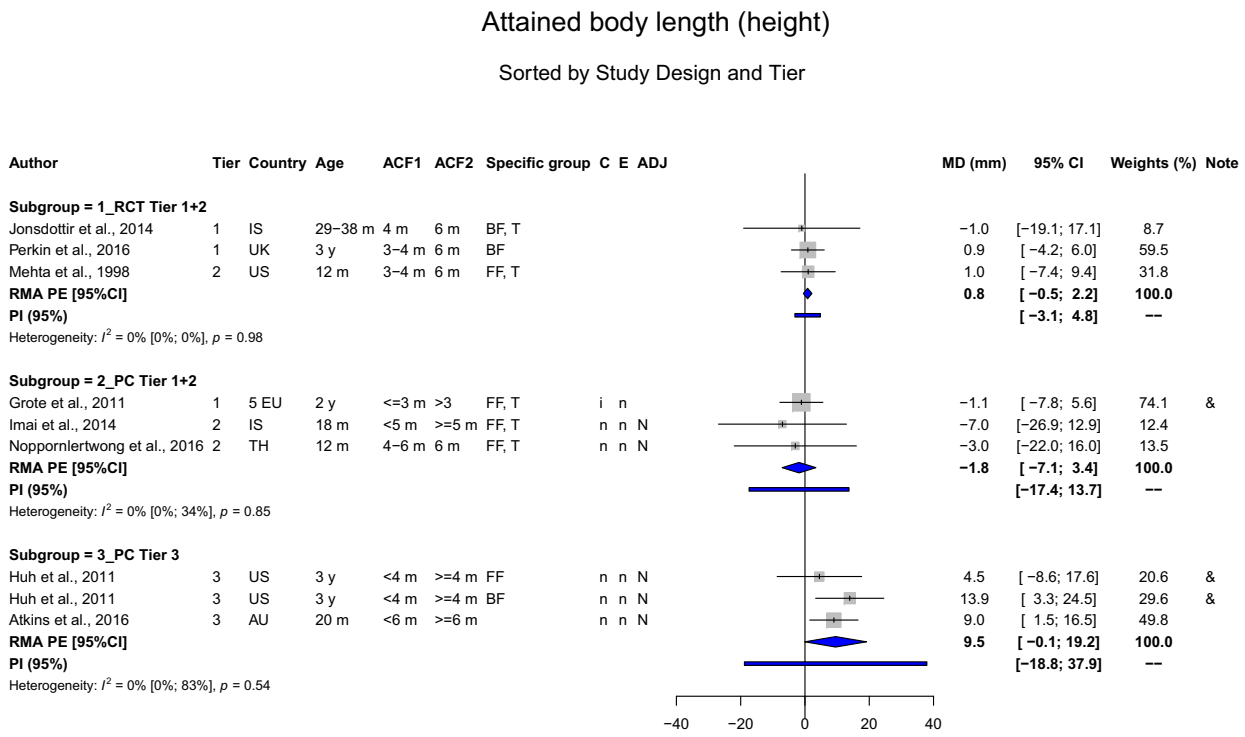
Sorted by Feeding Mode and Tier

Author	Tier	Study design	Country	Age	ACF1	ACF2	Reference data or cut−offs	C	E	MD (z−score)	95% CI	Weights (%)	Note
Subgroup = BF													
Perkin et al., 2016	1	RCT	UK	3 y	3−4 m	6 m	WHO 2006			0.03	[−0.08; 0.14]	53.1	
Dewey et al., 1999	2	RCT	HN	12 m	4 m	6 m	CDC 1977			0.10	[−0.23; 0.43]	18.6	*
Haschke and van't Hof, 2000	2	PC	12 EU	3 y	<4 m	>4 m	internal	n	i	0.27	[0.03; 0.51]	28.3	*
RMA PE [95%CI]										**0.10**	**[−0.21; 0.41]**	**100.0**	
PI (95%)											**[−1.29; 1.50]**	**--**	
Heterogeneity: I^2 = 36% [0%; 79%], p = 0.21													
Subgroup = FF													
Grote et al., 2011	1	PC	5 EU	2 y	<=3 m	>3 m	WHO 2006	i	n	−0.13	[−0.34; 0.08]	100.0	&
RMA PE [95%CI]										**−0.13**	**[−0.34; 0.08]**	**100.0**	
PI (95%)												**--**	
Heterogeneity: not applicable													



* Imputed standard deviation, & Combined estimates across study ACF groups adjusted for correlation.
Confounders: C = Previous measurements, E = Parental height.
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, CDC = Centers for Disease Control and Prevention, CI = confidence interval, EU = European Union, FF = formula fed, HN = Honduras, i = included, m = months, MD = mean difference, n = not considered, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = Random effects meta analysis, UK = United Kingdom, WHO = World Health Organization, y = years.

A.8. Attained body length/height comparing early introduction with later introduction of CFs

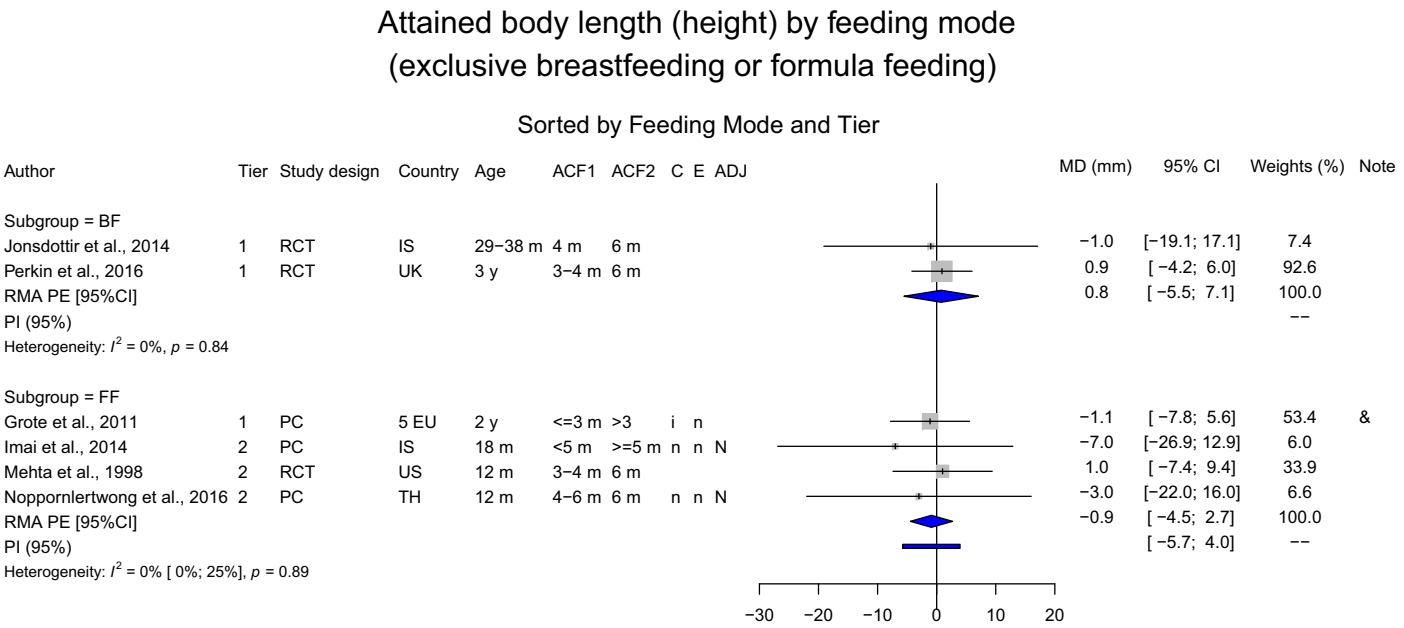


& Combined estimates across study ACF groups adjusted for correlation.
Confounders: C = Previous measurements; E = Parental height.
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, AU = Australia, BF = breastfed, CI = confidence interval, EU = European Union, FF = formula fed, i = included, IS = Iceland, m = months, MD = mean difference, n = not considered, N = unadjusted, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, T = term infants, TH = Thailand, UK = United Kingdom, US = United States, y = years.

Random effects meta-analysis calculated using the DerSimonian and Laird approach <u>without</u> the Hartung and Knapp modification:

- subgroup of RCTs rated as Tiers 1 and 2: PE: 0.8; 95% CI [−3.4; 5.0]
- subgroup of prospective cohort studies rated as Tiers 1 and 2: PE = −1.8; 95% CI [−7.9; 4.2]

A.9. Attained body length/height by feeding mode (exclusive breastfeeding or formula feeding) for studies rated as Tiers 1 and 2 comparing early introduction with later introduction of CFs

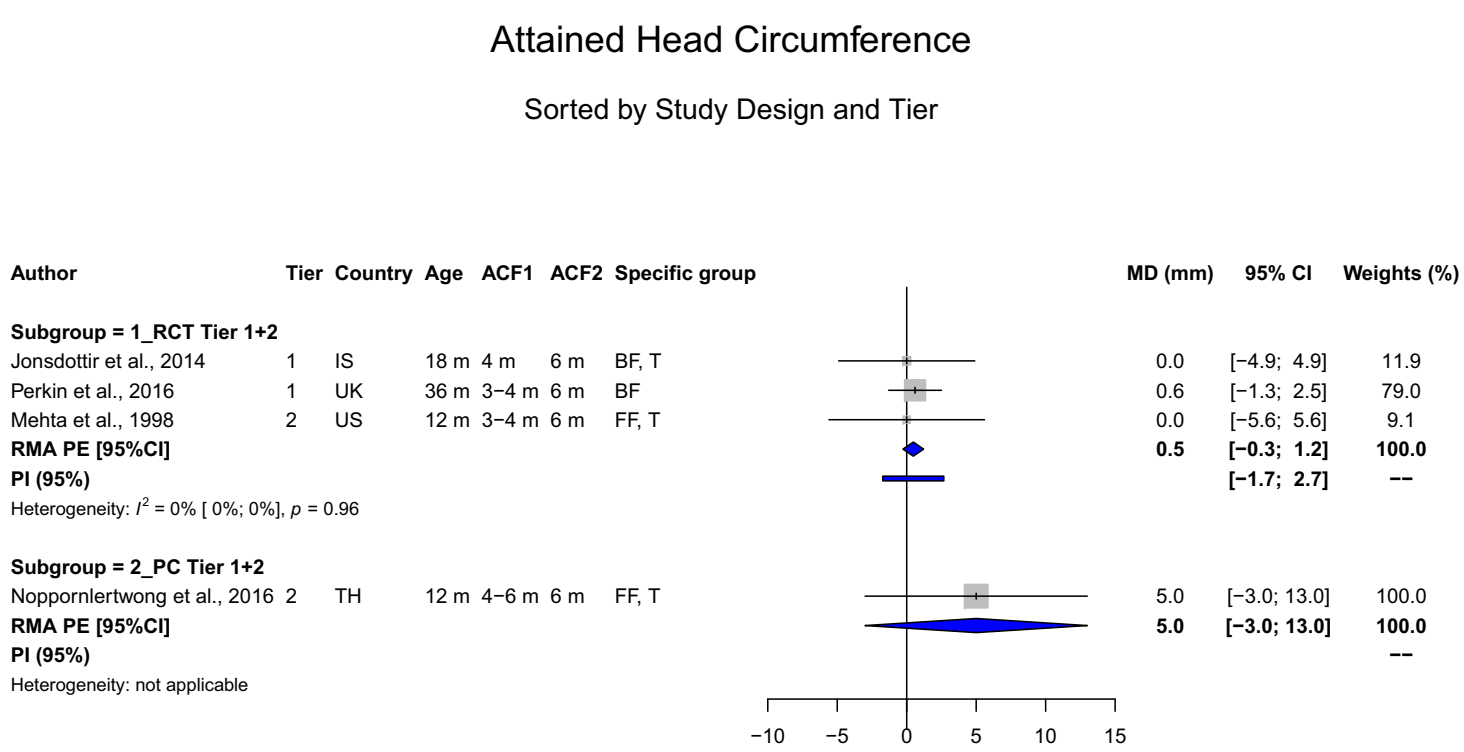


& Combined estimates across study ACF groups adjusted for correlation.
Confounders: C = Previous measurements, E = Parental height.
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, CI = confidence interval, EU = European Union, FF = formula fed, i = included, IS = Iceland, m = months, MD = mean difference, n = not considered, N = unadjusted, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, TH = Thailand, UK = United Kingdom, US = United States, y = years.

Random effects meta-analysis calculated using the DerSimonian and Laird approach without the Hartung and Knapp modification:

- subgroup of formula fed infants PE = −0.9; 95% CI [−5.8; 4.0]

A.10. Attained head circumference comparing early introduction with later introduction of CFs



Abbreviations: ACF = age at complementary feeding, BF = breastfed, CI = confidence interval, FF = formula fed, IS = Iceland, m = months, MD = mean difference, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, T = term infants, TH = Thailand, UK = United Kingdom, US = United States.

Random effects meta-analysis calculated using the DerSimonian and Laird approach without the Hartung and Knapp modification:

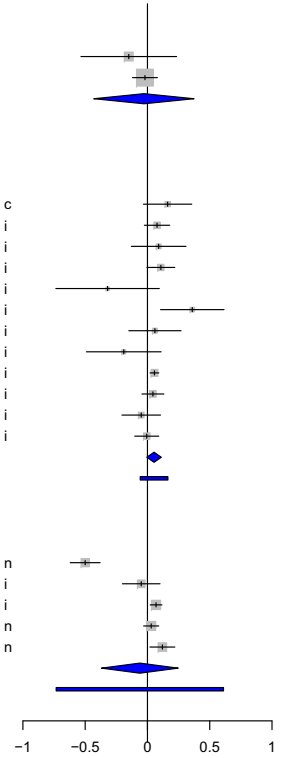
- subgroups of RCTs rated as Tiers 1 and 2 PE = 0.5; 95% CI [−1.2; 2.2]

A.11. BMIZ comparing early introduction with later introduction of CFs

BMI z−score (BMIZ)

Sorted by Study Design and Tier

Author	Tier	Country	Age	ACF1	ACF2	Specific group	Reference data or cut−offs	A	B	C	D	MD (z−score)	95% CI	Weights (%)	Note
Subgroup = 1_RCT Tier 1+2															
Jonsdottir et al., 2014	1	IS	29−38 m	4 m	6 m	BF, T	WHO 2006					−0.15	[−0.53; 0.23]	21.7	
Perkin et al., 2016	1	UK	3 y	3−4 m	6 m	BF	WHO 2006					−0.02	[−0.12; 0.08]	78.3	
RMA PE [95%CI]												**−0.03**	**[−0.43; 0.37]**	**100.0**	
PI (95%)														**--**	
Heterogeneity: I^2 = 0%, p = 0.52															
Subgroup = 2_PC Tier 1+2															
Grote et al., 2011	1	5 EU	2 y	<=3 m	>3 m	FF, T	WHO 2006	c	n	i	c	0.16	[−0.03; 0.36]	7.3	&
Azad et al., 2018	2	CA	12 m	<4 m	>= 4 m	T	WHO 2006	i	n	n	i	0.08	[−0.02; 0.18]	11.1	&
Burdette et al., 2006	2	US	5 y	<4 m	>=4 m	T	CDC 2000	i	i	n	i	0.09	[−0.13; 0.31]	6.5	
de Beer et al., 2015	2	NL	5−6 y	<4 m	>= 4 m	T	internal	i	n	i	i	0.11	[0.00; 0.22]	10.6	&
Huh et al., 2011	2	US	3 y	4−5 m	>=6 m	FF	CDC 2000	i	i	i	i	−0.32	[−0.74; 0.10]	2.7	
Huh et al., 2011	2	US	3 y	<4 m	4−5 m	FF	CDC 2000	i	i	i	i	0.36	[0.11; 0.61]	5.5	
Huh et al., 2011	2	US	3 y	4−5 m	>=6 m	BF	CDC 2000	i	i	i	i	0.06	[−0.15; 0.27]	6.8	
Huh et al., 2011	2	US	3 y	<4 m	4−5 m	BF	CDC 2000	i	i	i	i	−0.19	[−0.49; 0.11]	4.4	
Zheng et al., 2015	2	CN	4−5 y old	<=3 m	>3 m		WHO 2006	i	n	i	i	0.06	[0.02; 0.09]	13.4	*&
Vogelezang et al. 2018	2	NL	10 y	<4 m	>=4 m		Internal	i	n	n	i	0.04	[−0.04; 0.13]	11.6	&
Fairley et al., 2015	2	UK	3 y	<4 m	>=4 m		WHO 2006	i	n	n	i	−0.05	[−0.20; 0.10]	8.8	
Leary et al., 2015	2	UK	15 y	<=2 m	>2 m		Internal	i	i	n	i	−0.01	[−0.10; 0.09]	11.3	&
RMA PE [95%CI]												**0.05**	**[−0.01; 0.11]**	**100.0**	
PI (95%)													**[−0.06; 0.16]**	**--**	
Heterogeneity: I^2 = 35% [0%; 67%], p = 0.11															
Subgroup = 3_PC Tier 3															
Haschke and van't Hof, 2000	3	12 EU	3 y	<4 m	>4 m	BF, T	internal	i	n	n	n	−0.50	[−0.62; −0.38]	18.3	*
Iguacel et al., 2018	3	AU	10 y	<4 m	>=4m		CDC 2000	n	i	n	i	−0.05	[−0.20; 0.10]	16.0	
Schmidt Morgen et al., 2018	3	DK	11 y	<4 m	>=4 m	T	internal	n	i	n	i	0.07	[0.02; 0.12]	23.3	
Wilson et al., 1998	3	UK	7.2 yrs	<3.5 m	>= 3.5 m	BF, T	UK 1995 BMI	n	c	i	n	0.03	[−0.03; 0.09]	22.5	
Wilson et al., 1998	3	UK	7.2 yrs	<3.5 m	>= 3.5 m	FF, T	UK 1995 BMI	n	c	i	n	0.12	[0.02; 0.22]	19.9	
RMA PE [95%CI]												**−0.06**	**[−0.37; 0.25]**	**100.0**	
PI (95%)													**[−0.73; 0.61]**	**--**	
Heterogeneity: I^2 = 95% [91%; 97%], p < 0.01															



* Imputed standard deviation, & Combined estimates across study ACF groups adjusted for correlation.

Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass index (BMI).

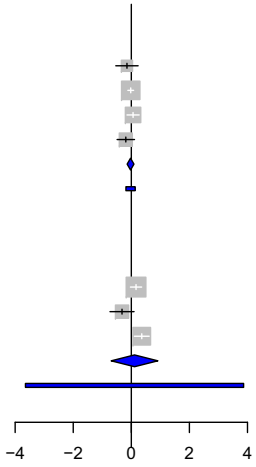
Abbreviations: ACF = age at complementary feeding, AU = Australia, BF = breastfed, BMI = Body Mass Index, c = considered, CA = Canada, CI = confidence interval, CDC = Center for Disease Control and Prevention, CN = China, DK = Denmark, EU = European Union, FF = formula fed, i = included, IS = Iceland, m = months, MD = mean difference, n = not considered, NL = Netherlands, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, SD = standard deviation, T = term infants, UK = United Kingdom, US = United States, WHO = World Health Organization, y = years.

A.12. BMIZ by feeding mode (exclusive breastfeeding or formula feeding) for studies rated as Tiers 1 and 2 comparing early introduction with later introduction of CFs

BMI z−score by feeding mode
(exclusive breastfeeding or formula feeding)

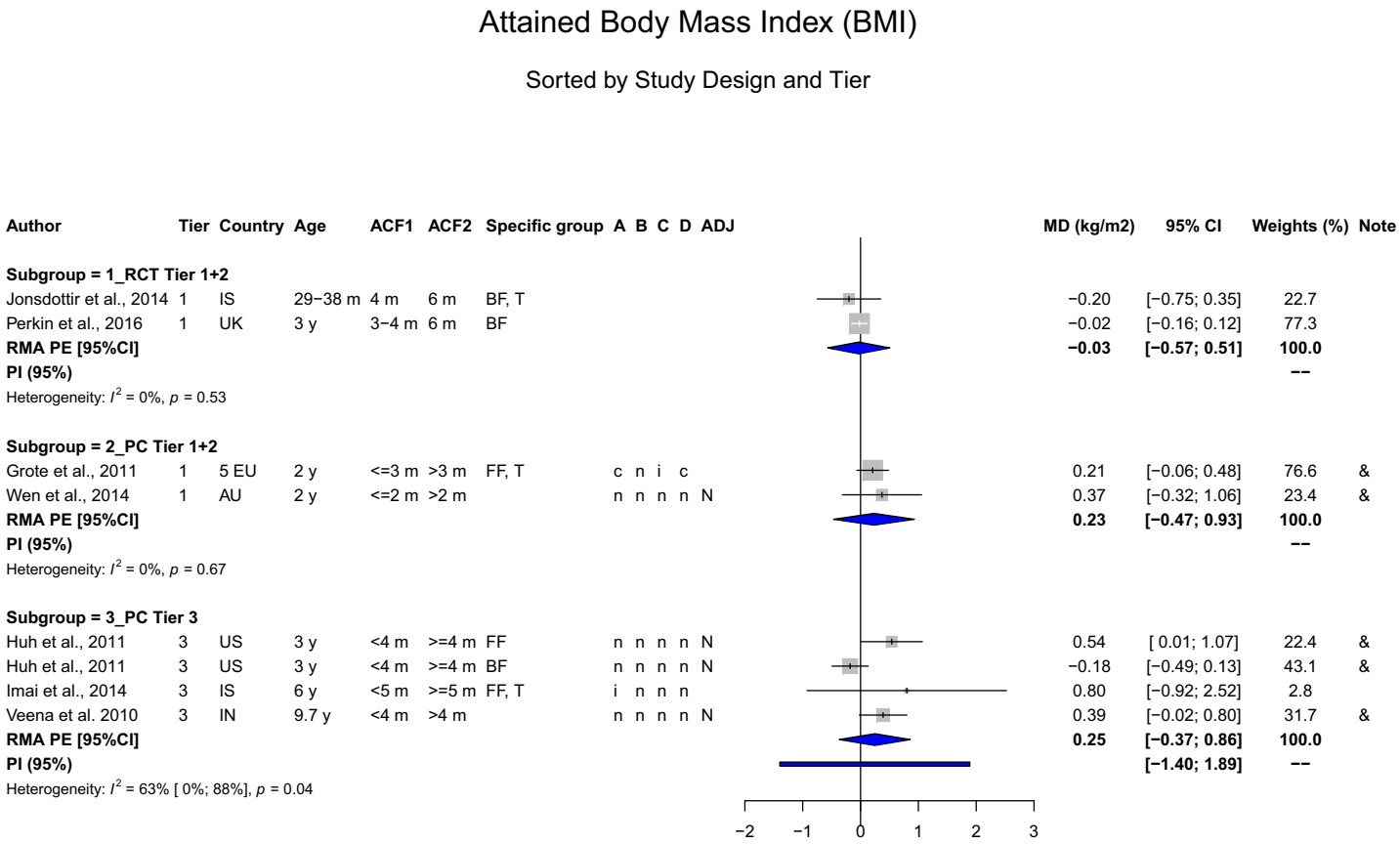
Sorted by Feeding Mode and Tier

Author	Tier	Study design	Country	Age	ACF1	ACF2	Reference data or cut−offs	A	B	C	D	MD (z−score)	95% CI	Weights (%)	Note
Subgroup = BF															
Jonsdottir et al., 2014	1	RCT	IS	29−38 m	4 m	6 m	WHO 2006					−0.15	[−0.53; 0.23]	14.3	
Perkin et al., 2016	1	RCT	UK	3 y	3−4 m	6 m	WHO 2006					−0.02	[−0.12; 0.08]	38.9	
Huh et al., 2011	2	PC	US	3 y	4−5 m	>=6 m	CDC 2000	i	i	i	i	0.06	[−0.15; 0.27]	27.3	
Huh et al., 2011	2	PC	US	3 y	<4 m	4−5 m	CDC 2000	i	i	i	i	−0.19	[−0.49; 0.11]	19.5	
RMA PE [95%CI]												**−0.03**	**[−0.14; 0.09]**	**100.0**	
PI (95%)													**[−0.19; 0.13]**	**−−**	
Heterogeneity: I^2 = 0% [0%; 79%], p = 0.53															
Subgroup = FF															
Grote et al., 2011	1	PC	5 EU	2 y	<=3 m	>3 m	WHO 2006	c	n	i	c	0.16	[−0.03; 0.36]	44.6	&
Huh et al., 2011	2	PC	US	3 y	4−5 m	>=6 m	CDC 2000	i	i	i	i	−0.32	[−0.73; 0.09]	19.9	
Huh et al., 2011	2	PC	US	3 y	<4 m	4−5 m	CDC 2000	i	i	i	i	0.36	[0.11; 0.61]	35.6	
RMA PE [95%CI]												**0.11**	**[−0.69; 0.91]**	**100.0**	
PI (95%)													**[−3.65; 3.87]**	**−−**	
Heterogeneity: I^2 = 73% [10%; 92%], p = 0.02															



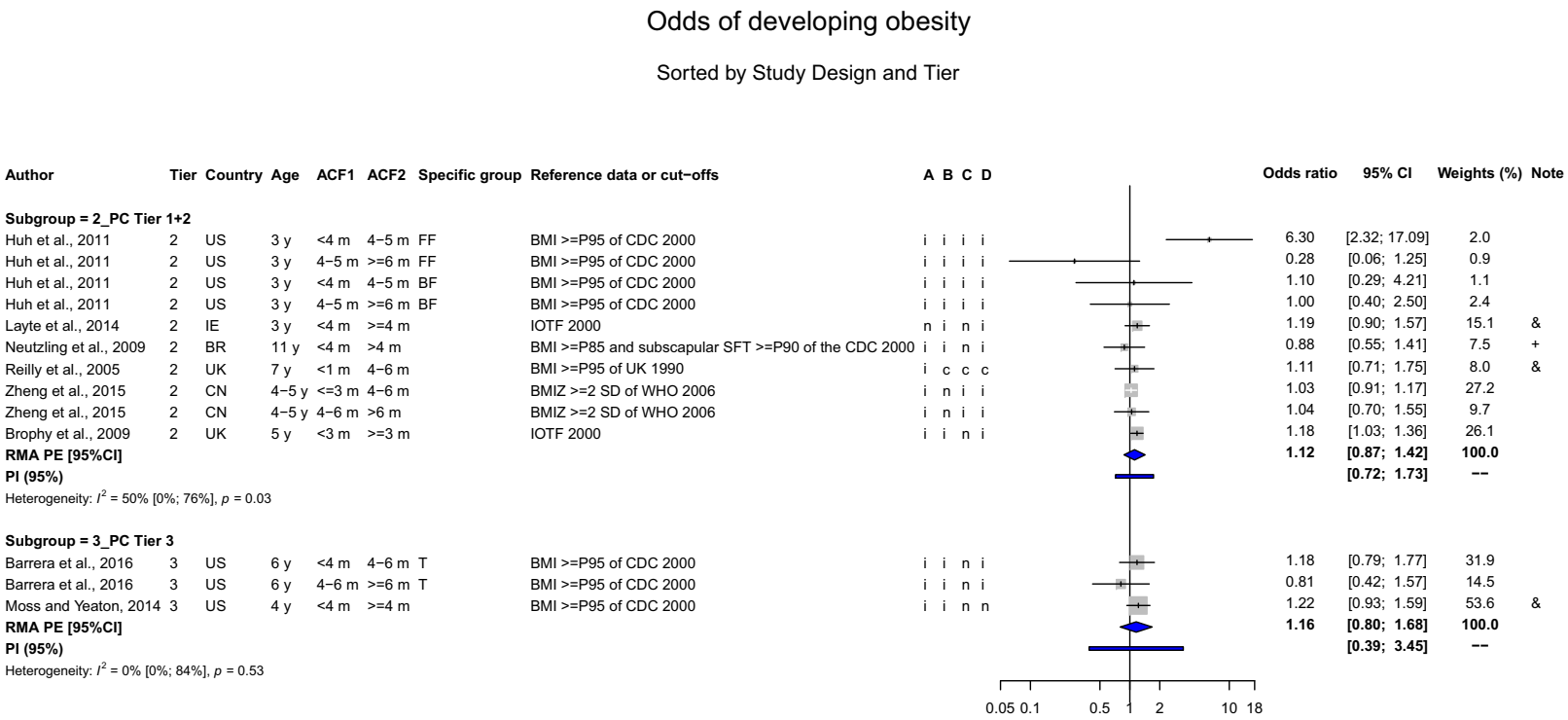
& Combined estimates across study ACF groups adjusted for correlation.
Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass index (BMI).
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, c = considered, CI = confidence interval, CDC = Center for Disease Control and Prevention, EU = European Union, FF = formula fed, i = included, IS = Iceland, m = months, MD = mean difference, n = not considered, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, UK = United Kingdom, US = United States, WHO = World Health Organization, y = years.

A.13. Attained BMI comparing early introduction with later introduction of CFs



& Combined estimates across study ACF groups adjusted for correlation.
Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass Index (BMI).
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, AU = Australia, BF = breastfed, c = considered, CI = confidence interval, EU = European Union, FF = formula fed, i = included, IN = India, IS = Iceland, m = months, MD = mean difference, n = not considered, N = unadjusted, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RCT = randomised controlled trial, RMA = random effects meta−analysis, T = term infants, UK = United Kingdom, US = United States, y = years.

A.14. Odds of developing obesity comparing early introduction with later introduction of CFs



+ Risk Ratio (RR), & Combined estimates across study ACF groups adjusted for correlation.
Confounders: A = Education of the caregivers, B = Socioeconomic status (SES), C = Previous measurements, D = Parental Body Mass Index (BMI).
Abbreviations: ACF = age at complementary feeding, ADJ = adjusted, BF = breastfed, BMI = Body Mass Index, BMIZ = Body Mass Index z−score, BR = Brazil, c = considered, CI = confidence interval, CDC = Centers for Disease Control and Prevention, CN = China, FF = formula fed, i = included, IE = Ireland, IOTF = International Obesity Task Force, m = months, n = not considered, PC = prospective cohort, PE = pooled estimate, PI = prediction interval, RMA = random effects meta−analysis, SD = standard deviation, SFT = skinfold thickness, T = term infants, UK = United Kingdom, US = United States, WHO = World Health Organization, y = years.