APPENDIX 2

Recommendations 9-13

A2. Complementary Feeding (CF) onset age

Key questions

- ***Does the onset of CF before 6 months of life lead to different nutritional and metabolic outcomes, in the short and long term, compared to exclusive breastfeeding for up to 6 months of age?***

- ***Does the onset of CF before 6 months of life lead to different nutritional and metabolic outcomes, in the short and long term, compared to feeding exclusively with infant formula or mixed (breastfeed + infant formula) for up to 6 months of age?***

PICOs

a.
P Healthy infant exclusively breastfed
I The onset of Complementary Feeding (CF) before 6 months completed (between 4 and 6 months of age)
C Compared to an onset of the Complementary Feeding (CF) at 6 months completed
O Different nutritional and metabolic outcomes in the short and long term

b.
P Healthy infant exclusively or predominantly fed with infant formula.
I The onset of Complementary Feeding (CF) before 6 months completed (between 4 and 6 months of age)
C Compared to an onset of the Complementary Feeding (CF) at 6 months completed
O Different nutritional and metabolic outcomes in the short and long term

KEYWORDS

Population

A. Infant
B. Child
C. [child]/lim
D. [infant]/lim

Exposure Factors / Comparison

MeSH Terms/ Text word: weaning; diet; food; infant; beverages; infant nutritional physiological phenomena; meals; food and beverages; infant food; eating; bottle feeding: bottle-fed; diet; diets; breastfeeding

A. Feeding, Breast

B. Breastfeeding
C. Breast Feeding, Exclusive
D. Exclusive Breast Feeding
E. Breastfeeding, Exclusive
F. Exclusive Breastfeeding
G. Bottle feeding duration
H. Breastfeeding duration
I. Solid food
J. Complementary feeding
K. Early weaning
L. Early complementary feeding
M. 'complementary feeding'/exp
N. 'weaning'/exp

Outcomes

A. Overnutrition
B. Obesity
C. Growth
D. Body Size
E. Body Height
F. Diabetes Mellitus
G. Noncommunicable Diseases
H. Nutritional and Metabolic Diseases
I. Pediatric Obesity
J. Overweight
K. Body Mass Index
L. Body Weight Changes
M. Body Weight
N. Body Composition
O. Nutritional Status
P. Growth and Development
Q. Fat body
R. Adipose tissue
S. Body fat
T. Adiposity rebound
U. 'obesity'/exp
V. 'body mass'/exp
W. 'overweight'
X. 'body weight'/exp
Y. growth
Z. 'growth'/exp
AA. 'adiposity rebound'/exp

Guidelines search

Temporal limitation: 2014-2021

PUBMED https://www.ncbi.nlm.nih.gov/pubmed/

#1

(((((("Infant Nutritional Physiological Phenomena"[Mesh]) AND "Overnutrition"[Mesh]) OR "Growth"[Mesh]) OR "Diabetes Mellitus"[Mesh]) OR "Nutritional and Metabolic Diseases"[Mesh]) OR "Noncommunicable Diseases"[Mesh]

#2

(Complementary OR supplementary OR wean* OR transition* OR introduc* OR "Infant Nutritional Physiological Phenomena"[Mesh:noexp] OR weaning[mesh] OR ((Solid food*) OR solids)) OR “infant food”[mesh] OR infant feed*) AND (feeding* OR food* OR beverage*[tiab] OR beverages[mh] OR eating OR diet[tiab] OR diet[mh] OR meal*[tiab] OR meals[mh] OR "Food and Beverages"[Mesh] OR diets[tiab] OR “infant food”[mesh] OR infant feed* OR Bottle feeding[mh] OR bottle feeding*[tiab] OR bottle feeding OR bottle-feeding*[tiab] OR bottle-feedings OR bottle-fed[tiab] OR “bottle fed”[tiab] OR solid food

Filters activated: Guideline, Practice Guideline, published in the last 5 years.

#3

((((((("Bottle Feeding"[Mesh]) OR "Breast Feeding"[Mesh]) OR "Infant Nutritional Physiological Phenomena"[Mesh]) OR "Weaning"[Mesh]) Or "Early weaning") OR "early introduction complementary feeding")

#4

((("Weaning"[All Fields]) OR "Infant Nutritional Physiological Phenomena"[MeSH]) OR "complementary feeding"[All Fields]) AND ((((((((((("Obesity"[Mesh] OR "Pediatric Obesity"[Mesh]) OR "Overweight"[Mesh]) OR "Body Mass Index"[Mesh]) OR "Body Weight Changes"[Mesh]) OR "Body Weight"[Mesh]) OR "Body Composition"[Mesh]) OR "Nutritional Status"[Mesh]) OR "Growth and Development"[Mesh]) OR "Growth"[Mesh]) OR "fat body"[MeSH Terms]) OR "adipose tissue"[MeSH Terms]) OR body fat[Text Word]) OR “adiposity rebound” [Text Word]) AND "2014/05/08"[PDat]:"2021/08/14"[PDat] AND "infant"[MeSH Terms])

#5

(("weaning"[MeSH Terms] OR "weaning"[All Fields]) OR ("eating"[MeSH Terms] OR "eating"[All Fields]) OR "Feeding Behavior"[All Fields] OR "Complementary Feeding"[All Fields]) AND timing[All Fields] AND ("Growth and Development"[All Fields] OR ("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms]) OR "Nutritional Status"[All Fields] OR "Noncommunicable Diseases"[All Fields]) AND ((Practice Guideline[ptyp] OR Guideline[ptyp]) AND "2014/08/22"[PDat] : "2021/08/14"[PDat])

#6

("Nutritional Physiological Phenomena"[All Fields] OR "Infant Nutritional Physiological Phenomena"[All Fields] OR ("weaning"[MeSH Terms] OR "weaning"[All Fields])) AND ("Breast feeding"[All Fields] OR "Exclusive Breast Feeding"[All Fields] OR "bottle feeding"[All Fields] OR "formula feeding"[All Fields] OR "Exclusive bottle feeding"[All Fields] OR "Exclusive formula feeding"[All Fields]) AND ((timing[All Fields] AND ("food"[MeSH Terms] OR "food"[All Fields]) AND introduction[All Fields]) OR "Early infant feeding practice"[All Fields] OR "Early complementary feeding"[All Fields] OR (Timing[All Fields] AND ("food"[MeSH Terms] OR "food"[All Fields]) AND introduction[All Fields])) AND ("body composition"[All Fields] OR "fat

mass"[All Fields] OR "Noncommunicable Disease"[All Fields] OR "Non Communicable Disease"[All Fields])

EMBASE https://www.embase.com

#1

(('bottle feeding'/exp OR 'bottle feeding' OR 'bottle feeding duration' OR 'breast feeding'/exp OR 'breast feeding' OR 'breast feeding duration'/exp OR 'breast feeding duration') AND ('weaning'/exp OR 'weaning' OR 'complementary feeding'/exp OR 'complementary feeding' OR 'early weaning' OR 'early complementary feeding')) AND ([2014-2021]/py AND ('practice guideline'/exp OR 'practice guideline' OR 'guideline'/exp OR guideline))

#2

l622344621/sim

#3

('complementary feeding'/exp OR 'complementary feeding' OR 'weaning'/exp OR weaning) AND ('obesity'/exp OR obesity OR 'body weight'/exp OR 'body weight' OR 'growth'/exp OR growth OR 'adiposity rebound'/exp OR 'adiposity rebound')

#3 AND (2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py) AND 'practice guideline'/de

UPTODATE https://www.uptodate.com/home

Society Guideline Links: *Breastfeeding and infant nutrition*

SOCIETY GUIDELINE LINKS: *Complementary feeding, Weaning, Alimentary – nutrition, Breastfeeding, and Complementary Feeding*

National Guideline Clearinghouse (NGC) https://www.ahrq.gov/gam/index.html

Canadians Medical Association (CMA) https://www.cma.ca/clinicalresources/practiceguidelines

National Guideline Centre (NGC) - National Institute of Health and Care Excellence (NICE) https://www.rcplondon.ac.uk/about-us/what-we-do/national-guideline-centre-ngc

Scottish Intercollegiate Guidelines Network (SIGN) https://www.sign.ac.uk/our-guidelines.html

Australian Clinical Practice Guidelines (ACPG) https://www.clinicalguidelines.gov.au/

New Zealand Guidelines Group (NZGG) https://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group

American Academy of Pediatrics (AAP) https://www.aap.org/en-us/Pages/Default.aspx
DateRange (01/01/2013-03/19/2021) AND ((complementary feeding) OR (weaning)) AND (Guideline)

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) https://www.naspghan.org/

European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) http://www.espghan.org/

Geneva Foundation for Medical Education and Research (GFMER) https://www.gfmer.ch/Guidelines/Allattamento_it/Allattamento_alimentazione_complementare.htm

Società Italiana di Nutrizione Umana (SINU) http://www.sinu.it

Società Italiana di Pediatria (SIP) http://www-sip.it/

Società Italiana di Pediatria Preventiva e Sociale (SIPPS) https://www.sipps.it/

Società Italiana di Nutrizione Pediatrica (SINUPE) https://www.sip.it/2017/09/21/sinupe-societa-italiana-di-nutrizione-pediatrica/

Società Italiana di Endocrinologia e Diabetologia Pediatrica (SIEDP) http://www.siedp.it/pagina/84/linee+guida%2C+raccomandazioni+e+consensus

Systematic Reviews search

Temporal limitation: 2011-2021

PUBMED

#1

(Child Nutritional Physiological Phenomena OR Infant Nutritional Physiological Phenomena OR Weaning) AND (Breastfeeding OR Exclusive Breast Feeding OR bottle feeding OR formula feeding OR, Exclusive bottle-feeding OR Exclusive formula feeding) AND (timing food introduction OR Early infant feeding practice OR Early complementary feeding OR Timing of food introduction) AND (body composition OR fat mass OR Noncommunicable Disease OR non-communicable Disease)
Filters activated: Meta-Analysis, Systematic Reviews, Review, published in the last 10 years, Humans, Infant: birth-23 months

#2

systematic[sb] AND ((((((("Infant Nutritional Physiological Phenomena"[Mesh]) AND "Overnutrition"[Mesh]) OR "Growth"[Mesh]) OR "Diabetes Mellitus"[Mesh]) OR "Nutritional and Metabolic Diseases"[Mesh]) OR "Noncommunicable Diseases"[Mesh])

Filters activated: Systematic Reviews, Meta-Analysis, published in the last 5 years, Child: birth-18 years.

#3

(((((("Bottle Feeding"[Mesh]) OR "Breast Feeding"[Mesh]) OR "Infant Nutritional Physiological Phenomena"[Mesh]) OR "Weaning"[Mesh]) Or "Early weaning") OR "early introduction complementary feeding"

Filters activated: Systematic Reviews, Meta-Analysis, published in the last 10 years.

EMBASE

#1

('bottle feeding'/exp OR 'bottle feeding' OR 'exclusive breastfeeding'/exp OR 'exclusive breast feeding'/exp OR 'exclusive breastfeeding' OR 'exclusive breast feeding' OR 'exclusive bottle feeding' OR 'bottle feeding duration' OR 'breast feeding'/exp OR 'breast feeding' OR 'breast feeding duration'/exp OR 'breast feeding duration' OR 'weaning'/exp OR 'weaning' OR 'complementary feeding'/exp OR 'complementary feeding' OR 'early weaning' OR 'early complementary feeding') AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim) AND [2011-2021]/py

#2

l622344621/sim

COCHRANE LIBRARY

#1

Child Nutritional Physiological Phenomena OR Infant Nutritional Physiological Phenomena OR Weaning) AND (Breastfeeding OR Exclusive Breast Feeding OR bottle feeding OR formula feeding OR, Exclusive bottle-feeding OR Exclusive formula feeding) AND (timing food introduction OR Early infant feeding practice OR Early complementary feeding OR Timing of food introduction) AND (body composition OR fat mass OR Noncommunicable Disease OR non-communicable Disease

#2

MeSH term – Weaning

#3

Phrase Matches - Infant Nutritional Physiological Phenomena

#4

MeSH descriptor – Obesity

publication date Between Jan 2011 and Dec 2021 (Word variations searched)

Studies search

PUBMED

#1

("Bottle Feeding"[Mesh] OR "Breast Feeding"[Mesh] OR "Infant Nutritional Physiological Phenomena"[Mesh] OR "Weaning"[Mesh] Or "Early weaning" OR "early introduction

complementary feeding") AND ("Growth and Development"[All Fields] OR ("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms]) OR "Nutritional Status"[All Fields] OR "Noncommunicable Diseases"[All Fields]) AND "2015/08/22"[PDat] : "2021/08/14"[PDat])

#2

((("Weaning"[All Fields]) OR "Infant Nutritional Physiological Phenomena"[MeSH]) OR "complementary feeding"[All Fields]) AND ((((((((((("Obesity"[Mesh] OR "Pediatric Obesity"[Mesh]) OR "Overweight"[Mesh]) OR "Body Mass Index"[Mesh]) OR "Body Weight Changes"[Mesh]) OR "Body Weight"[Mesh]) OR "Body Composition"[Mesh]) OR "Nutritional Status"[Mesh]) OR "Growth and Development"[Mesh]) OR "Growth"[Mesh]) OR "fat body"[MeSH Terms]) OR "adipose tissue"[MeSH Terms]) OR body fat[Text Word]) OR “adiposity rebound” [Text Word]) AND "2015/05/08"[PDat]:" 2021/08/14"[PDat] AND "infant"[MeSH Terms])

#3

(("weaning"[MeSH Terms] OR "weaning"[All Fields]) OR ("eating"[MeSH Terms] OR "eating"[All Fields]) OR "Feeding Behavior"[All Fields] OR "Complementary Feeding"[All Fields]) AND timing[All Fields] AND ("Growth and Development"[All Fields] OR ("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms]) OR "Nutritional Status"[All Fields] OR "Noncommunicable Diseases"[All Fields]) AND "2015/08/22"[PDat] : "2021/08/14"[PDat])

EMBASE

#1

('bottle feeding'/exp OR 'bottle feeding' OR 'bottle feeding duration' OR 'breast feeding'/exp OR 'breast feeding' OR 'breast feeding duration'/exp OR 'breast feeding duration') AND ('weaning'/exp OR 'weaning' OR 'complementary feeding'/exp OR 'complementary feeding' OR 'early weaning' OR 'early complementary feeding') AND ('clinical trial'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'cross-sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de) AND (2019:py OR 2020:py OR 2021:py)

#2

('complementary feeding'/exp OR 'complementary feeding' OR 'weaning'/exp OR weaning) AND ('obesity'/exp OR obesity OR 'body weight'/exp OR 'body weight' OR 'growth'/exp OR growth OR 'adiposity rebound'/exp OR 'adiposity rebound') AND ('clinical trial'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'cross-sectional study'/de OR 'longitudinal study'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'retrospective study'/de) AND (2019:py OR 2020:py OR 2021:py)

COCHRANE LIBRARY

#1

(Infant Nutritional Physiological Phenomena) AND (growth OR obesity OR noncommunicable disease)

in Title Abstract Keyword - with Cochrane Library publication date Between Jan 2017 and Dec 2021 (Word variations searched)

#2

(Child Nutritional Physiological Phenomena OR Infant Nutritional Physiological Phenomena OR Weaning) AND (Breastfeeding OR Exclusive Breast Feeding OR bottle feeding OR formula feeding OR, Exclusive bottle-feeding OR Exclusive formula feeding) AND (timing food introduction OR Early infant feeding practice OR Early complementary feeding OR Timing of food introduction) AND (body composition OR fat mass OR Noncommunicable Disease OR non-communicable Disease)

In All Text

#3

Trials matching MeSH descriptor (explode all trees):
- Weaning
- Growth
- Body Size
- Pediatric Obesity
- Noncommunicable Diseases

range 2016-2021

#4

Phrase Matches - Any Word Match

- Infant Nutritional Physiological Phenomena

range 2016-2021

CLINICALTRIALS.GOV https://clinicaltrials.gov/

#1

Complementary feeding

Figure a2.1. Guidelines search flow diagram

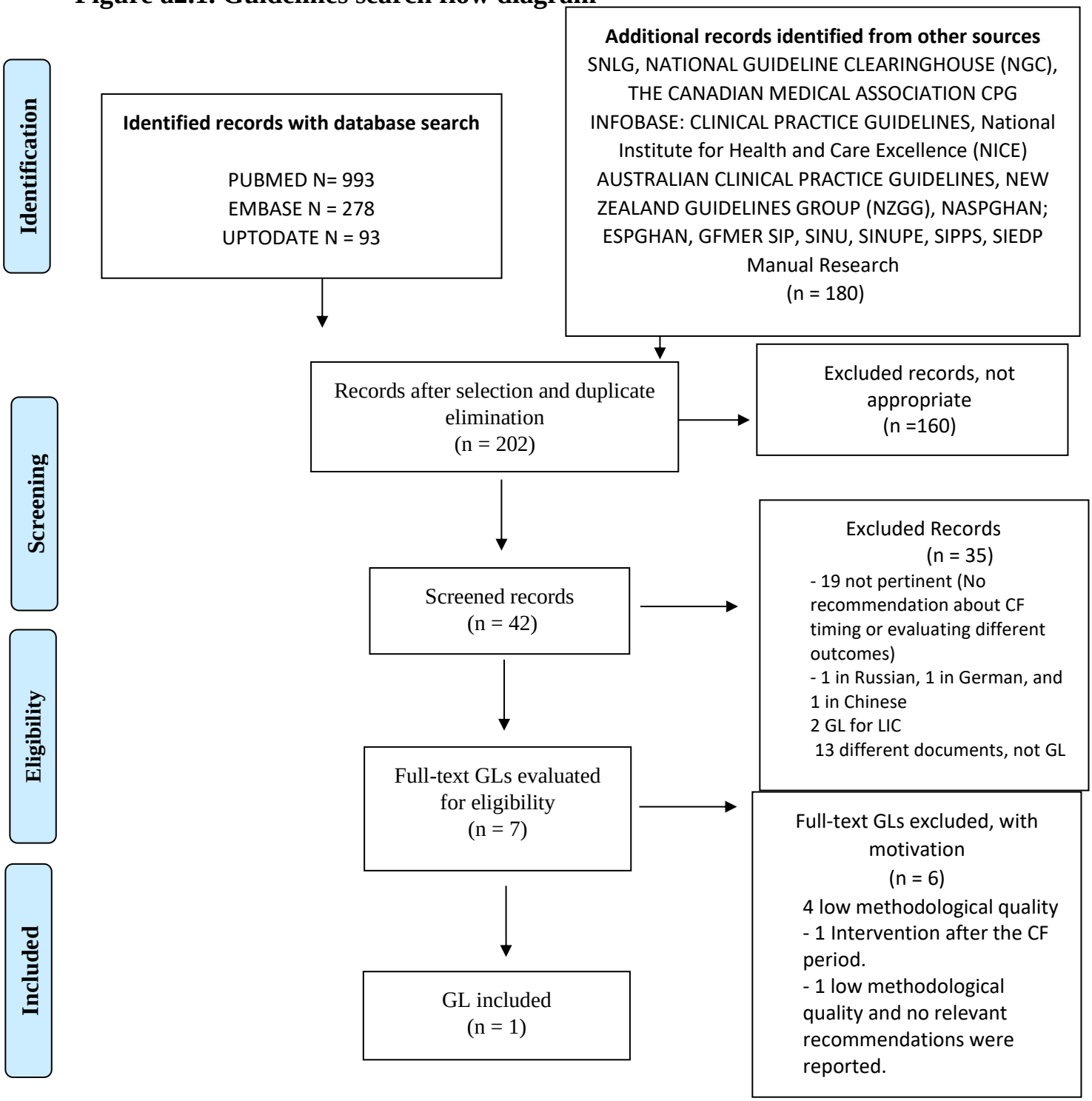


Figure a2.2. SRs search flow diagram

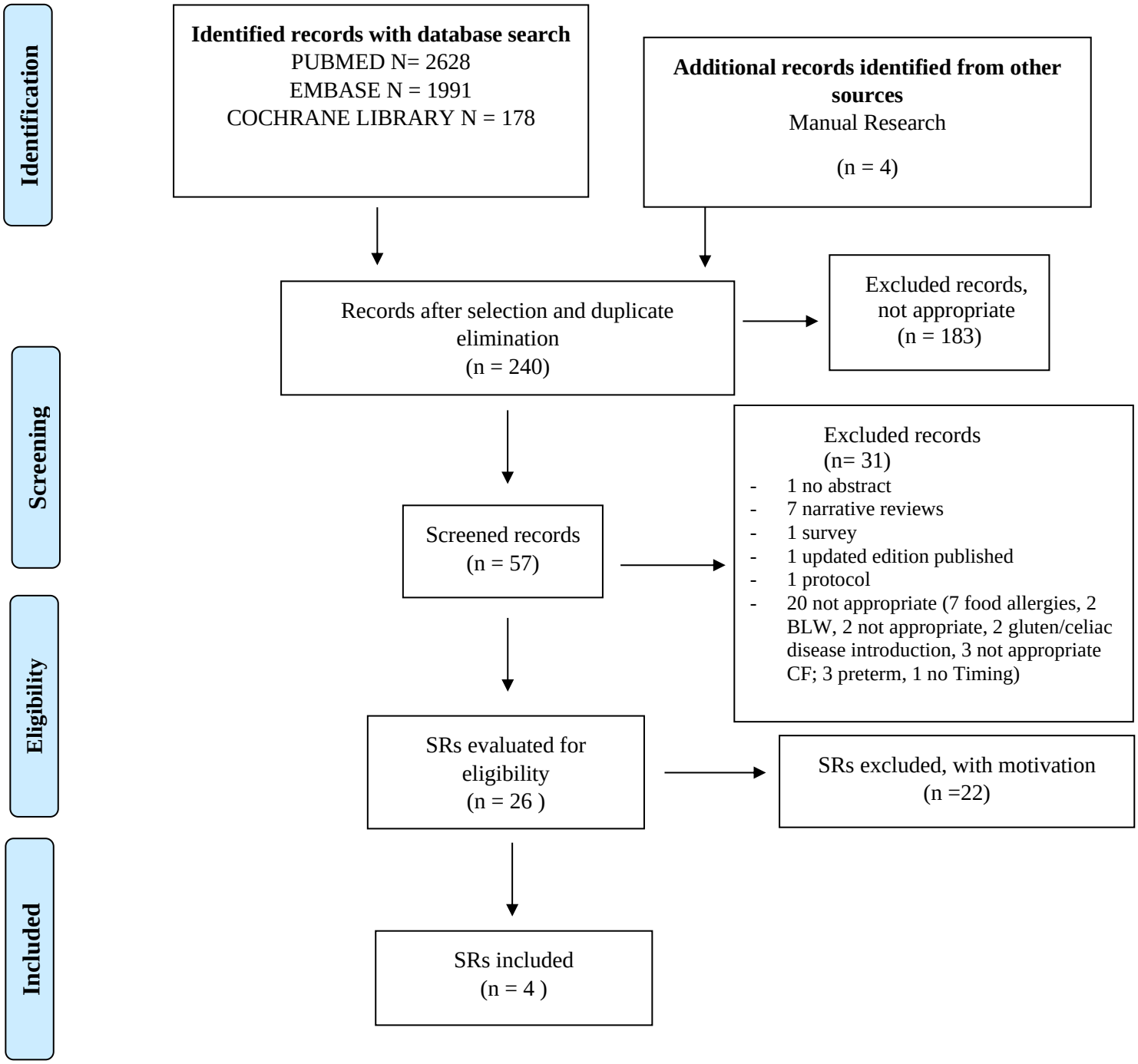
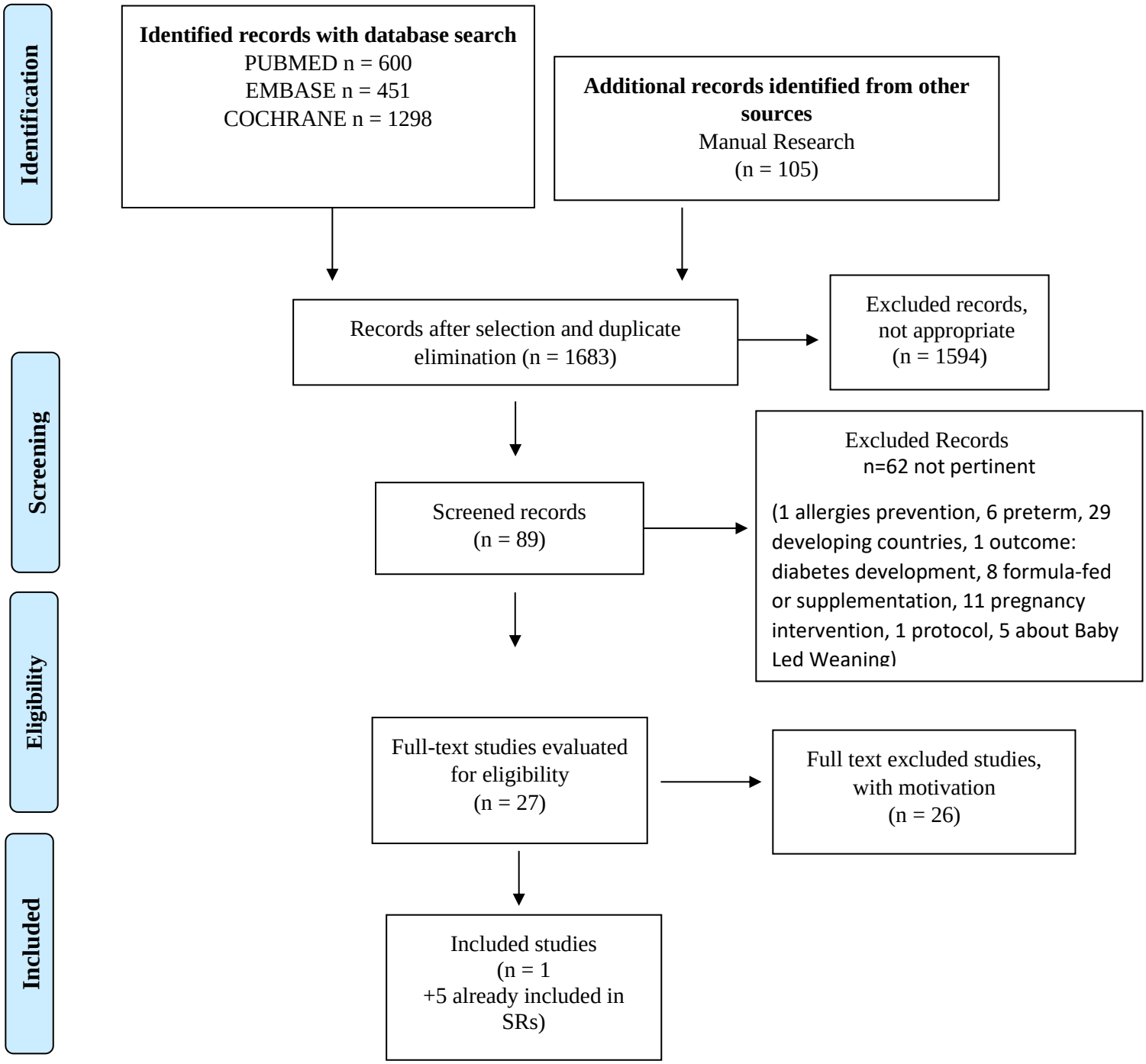


Figure a2.3. Studies search flow diagram



A2. METHODOLOGICAL ASSESSMENT

Table a2.1. Appraisal of the Clinical Guidelines and Documents

Guidelines and Clinical Guidance Documents	Methodological Evaluation			
	Multidisciplinary panel	**Systematic evidence research**	**Grading of recommendations**	**GL overall assessment**
SIEDP-SIP 2018 [1]	Yes	No, only MEDLINE	Yes	Moderate methodological quality.

Table a2.2. Clinical Guidelines and Guidance Documents excluded.

GL Excluded	Multidisciplinary panel	Systematic evidence research	Grading of recommendations	Reason for exclusion
Alvisi et al. 2015 [2]	Limited to Pediatricians and Nutritionists.	No	No	Review, with recommendations for clinical guidance. Low methodological quality.
Fewtrell et al. 2017. ESPGHAN Complementary feeding [3]	No	Declared but not published.	No	Low methodological quality.
Davanzo et al. 2015. Breastfeeding [4]	No	No	No	Low methodological quality.
NICE 2015 Preventing excess weight gain [5]	===	====	===	Interventions after the CF period.
Romero-Velardea et al. 2016. Alimentation complementaria [6]	Limited To Pediatricians And Nutrition Experts.	No	No	Low methodological quality.
ACOG 2021 [7]	No	No	No	Low methodological quality. No relevant recommendations were reported.

Table a2.3. Appraisal of the Systematic Reviews.

AMSTAR 2	Qasem et al. 2015 [8]	Smith et al. 2016 [9]	USDA et al. 2019 [10]	EFSA et al. 2019 [11]
1. Did the research questions and inclusion criteria for the review include the components of PICO? **(Yes/No)**	No	Yes	Yes	Yes
2. Did the review report contain an explicit statement that the review methods were established before conducting the review, and did the report justify any significant deviations from the protocol? **(Yes/Partial Yes/No)**	Yes	Yes	Yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review? **(Yes/No)**	Yes	Yes	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy? **(Yes/Partial Yes/No)**	Partial Yes	Partial Yes	Partial Yes	Partial Yes
5. Did the review authors perform study selection in duplicate? **(Yes/No)**	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate? **(Yes/No)**	Yes	Yes	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions? **(Yes/Partial Yes/No)**	Yes	Yes	Yes	Yes (Declared)
8. Did the review authors describe the included studies in adequate detail? **(Yes/Partial Yes/No)**	Yes	Yes	Yes	Yes

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **(Yes/Partial Yes/No/Includes only NRSI-RCT)**	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review? **(Yes/No)**	No	Yes	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **(Yes / No / No meta-analysis conducted)**	No Meta-Analysis Performed.	Yes	No Meta-Analysis Performed.	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? **(Yes / No / No meta-analysis conducted)**	No Meta-Analysis Performed.	Yes	No Meta-Analysis Performed.	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? **(Yes/No)**	Yes	Yes	Yes	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? **(Yes/No)**	Yes	Yes	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? **(Yes / No / No meta-analysis conducted)**	< 10 Studies In Meta-Analysis	< 10 Studies In Meta-Analysis	< 10 Studies In Meta-Analysis	< 10 Studies In Meta-Analysis

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? **(Yes/No)**	Yes	Yes	Yes	Yes
OVERALL EVALUATION	**MODERATE QUALITY**	**HIGH QUALITY**	**MODERATE QUALITY**	**MODERATE/HIGH QUALITY**
***** presence of 1 critical item and 2 failed non-critical items (n. 3, 15 e 16)				

Table a2.4. SRs excluded with motivation.

SRs excluded	Reason for exclusion
Araújo et al. 2019 [12]	Timing of intervention and comparison not relevant (6-7 vs. 3-4 months)
Brown et al. 2019 [13]	No timing CF
Cordero et al. 2015 [14]	No timing CF
Daniels et al. 2015 [15]	Low methodological quality.
English et al. 2019 [16]	Same SR USDA 2019
Grabia et al. 2021 [17]	Low methodological quality. No timing CF.
Harrison et al. 2017 [18]	No timing CF
He et al. 2021 [19]	Not pertinent
Horta _WHO et al. 2013 [20]	No timing CF
Horta et al. 2015 [21]	Low methodological quality. No CF timing.
Horta et al. 2019 [22]	Low methodological quality.
Kramer et al. 2012 [23]	Timing of intervention and comparison not relevant (6-7 vs 3-4 months)
Martin et al. 2016 [24]	Intervention: 3 WHO recommendation.
Mathew et al. 2015 [25]	The section on anemia from RS Qasem 2015.
Mazarello Paes et al. 2015 [26]	No timing CF.
Moorcroft et al. 2011 [27]	Includes only one study already in most recent reviews (Kramer 1985).
Pearce et al. 2013 [28]	Timing of intervention and comparison not relevant
Qiao et al. 2020 [29]	methodological quality.
Spill et al. 2019 [30]	No timing CF
Vail et al. 2015 [31]	Low methodological quality.
Weng et al. 2012 [32]	Timing of intervention and comparison not relevant (<4 vs >4 mo)
Yan et al. 2014 [33]	The timing of intervention and comparison is not relevant.

Table a2.5. Appraisal of the Studies

a2.5.1

	Newcastle Quality Assessment Scale CASE-CONTROL STUDIES								
	Selection				Comparability	Exposure			
Study	**Adequate case definition**	**Case Representativeness**	**Selection of Controls (community)**	**Definition of Controls (no outcome)**	**Comparability of cases and controls based on the design or analysis.**	**Ascertainment of exposure**	**The same method of ascertainment for cases and controls**	**Non-Response rate**	**Total**
Lopes et al. 2016 [34]	1a	1a	1a	1a	1+1 a,b	0c (Structured and validated questionnaires administered by experienced non-blinded personnel for cases and controls)	1a	0b	7

a2.5.2

	Newcastle Quality Assessment Scale COHORT STUDIES								
	Selection				Comparability	Outcome			
Study	**Representativeness of the exposed cohort**	**Selection of the non exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of the study**	**Comparability of cohorts based on the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Total**

Huh et al. 2011 [35]	1b	1a	1b	1a	1b	1b	1a	1a	8

a2.5.3

	Newcastle Quality Assessment Scale STUDI CROSS-SECTIONAL STUDIES							
	Selection				**Comparability**	**Outcome**		
Study	**Representativeness of the sample**	**Sample size:**	**Non-respondents**	**Ascertainment of the exposure (max 2)**	**Comparability between groups, confounders are controlled (Maximum 2 stars)**	**Outcome evaluation (max 2)**	**Statistical test**	**Total**
Vail et al. 2015 [36]	1b	0	1	1	1	2	1	7

RCT

Figure a2.4. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

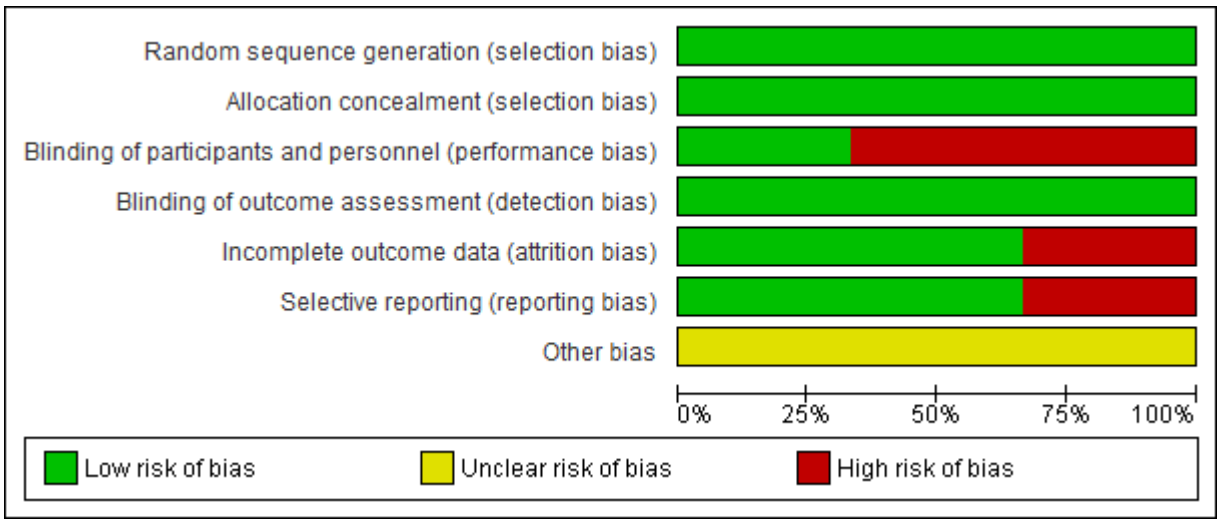


Figure a2.5. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies [37,38,39]

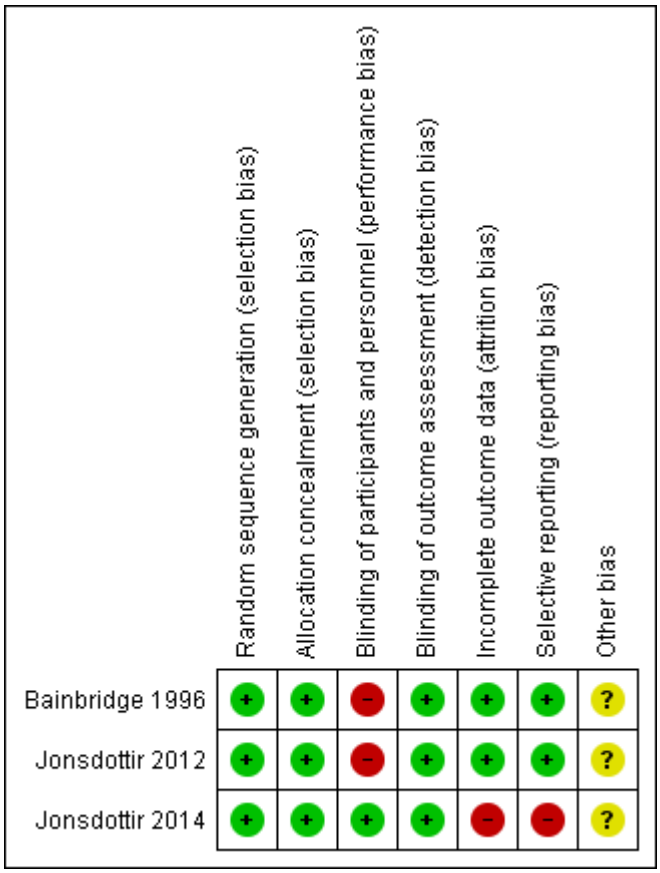


Table a2.6. Excluded studies

Excluded studies	Reason for exclusion
Ardic et al. 2019 [40]	Timing CF intervention and/or comparison not pertinent.
Baldassarre et al. 2017 [41]	Timing CF intervention and/or comparison not pertinent.
Barrera et al. 2016 [42]	Low methodological quality: post hoc analysis, high dropout at follow-up.
Bell et al. 2018 [43]	Low methodological quality: post hoc analysis, 51% included in the final analysis, sample not representative of the original population.
Carruth et al. 2000 [44]	Low methodological quality, low sample size for multiple comparisons.
Carvalhaes et al. 2017 [45]	Not pertinent. Not assessing short and/or long-term outcomes.
Differing et al. 2020 [46]	Timing CF intervention and/or comparison not pertinent (< 4 vs > 4 mo).
Gingras et al. 2019 [47]	Low methodological quality (Loss to follow-up ~40%)
Grote et al. 2011 [48]	Low methodological quality (Loss to follow-up > 20%)
Horodynski et al. 2017 [49]	Timing CF intervention and/or comparison not pertinent.
Huus et al. 2008 [50]	Low methodological quality (Loss to follow-up > 50%. Self-reported data).
Mannan et al. 2018 [51]	Timing CF intervention and/or comparison not pertinent (< 4 vs > 4 mo).
Martin et al. 2017 [52]	Timing CF intervention and/or comparison not pertinent.
Morghen et al. 2018 [53]	Timing CF intervention and/or comparison not pertinent (< 4 mo).
Newby et al. 2015 [54]	Dietary Habits Survey. Not evaluating short and/or long-term outcomes.
Olaya et al. 2013 [55]	Not assessing the timing of the beginning of CF.
Olaya et al. 2017 [56]	Assesses surrogate outcomes (iron status).
Papotsou et al. 2018 [57]	Timing CF intervention and/or comparison not pertinent.
Pluymen et al. 2018 [58]	Timing CF intervention and/or comparison not pertinent.
Sandoval Jurado et al. 2016 [59]	Timing CF intervention and/or comparison not pertinent.
Schmidt Morgen et al. 2018 [60]	Timing CF intervention and/or comparison not pertinent.
Seach et al. 2010 [61]	Low methodological quality. Time intervals of CF initiation not specified, nor diet after 1 year of age. Loss to follow-up was not uniform between the 2 groups (those who completed the study had higher socioeconomic status and greater age).
Sirkka et al. 2018 [62]	Timing CF intervention and/or comparison not pertinent.
Trovão et al. 2020 [63]	Timing CF intervention and/or comparison not pertinent. (< 3 vs > 3 mo).
Usheva et al. 2021 [64]	Timing CF intervention and/or comparison not pertinent.
Wells et al. 2012 [65]	Same sample as Jonsdottir et al. 2012, different primary outcomes.

A2. RECOMMENDATIONS OF THE GLs, RESULTS OF THE SRs AND STUDIES

a. ***Does the onset of CF before 6 months of life lead to different nutritional and metabolic outcomes, in the short and long term, compared to exclusive breastfeeding for up to 6 months of age?***	**P** Healthy infant exclusively breastfed **I** The onset of Complementary Feeding (CF) before 6 months completed (between 4 and 6 months) **C** Compared to an onset of the Complementary Feeding (CF) at 6 months completed **O** Different nutritional and metabolic outcomes in the short and long term

Table a2.7. Recommendations of Guidelines and other Documents

Guidelines – other Documents		Recommendations	Grading
SIEDP-SIP 2018 [1]	Diagnosis, Therapy, and Prevention of Obesity in Pediatric Age (0-18 years)	**THERAPY** - Care intervention of the first level is the responsibility of the family pediatrician. The family pediatrician is in charge of individuating the children at risk of developing obesity Condition. Identification of effective early-life interventions targeting these modifiable factors is critical for obesity prevention. Pediatrician task To check beginning complementary feeding **PREVENTION** - Prevention of pediatric obesity is based, from the prenatal age, on the modification of dysfunctional behaviors (nutrition, physical activity, and sedentary lifestyle) which, by altering energy homeostasis, lead to excess weight. - Exclusive breastfeeding until 6 mo is recommended. - It is recommended that solids and liquids foods other than breast milk or infant formula are introduced no earlier than 4 mo and no later than 6 mo.	Level of evidence III, strength of recommendation A. Rif #310-311 (Sargent 2011, Daniels 2015) Level of evidence I, strength of recommendation A. Level of evidence III, strength of recommendation A Rif #344-347 Horta 2013, Yan 2014, Horta 2015) Level of evidence III, strength of recommendation B Rif #348-352 (Pearce 2013, Weng 2012, Vail 2015, Seach 2010, Huh 2011)

Table a2.8. Characteristics, Results, and Conclusions of SRs

Systematic Review	Population and purpose of the SR	Results	Conclusions
Qasem et al. 2015 [8]	Exclusively breastfed children between 4 and 6 mo.	Jonsdottir et al. 2012* – Growth 6 mo RCT n° 100 [Media (DS)] Wt gain (z score): 6 m= -0.01(0.42); 4 m = -0.02(0.31); p= 0.90	No significant difference has been found among the groups.

	Evaluate the scientific evidence and assess the relationship between the age of introduction of the CF with the iron asset and the growth in breastfed children.	Length gain (z score): 6m= 0.04 (0.51); 4m = 0.03 (0.50); p= 0.96 <u>Wells et al. 2012* – growth 6 mo RCT– n° 100</u> Wt (z score): 6 mo= 0.36 (0.99); 4 mo= 0.28 (1.08); p= 0.7 Length (z score): 6 mo = 0.77 (0.84); 4 mo = 0.60 (0.92); p= 0.3 BMI (z score): 6 mo = -0.10 (1.04); 4 mo = -0.08 (1.14); p= 0.9 * *<u>two articles from a single RCT</u>* <u>Jonsdottir et al. 2012* – martial asset RCT _ n° 100</u> Hb: mean difference [MD]: 0.2 g/L; 95 % CI: -2.4, 2.8 g/L; p = 0.88 Ferritin: MD: 26.0 µg/L; 95 % CI: −0.1, 52.1 µg/L, p= 0.05	No significant difference has been found among the groups in terms of growth and body composition. In infants of developed countries, the introduction of CF at 4 mo did not improve the martial asset compared to the introduction of CF at 6 mo.
Smith et al. 2016 [9]	Healthy children born to term and breastfed Assess the benefits and risks of additional food or liquids; examine the introduction and type of additional food or liquids.	Jonsdottir et al. 2012* – <u>Growth 6 mo RCT</u> n° 100 (50+50) Metanalysis Wt gain (z score): MD [95%IC]= -0.01[-0.15, 0.13]; p= 0.89	No significant difference has been found among the groups.
USDA et al. 2019 [10] (Research deadline on July-August 2016)	Infants and children generally healthy who have been fed with complimentary food and drink from 0 to 24 mo Evaluate growth, size, and/or body composition. SR as part of the Pregnancy and Birth to 24 Mo Project (P/B-24 Project) by the Nutrition Evidence Systematic Review (NESR) team of the Center for Nutrition Policy and Promotion, Food and Nutrition Service, USDA.	<u>Jonsdottir et al. 2012* – Growth 6 mo RCT _ n° 100</u> <u>Wells et al. 2012* – Growth 6 mo RCT – n° 100</u> <u>Jonsdottir, 2014 – RCT- overweight/obesity at 18, 28, and 38 mo</u> BMI-for-age at 18, o 29-38 mo, WAZ at 18, or 29-38 mo LAZ at 18, or 29-38 mo	No significant difference has been found among the groups. Difference not significant Difference not significant
EFSA et al. 2019 [11] (Research deadline on May 2019)		<u>Jonsdottir et al., 2014 - RCT- overweight/obesity at 29-36 mo</u> BMIZ CA 4 m vs. 6 mo: MD (z−score) [95%IC]= -0.15[-0.53, 0.23] <u>Huh et al., 2011 - Cohort- overweight/obesity at 3 years</u> BMIZ AC 4 m (n°= 427) vs. 6 mo (n°= 98): MD (z−score) [95%IC]= -0.06[-0.15, 0.27] Odds obesity development at 3 years: OR [95%IC]= 0.28 [0.06; 1.25]	Difference not significant Difference not significant Difference not significant

Table a2.9. Included studies: Characteristics and Results

Study (First Author, Year, Country/Setting)	Study design	Population (sample size, baseline characteristics)	Intervention/exposure and comparator	Primary Outcome	Effect measures	Secondary Outcomes	Follow-up	Results
Jonsdottir et al. 2012 [38] 7 Health Care Centers in Iceland	RCT	119 healthy term (≥37 weeks) singleton infants	complementary foods in addition to breast milk from 4 mo of age compared with exclusively breastfed and complementary foods in addition to breast milk from 6 mo of age	Serum iron status at 6 months (Blood for hemoglobin (Hb), mean corpuscular volume (MCV), red blood cell distribution width (RDW), serum ferritin (SF), and total iron-binding capacity (TIBC))	Mean Difference (95% CI)	Gains (z-Scores) in infant weight, length, and head circumference during the study period	6 wks, and 3, 4, 5, and 6 mo	Data are mean (SD) Serum iron status at 6 months in the 2 Intervention Groups, CF and EBF - N=94 Hb (g/L) CF= 113.9 (6.1) EBF= 113.7 (7.3): p=0,91 SF (mg/L) CF = 70.0 (73.3) EBF =44.0 (53.8); p= 0,02 Growth Rate in z Scores N=100 Wt gain from 0 to 6 mo CF: - 0.55 (1,12); EBF: - 0.46 (1,17); p=0,71 Length gain from 0 to 6 mo CF: - 0.41 (0.95) EBF: - 0.37 (1.18); p=0,85
Vail et al. 2015 CBGS Study [36] Rosie Maternity Hospital in Cambridge, UK	Cross-sectional study	571 healthy infants, full-term birth (≥36 weeks); singleton birth	complementary foods from: 3.0-3.9 mo 4.0-4.9 mo 5.0-5.9 mo 6.0-6.9 mo	To test whether earlier age at weaning (age 3-6 mo) may promote faster growth during infancy Anthropometric values were transformed into age- and sex-adjusted z-scores. .	regression coefficient with zBMI		Birth, 3 mo and 12 mo	Age at weaning: 146 (25.6%) 4.0 - 4.9 mo, 226 (39.6%) 5.0 - 5.9 mo, 155 (27.1%) 6.0 - 6.9 mo Exclusive BF N= 263 BMI z-score 12 mo – unstandardized regression coefficient; Model 1: Adjusted for age, sex, maternal age, parity, and deprivation score 0.06 (-0.02 to 0.14) p=0.13 Model 2: Model 1 with additional adjustment for milk feeding at 3 mo. 0.02 (-0.06 to 0.11) p=0.56
Jonsdottir et al. 2014 [39] 7 Health Care Centers in Iceland	RCT	119 healthy infant, Iceland, full-term birth (≥37 weeks); singleton birth	to receive complementary foods from the age of 4 mo in addition to breast milk (CF) compared with to continue exclusive	To test whether the duration of exclusive breastfeeding is protective of overweight and obesity later in life	BMI for age mean difference (95% CI)		Weight, length, and head circumference at 6 wks, 3, 4, 5, 6, 8, 10, 12, and 18 mo and weight and	No effects of exclusive breastfeeding for 4 or 6 mo on the growth pattern or the risk of being overweight or obese in early childhood 18 months of age **CF EBF MD (95% CI) p-value** BMI-for-age 0.60±0.92 0.59±0.95 0.009 (-0.38, 0.39) 0.96 29–38 months of age

			breastfeeding to the age of 6 mo (EBF)				height at 29–38 mo. Data are presented as mean (SD The risk of being overweight was defined as BMI-for-age >1 standard deviation (SD) above the WHO growth standard median. Overweight or obese was defined as a value >2 and >3 SDs, respectively, above the WHO growth standard median	BMI-for-age 0.64±0.86 0.79±0.83 -0.15 (-0.53, 0.24) 0.45
Huh et al. 2011 [35] Obstetrical offices of a multispecialty group practice in eastern Massachusetts	Cohort study	847 full-term infants,	Introduction of solid foods, categorized as: <4 mo, 4 to 5 mo, and ≥6 mo.	obesity at 3 years of age (BMI for age and gender ≥95th percentile)	Odds of obesity (BMI ≥95th percentile), OR (95% CI)		3 y	Among formula-fed infants or infants weaned before the age of 4 mo, the introduction of solid foods before the age of 4 mo was associated with increased odds of obesity at age 3 years <u>Breastfed Age at Introduction of Solids</u>: <4 mo: N= 43 4-5 mo: N= 427 ≥ 6 mo: N= 98 <u>Odds of obesity (BMI ≥95th percentile), OR (95% CI)</u> Multivariable plus change in weight- for-age *z* score 0–4 mo <4 mo= 1 (0,3-4,4) 4-5 mo= 0,0 (Reference) ≥ 6 mo= 1 (0,4 to 2,5)
Lopes et al. 2016 [34] Public schools of Taubate (São Paulo, Brazil)	Case-control study	463 children	different ages of the introduction of CFs	To verify if in children in the early preschool age the prevalence of overweight and if introducing complementary feeding is associated with this	Correlation index with zBMI	To verify as the type of food introduced is associated with the prevalence of overweight	N.A.	The bivariate analysis and then linear regression analysis of multiple variables were conducted. The prevalence of overweight was elevated (27.5%). Only birth weight showed a significantly correlation concerning zBMI ($r = 0.22$, $p < 0.0001$)The early introduction of new foods is not a risk factor for the development of overweight at the beginning of preschool age.

				condition in this age group		in this age group		

b. ***Does the onset of CF before 6 months of life lead to different nutritional and metabolic outcomes, in the short and long term, compared to feeding exclusively with infant formula or mixed (breastfeed + infant formula) for up to 6 months of age?***	**P** Healthy infant exclusively or predominantly fed with infant formula. **I** The onset of Complementary Feeding (CF) before 6 months completed (between 4 and 6 months of age) **C** Compared to an onset of the Complementary Feeding (CF) at 6 months completed **O** Different nutritional and metabolic outcomes in the short and long term

Table a2.10. Recommendations of Guidelines and other Documents

Guidelines – other Documents	Patients	Recommendations	Grading
SIEDP-SIP 2018 [1]	Diagnosis, Therapy, and Prevention of Obesity in Pediatric Age (0-18 years)	**THERAPY** - Care intervention of the first level is the responsibility of the family pediatrician. The family pediatrician is in charge of individuating the children at risk of developing obesity Conditions. Presence of risk factor: early complementary feeding… Tasks. Control the age of onset of complementary feeding **PREVENTION** - Prevention of pediatric obesity is based, from the prenatal age, on the modification of dysfunctional behaviors (nutrition, physical activity, and sedentary lifestyle) which, by altering energy homeostasis, lead to excess weight. - It is recommended that solids and liquids foods other than breast milk or infant formula are introduced no earlier than 4 mo and no later than 6 mo.	Level of evidence III, strength of recommendation A. Rif #310-311 (Sargent 2011, Daniels 2015) Level of evidence I, strength of recommendation A. Level of evidence III, strength of recommendation B Rif #348-352 (Pearce 2013, Weng 2012, Vail 2015, Seach 2010, Huh 2011)

Table a2.11. Characteristics, Results, and Conclusions of SRs

Systematic Review	Population and purpose of the SR	Results	Conclusions

USDA et al. 2019 [10] (Research deadline on July-August 2016)	Infants and children generally healthy who have been fed with complementary food and drink from 0 to 24 mo Evaluate growth, size, and/or body composition. SR as part of the Pregnancy and Birth to 24 Mo Project (P/B-24 Project) by the Nutrition Evidence Systematic Review (NESR) team of the Center for Nutrition Policy and Promotion, Food and Nutrition Service, USDA.	Bainbridge, 1996 – RCT Growth at 26 weeks – n° 41 CFB at 16wk vs. EFF 16-26wk Weight change NSGD (Difference not significant) Length change at 26 weeks = NSGD; change 6-26 wk = 5.03, (SD 1.05) vs. 3.62 (SD:2.72), p=0.05.	Difference not significant
EFSA et al. 2019 [11] (Research deadline on May 2019)	Healthy infants or born preterm, or born small-for-gestational-age or with high growth velocity. The appropriate age for introduction of complementary feeding of infants has been evaluated considering the effects on health outcomes, nutritional aspects, and infant development	Huh et al., 2011 - Cohort- overweight/obesity at 3 years BMIZ CA 4 m (n°= 163) vs. 6 mo (n°= 25): MD (z–score) [95%IC]= -0.32[-0.74, 0.10 Odds obesity development at 3 years: OR [95%IC]= 1.00 [0.40; 2.50]	Difference not significant Difference not significant

Study (First Author, Year, Country/Setting)	Study design	Population (sample size, baseline characteristics)	Intervention/exposure	Primary Outcome	Measures of treatment effect	Secondary Outcomes	Follow-up	Results
Bainbridge et al. 1996 [37] University of Cincinnati Medical Center and 3 affiliated hospitals	RCT	41 healthy infant, full-term birth (37-41 wks), and appropriate for gestational age	The introduction of Rice cereal to the formula for 2 mo at 4 mo of age	To test whether intake of formula plus cereals between 16-26 wks (as compared to formula alone) would lead to lower bone mineral content, higher parathyroid hormone concentration, lower serum calcium, magnesium, and osteocalcin, and increased continuous night sleep	mean difference (p-value >/< 0,05)	differences of standard anthropometric measurements	2,4,5, and 6 mo	No significant differences between the two groups
Huh et al. 2011 [35] Obstetrical offices of a multispecialty group practice in eastern Massachusetts	Cohort study	847 full-term infants,	Introduction of solid foods, categorized as: <4 mo, 4 to 5 mo, and ≥6 mo.	obesity at 3 years of age (BMI for age and gender ≥95th percentile)	Odds of obesity (BMI ≥95th percentile), OR (95% CI)		3 y	Formula-Fed Age at Introduction of Solids Odds of obesity (BMI ≥95th percentile), OR (95% CI) Multivariable plus change in weight-for-age z score 0–4 mo <4 mo (n=91)= 6,3 (2,3 to 16,9)

								4-5 mo (n=193)= 0,0 (Reference) ≥ 6 mo (n=25)= 3,6 (0,8 to 16,3)
Vail et al. 2015 CBGS Study [36] Rosie Maternity Hospital in Cambridge, UK	Cross-sectional study	571 healthy infants, full-term birth (≥36 weeks); singleton birth	complementary foods from: 3.0-3.9 mo 4.0-4.9 mo 5.0-5.9 mo 6.0-6.9 mo	To test whether earlier age at weaning (age 3-6 mo) may promote faster growth during infancy Anthropometric values were transformed into age- and sex-adjusted z-scores. .	regression coefficient with zBMI		Birth, 3 mo and 12 mo	Age at weaning: 146 (25.6%) 4.0-4.9 mo, 226 (39.6%) 5.0-5.9 mo, 155 (27.1%) 6.0-6.9 mo Exclusive or partially FF No = 295 BMI z-score 12 mo – unstandardized regression coefficient Model 1: Adjusted for age, sex, maternal age, parity, and deprivation score 0.06 (-0.02 to 0.14) p=0.13 Model 2: Model 1 with additional adjustment for milk feeding at 3 mo. -0.02 (-0.06 to 0.11) p= 0.56

A2. EVIDENCE PROFILE GRADE

Table a2.13. Growth. Blood iron level

[Introduction CF at 4-6 months] than [Introduction CF at 6 months] to [ensure adequate growth at 6-12-18-24 months]

Patient or population: [ensure adequate growth at 6-12-18-24 mo]

Setting: Outpatient

Intervention: [Introduction CF at 4-6 month]

Comparator: [Introduction CF at 6 month]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
Weight gain Z-score (follow up: mean 6 months)												
2 [1,2,a]	randomized trials	not serious	serious [b]	not serious	not serious	none	68	73	-	MD **0 - 0.01** (0.15 lower to 0.13 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Table a2.13. Growth. Blood iron level

[Introduction CF at 4-6 months] than [Introduction CF at 6 months] to [ensure adequate growth at 6-12-18-24 months]

Patient or population: [ensure adequate growth at 6-12-18-24 mo]

Setting: Outpatient

Intervention: [Introduction CF at 4-6 month]

Comparator: [Introduction CF at 6 month]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
Length gain Z-score (follow up: 6 months)												
2 [1,2,a]	randomized trials	not serious	serious [b]	not serious	not serious	none	68	73	-	MD **0 - 0.01** (0.21 lower to 0.19 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Hb Plasmatica (follow up: 6 months; assessed with: gr/L)												

Table a2.13. Growth. Blood iron level

[Introduction CF at 4-6 months] than [Introduction CF at 6 months] to [ensure adequate growth at 6-12-18-24 months]

Patient or population: [ensure adequate growth at 6-12-18-24 mo]

Setting: Outpatient

Intervention: [Introduction CF at 4-6 month]

Comparator: [Introduction CF at 6 month]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomized trials	not serious	not serious	not serious	serious [c]	none	50	50	-	MD **0 0.2** (2.44 lower to 2.48 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Ferritin Plasmatica (follow up: 6 months; assessed with: ug/L)

1 [2]	randomized trials	not serious	not serious	not serious	serious [c]	none	50	50	-	MD **0 26** (0.1 lower to 52.1 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Table a2.13. Growth. Blood iron level

[Introduction CF at 4-6 months] than [Introduction CF at 6 months] to [ensure adequate growth at 6-12-18-24 months]

Patient or population: [ensure adequate growth at 6-12-18-24 mo]

Setting: Outpatient

Intervention: [Introduction CF at 4-6 month]

Comparator: [Introduction CF at 6 month]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
Weight Z-score (follow up: 12 months)												
1 [3]	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	N° patients introduction 4-6 n°= 372 WZS at 12 mo = 0.58 (0.99) - 0.39 (0.95) N° patients introduction at 6 mo = 155. WZ at 12 mo = 0.25 (0.92) p= 0.01. Association with AC introduction age, adjusted for age, sex, maternal age, parity, deprivation score, milky feeding at 3 mo and growth at the previous cut point (Model 3) = 0.01 (-0.06 to 0.07), p= 0.88				⊕⊕⊕◯ MODERATE	IMPORTANT
Length Z-score (follow up: 12 mo)												

Table a2.13. Growth. Blood iron level

[Introduction CF at 4-6 months] than [Introduction CF at 6 months] to [ensure adequate growth at 6-12-18-24 months]

Patient or population: [ensure adequate growth at 6-12-18-24 mo]

Setting: Outpatient

Intervention: [Introduction CF at 4-6 month]

Comparator: [Introduction CF at 6 month]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
1 [3]	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Patients introduction AC 4-6 mo LZS at 12 mo = 0.48 (1.05), 0.23 (1.04). Patients introduction AC at 6 mo LZS at 12 mo = 0.00 (1.04) p<0.01. Association with age of introduction adjusted for confounding factors (Model 3) 0.04 (-0.01 to 0.11) p= 0.20				⊕⊕⊕◯ MODERATE	IMPORTANT

BMI Z-score (follow up: 12 mo)

Table a2.13. Growth. Blood iron level

[Introduction CF at 4-6 months] than [Introduction CF at 6 months] to [ensure adequate growth at 6-12-18-24 months]

Patient or population: [ensure adequate growth at 6-12-18-24 mo]

Setting: Outpatient

Intervention: [Introduction CF at 4-6 month]

Comparator: [Introduction CF at 6 month]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
1 [3]	observational studies	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	Introduction AC 4-6 mo BMIZ at 12 mo 0.42 (0.94) -0.36 (0.83) Introduction AC 6 mo, BMIZ at 12 mo 0.33 (0.84) p=0.33. Association with AC introduction age-adjusted for confounding factors (Model 3) -0.02 (-0-08 to 0.05) p= 0.64				⊕⊕⊕◯ MODERATE	IMPORTANT

BMI z-score (Mean Difference) a 29-36 mesi (follow up: range 29 mo to 36 mo; assessed with: Mean Difference (MD))

Table a2.13. Growth. Blood iron level

[Introduction CF at 4-6 months] than [Introduction CF at 6 months] to [ensure adequate growth at 6-12-18-24 months]

Patient or population: [ensure adequate growth at 6-12-18-24 mo]

Setting: Outpatient

Intervention: [Introduction CF at 4-6 month]

Comparator: [Introduction CF at 6 month]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomized trials	not serious	serious [a]	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [a,b]	50	50	-	MD **0.15 lower** (0.53 lower to 0.23 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. For each exposure factor (BF or FF) the study is unique and with a low sample number

b. Wide 95% CI

References

1. Jonsdottir et al. 2012 [38]

2. Bainbridge et al. 1996 [37]

3. Vail et al. 2015 CBGS Study [36]

Table a2.14. Risk of overweight/obesity

[4-6 month AC introduction] compared to [6 month AC introduction] to prevent overweight/obesity at 3-6 years

Patient or population: prevent overweight/obesity at 3-6 years

Setting: Outpatient

Intervention: [Introduction AC at 4-6 mo]

Comparison: [Introduction AC to 6 mo]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
Sovrappeso/Obesità a 3 anni (follow up: 3 anni; valutato con: RR (95% IC))												
1 [1]	randomized trials	serious [a]	not serious	not serious	not serious	none	4/48 (8.3%)	5/46 (10.9%)	**RR 1.30** (0.37 to 4.56)	**33 more per 1.000** (from 68 fewer to 387 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Table a2.14. Risk of overweight/obesity

[4-6 month AC introduction] compared to [6 month AC introduction] to prevent overweight/obesity at 3-6 years

Patient or population: prevent overweight/obesity at 3-6 years

Setting: Outpatient

Intervention: [Introduction AC at 4-6 mo]

Comparison: [Introduction AC to 6 mo]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
Overweight/Obesity at 18 mo (follow up: 18 mo; evaluated with BMI Z-score)												

Table a2.14. Risk of overweight/obesity

[4-6 month AC introduction] compared to [6 month AC introduction] to prevent overweight/obesity at 3-6 years

Patient or population: prevent overweight/obesity at 3-6 years

Setting: Outpatient

Intervention: [Introduction AC at 4-6 mo]

Comparison: [Introduction AC to 6 mo]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Introduzione AC a 4-6 mesi]	[Introduzione AC a 6 mesi]	Relative (95% CI)	Absolute (95% CI)		
2 [2,3]	observational studies	not serious	not serious	not serious [b]	not serious	none	2,463 children, of whom 28 (6.1%) were overweight/obese. Linear regression analysis did not reveal a statistically significant correlation with fruit and cereal age of introduction: coefficient β, respectively = 0.020 (p=0.743) and 0.011 (p=0.828). 3. START CF between 4 and 6 mo (n=427) or 6 mo (n=98). There is no difference in the likelihood of developing/overweight obesity at 3 years (RR = 0.80; 95%CI = 0.51-1.23) [2,4]				⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Low sample number

b. The results of the study are consistent with those of other published studies

References

1. Jonsdottir et al. 2014 [39]

2. Lopes et al. 2016 [34]

3. Huh et al. 2011 [35]

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