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1 NUTRITIONAL INTERVENTIONS OR EXPOSURES IN INFANTS AND  
2 CHILDREN AGED UP TO THREE YEARS AND THEIR EFFECTS ON  
3 SUBSEQUENT RISK OF OVERWEIGHT, OBESITY, AND BODY FAT: A  
4 SYSTEMATIC REVIEW OF SYSTEMATIC REVIEWS  
5  
6

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32  
33

34 **Declaration of potential conflicts of interest**

35 **BPG** received a research training fellowship grant from Nestle Nutrition Institute.

36 **BMZ, MK** declare no conflict of interest.

37 **SK** A part of her PhD thesis is to assess the effects of an infant formula with an  
38 optimized amino acid composition and a lower protein content on growth and body  
39 composition.

40 **KMG** received reimbursement for speaking at conferences sponsored by companies  
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53 different nutritional companies, predominantly as part of publically funded research  
54 projects with support of the European Commission or German governmental  
55 research support.

56 **JBvG** is founder and director of the Dutch Human Donor Milk Bank and is a member  
57 of the Dutch Health Council. He holds patents on amino acid composition of infant  
58 formula.

59 **HS** has participated as a clinical investigator and/or speaker for companies selling  
60 nutritional products (Arla, Danone, HiPP, Nestle', Nestle' Mead Johnson).

61 **LP** has received support for scientific and educational activities from companies  
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86

87 **Abbreviations**

88 RCT - randomized controlled trial  
89 BMI - body mass index  
90 BF - breastfeeding  
91 CF - complementary feeding  
92 CHOP - Childhood Obesity Program

93  
94  
95

96 **ABSTRACT**

97 This study performed as part of the international EarlyNutrition research project  
98 ([www.project-earlynutrition.eu](http://www.project-earlynutrition.eu)) provides a systematic review of systematic reviews  
99 on the effects of nutritional interventions or exposures in children (up to three years  
100 of age) on the subsequent risk of obesity, overweight, and adiposity. Electronic  
101 databases (including MEDLINE, EMBASE, and Cochrane Library) were searched up  
102 until September 2015. Forty systematic reviews were included. A consistent  
103 association of breastfeeding with a modest reduction in the risk of later overweight  
104 and obesity in childhood and adulthood was found (the odds decreased by 13%  
105 based on high quality studies), but residual confounding cannot be excluded.  
106 Lowering the protein content of infant formula is a promising intervention to reduce  
107 the risk of later overweight and obesity in children. There is no consistent evidence of  
108 an association of the age of introducing complementary foods, sugar-sweetened  
109 beverage, or energy intake in early childhood, with later overweight/obesity, but  
110 there are some indications of an association of protein intake during the  
111 complementary feeding period with later overweight/obesity. There was inadequate  
112 evidence to determine effects of other nutritional interventions or exposures,  
113 including modifications of infant formula composition, fat intake, or consumption of  
114 different food groups.

115 **INTRODUCTION**

116 Early life exposures to suboptimal nutrition have been widely implicated in causal  
117 pathways leading to increased risk of disease in later life.<sup>1</sup> This concept has become  
118 known as ‘early metabolic programming’ or ‘developmental programming’ and was  
119 derived by evidence from animal studies<sup>2</sup> and later human epidemiological studies  
120 associating low birth weight with adverse cardiovascular and metabolic outcomes in  
121 adulthood.<sup>3,4</sup> One of the hypotheses focuses on postnatal accelerated weight gain,  
122 suggesting that rapid weight gain in infancy can lead to increased risk of later obesity  
123 and related disorders.<sup>5,6,7</sup> For example, higher protein intake in infancy has been  
124 reported to stimulate the secretion of insulin and insulin-like growth factor I and,  
125 thereby, increase weight gain and further obesity risk.<sup>8</sup> In contrast, there is evidence  
126 suggesting that breastfeeding has a protective effect against overweight and obesity.<sup>9</sup>  
127 Many observational studies have examined the relationship between nutrition in  
128 infancy and early childhood and growth and child health outcomes, whereas  
129 intervention studies that can directly address causality are limited in number. A  
130 consequence of the paucity of intervention studies conducted in humans is that  
131 observational data are increasingly contributing to guideline development for dietary  
132 advice in infancy and early childhood,<sup>10</sup> a practice widely accepted to have  
133 considerable limitations. Systematic reviews have failed to improve clarity because of  
134 widely varying approaches. Moreover, guidelines on nutrition for infants and young  
135 children often fail to address longer-term outcomes, including the risk of  
136 cardiovascular disease, hypertension, overweight, obesity, and diabetes. There is also  
137 inconsistency amongst these recommendations for some health outcomes.<sup>11</sup> This  
138 prompted the EarlyNutrition Project ([www.project-earlynutrition.eu](http://www.project-earlynutrition.eu)) to undertake a  
139 systematic review of published systematic reviews on the effects of nutritional  
140 interventions or exposures in children (up to three years of age) on the subsequent  
141 risk of obesity, overweight, and adiposity in order to develop new, improved  
142 strategies and recommendations on nutrition in this population.

143

144 This review was initiated as part of the development of recommendations by the  
145 EarlyNutrition Project on nutrition during pregnancy, lactation, and early childhood  
146 and consequences for offspring health and risk of later obesity.

147

148

## 149 **METHODS**

### 150 **Criteria for considering studies for this review**

#### 151 *Types of studies*

152 We included systematic reviews (of randomized controlled trials [RCTs] and/or  
153 observational studies) with/ or without a meta-analysis. Systematic reviews of  
154 systematic reviews were also eligible for inclusion. We considered a review as  
155 'systematic' if it was indicated to be by the authors and/ or it had key characteristics  
156 of a systematic review, following the Cochrane Handbook:<sup>12</sup> *'a clearly stated set of*  
157 *objectives with pre-defined eligibility criteria for studies; an explicit, reproducible*  
158 *methodology; a systematic search that attempts to identify all studies that would meet the*  
159 *eligibility criteria; an assessment of the validity of the findings of the included studies, for*  
160 *example through the assessment of risk of bias; and a systematic presentation, and synthesis,*  
161 *of the characteristics and findings of the included studies.'* Non-systematic reviews and  
162 reviews of guidelines were excluded.

163

#### 164 *Types of participants/populations*

165 Reviews must have *included* infants and young children (aged up to three years)  
166 representing the general population (including those whose mothers and/ or fathers  
167 are overweight/ obese). Systematic reviews of studies that recruited infants and  
168 young children with a wider range of age also were eligible for inclusion; however,  
169 we must have been able to extract data on children up to three years of age. We  
170 *excluded* systematic reviews that focused on studies conducted (i) in infants and  
171 children with specific disorders, (ii) in preterm infants or in SGA (small for  
172 gestational age) infants, and (iii) in children from mothers/ fathers with specific  
173 disorders or conditions (mental or physical) other than overweight or obesity.

174

175 *Types of interventions/ exposures*

176 Reviews that assessed the effects of specific nutritional interventions/exposures in  
177 children were included. Behavior change interventions focused on improving  
178 nutrition were *not* a subject of this review. Similarly, mixed interventions/exposures  
179 (such as combinations of nutritional interventions/exposures together with physical  
180 activity) were not addressed in this review.

181

182 *Type of comparator(s)/ controls*

183 Usual standard care or diet; no intervention; various levels of exposure.

184

185 *Type of outcome(s)*

186 Our pre-specified primary *outcomes* measured at any age after birth included the  
187 following: obesity and overweight, as defined by the authors; body mass index (BMI)  
188 or changes in this parameter at different time intervals (as defined by the authors);  
189 fat mass; body fat percentage; and fat-mass index (measured with the use of different  
190 methods/devices). We excluded outcome measures focused on the presence of  
191 specific disorders such as asthma, epilepsy, etc. We chose the outcome assessment to  
192 be at any age after birth for few reasons: (i) the lack of a clearly defined cut-off time  
193 point to indicate the optimal time for assessment of the phenotypic effect of  
194 programming either in relation to the interval following the exposure or the age of  
195 the offspring; (ii) reviews often gather evidence on both immediate and longer-term  
196 effects of nutritional exposures; (iii) it is of interest to identify whether or not  
197 immediate and longer-term effects are in the same direction; differences in the  
198 direction of an effect could imply that mechanisms are dissimilar.

199

200 **Search strategy**

201 The Centre for Reviews and Dissemination (CRD, University of York) was involved  
202 in the development of our search strategy. Several electronic databases were  
203 searched for eligible systematic reviews, up until September 2015: Cochrane  
204 Database of Systematic Reviews (CDSR); The Database of Abstracts of Reviews of  
205 Effects (DARE); Ovid MEDLINE; and EMBASE (Biomedical and pharmacological



206 bibliographic database). The reference lists from identified reviews were searched.  
207 Attempts to obtain reviews from other sources were made by a references' hand  
208 search of the included reviews, as well as by contact with experts in the field. The  
209 detailed search strategy for Ovid MEDLINE is shown in **Table S1**. Four reviewers  
210 (BMZ, MK, BPG, and SK) independently carried out the literature search. No  
211 language restrictions were applied. Systematic reviews meeting our inclusion criteria  
212 that had been published after September 2015 were also eligible, if only we were  
213 aware of such publications. However, no formal search was undertaken after  
214 September 2015.

215

### 216 **Selection process**

217 For this review, at least two of our four reviewers (BPG, BMZ, MK, SK)  
218 independently screened the titles and abstracts. Full texts of potentially eligible  
219 systematic reviews were further evaluated. If an update of a particular review was  
220 published, we included the most recent publication. Disagreements concerning the  
221 eligibility for inclusion were resolved by discussion until a consensus was reached.  
222 All reviewers agreed on the final set of included reviews.

223

### 224 **Data extraction**

225 For each included review, three reviewers (BPG, BMZ, MK) performed data  
226 extraction using a standardized table. Data extracted included first author, search  
227 strategy timeframe, number of studies included in total and involving children aged  
228 up to three years, age of participants, study design, intervention/exposure, primary  
229 outcomes, results, evidence quality, and comments.

230

### 231 **Data synthesis**

232 A narrative synthesis was undertaken. We did not intend to and did not perform a  
233 meta-analysis of the meta-analyses of included reviews due to the following reasons:  
234 (i) expected heterogeneity of included systematic reviews resulting mainly from a  
235 broadly defined clinical question; (ii) difficulty in avoiding the use of data from  
236 individual studies more than once and, therefore, inadequately increasing the

237 statistical power when pooling data together.<sup>13</sup> Moreover, whenever possible, we  
238 aimed to base our conclusions on the most recent and robust reviews, trying to avoid  
239 overestimating the effect due to duplication of studies.

240

#### 241 **Quality assessment of the reviews**

242 Two reviewers independently assessed the methodological quality of each included  
243 review using the 'Assessment of Multiple Systematic Reviews' (AMSTAR) tool.<sup>14</sup> To  
244 our knowledge, the AMSTAR tool is the only validated tool to assess the  
245 methodological quality of systematic reviews.<sup>13</sup> The tool contains 11 questions with  
246 regard to the quality of the review. For the purposes of this document, subjectively,  
247 we assumed that scores of zero to four indicate a low quality review, five to eight, a  
248 moderate quality review, and, nine to 11, a high quality review.

249

250 Formally, we did not assess the quality of identified systematic reviews of systematic  
251 reviews due to incompatibility of this kind of review with the AMSTAR tool.

252

#### 253 **Risk of bias in included studies**

254 If originally assessed by the authors of the included reviews, we extracted data with  
255 respect to the risk of bias (methodological quality) of studies included in every  
256 eligible review. However, we neither performed a formal judgment of this  
257 assessment nor assessed individual studies ourselves. When formulating our  
258 conclusions, we took into account both the quality of the review and the overall  
259 quality of evidence that additionally resulted from the quality of the included  
260 studies.

261

262

## 263 **RESULTS/EFFECTS OF INTERVENTIONS/EXPOSURES**

### 264 **BREASTFEEDING**

265 Nine systematic reviews<sup>9,15,16,17,18,19,20,21,22</sup> and two systematic reviews of systematic  
266 reviews<sup>23,24</sup> have evaluated the association of breastfeeding (BF) with later  
267 overweight and obesity (**Table S2**).

268

269 Included reviews were heterogeneous in terms of methodology, clinical aspects, and  
270 methodological quality. Only one (a Cochrane review) was of high quality;<sup>18</sup> most  
271 were classified as being of moderate quality, and one, of low quality.<sup>16</sup> Only a few  
272 authors focused on a specific pattern of BF; more often studies included various BF  
273 patterns.

274

275 The PROBIT study<sup>25,26</sup> was the only randomized trial, but the primary outcome of  
276 this cluster randomized trial was the effect of BF promotion on BF duration and  
277 exclusivity, and the study was not powered to detect the effects of BF duration or  
278 intensity on later overweight and obesity.<sup>27</sup>

279

### 280 **Childhood body mass index, overweight/obesity**

281 Six systematic reviews examined the effects of BF on later BMI and risk of  
282 overweight and obesity<sup>9,17,19,20,21,22</sup> (all reviews rated as of moderate quality) as did  
283 two systematic reviews of systematic reviews.<sup>23,24</sup> Despite important differences in  
284 the included reviews, such as the inclusion/exclusion criteria, they consistently  
285 reported a protective effect of BF on overweight and obesity (assessed during  
286 different periods of life, from early childhood up to adulthood, depending on the  
287 included studies).

288

289 The most recent 2015 meta-analysis by *Horta et al.*<sup>22</sup> included 105 studies and  
290 confirmed that BF is associated with a reduced likelihood of obesity or overweight in  
291 childhood and adulthood (OR 0.74, 95% CI: 0.70 to 0.78), with similar findings but a  
292 somewhat smaller effect size in analyses restricted to high quality studies (OR 0.87,  
293 95% CI: 0.76 to 0.99). This is in line with the results of previously published  
294 reviews<sup>9,17,19,20,21</sup> and two systematic reviews of systematic reviews.<sup>23,24</sup>

295

296 In summary, a consistent association of BF with a modest reduction by 13% of the  
297 odds of later overweight and obesity in childhood and adult life was reported, but  
298 residual confounding cannot be excluded.

299

### 300 **Effect of the duration of exclusive breastfeeding**

301 A 2012, high quality, Cochrane review,<sup>18</sup> which compared the effects of exclusive BF  
302 for six months with exclusive BF for three to four months (with subsequent mixed BF  
303 to six months), concluded that '*exclusive breastfeeding for six months does not seem to*  
304 *confer any long-term (at least to early school age) protection against obesity*'. However, this  
305 conclusion was based solely on the findings of the underpowered PROBIT study.<sup>27</sup>

306

307 A 2013 review by *Hornell et al.*<sup>17</sup> (moderate quality) included five studies  
308 summarizing data on exclusive BF and its association with the subsequent risk of  
309 overweight/obesity from one to six years of age. Three prospective cohort studies  
310 reported a lower risk of overweight or obesity with a longer duration of exclusive BF.  
311 In contrast, two studies, one the PROBIT study, found no consistent association  
312 between BF duration and exclusivity with regard to risk of overweight and obesity  
313 assessed at the ages of one, two, three, and 6.5 years.

314

315 A 2005 review by *Owen et al.*<sup>19</sup> (moderate quality) reported on three studies  
316 evaluating exclusive BF for eight months or more versus a shorter duration of BF,  
317 where the mean difference in mean BMI between groups, measured between two  
318 and 12 years of age, was  $-0.39 \text{ kg m}^{-2}$  (95% CI:  $-0.51$  to  $-0.26$ ). However, this effect  
319 was no longer evident in two of the three included studies after adjustment for  
320 confounding factors such as socioeconomic status, maternal BMI, and maternal  
321 smoking in pregnancy (from  $-0.4$  to  $-0.02$ , after adjustment).

322

323 In summary, there is no conclusive evidence that exclusive BF, regardless of its  
324 duration, has a strong protective effect on the later risk of overweight and obesity.

325

### 326 **Effect of the duration of any breastfeeding**

327 Five systematic reviews<sup>9,16,17,20, 21</sup> assessed the later effect of the duration of any BF on  
328 BMI and/or the risk of overweight/obesity; some were of moderate quality, apart  
329 from that by *Harder et al.*<sup>16</sup> that was of low quality.

330

331 The systematic review by *Yan et al.*<sup>21</sup> (moderate quality) including 25 studies  
332 concluded that BF was associated with a reduced risk of obesity in children (adjusted  
333 OR 0.78; 95% CI: 0.74 to 0.81). Categorical analysis of 17 studies revealed a dose-  
334 response effect between BF duration and reduced risk of childhood obesity (any BF  
335 for seven and more months, adjusted OR 0.79, 95% CI: 0.70 to 0.88). The quality of the  
336 included studies was not assessed by the authors, decreasing the reliability of the  
337 conclusions.

338

339 Likewise, *Hornell et al.*<sup>17</sup> (moderate quality) reported a protective effect of duration of  
340 BF against later overweight and obesity in childhood, adolescence, and adulthood.  
341 The authors concluded that the evidence was convincing for this association with  
342 adolescent overweight/obesity and limited, but suggestive for adulthood  
343 overweight/obesity.

344

345 *Harder et al.*<sup>16</sup> (low quality) reported the results of a categorical analysis that  
346 confirmed a dose-response association between the duration of BF and risk of  
347 childhood and adulthood overweight based on BMI in the majority of the studies,  
348 assessed from 0 to 33 years (less than one month of BF, OR 1.0, 95% CI: 0.65 to 1.55;  
349 one to three months of BF, OR 0.81, 95% CI: 0.74 to 0.88; four to six months of BF, OR  
350 0.76, 95% CI: 0.67 to 0.86; seven to nine months of BF, OR 0.67, 95% CI: 0.55 to 0.82;  
351 more than nine months of BF, OR 0.68, 95% CI: 0.50 to 0.91). One month of BF was  
352 associated with a four percent decrease in risk (OR 0.96 per month of BF, 95% CI: 0.94  
353 to 0.98). The quality of the included studies was not assessed.

354

355 *Weng et al.*<sup>20</sup> (moderate quality) found conflicting evidence for duration of BF. Four of  
356 the five studies included in their review found no significant association between the  
357 duration of BF and risk of childhood overweight. However, the risk of bias differed  
358 greatly between the studies.

359

360 A 2005 review by Owen *et al.*<sup>19</sup> (moderate quality) found that compared with BF for a  
361 shorter time, prolonged BF (not defined) provided a greater protective effect on  
362 mean levels of adiposity in children and adults from one to 70 years (based on BMI).

363

364 In summary, there are some indications that BF of very short duration has a lesser  
365 protective effect than BF of longer duration on the later risk of overweight and  
366 obesity, although residual confounding cannot be excluded.

367

### 368 **Exclusive breastfeeding**

369 With respect to BF exclusivity and its association with BMI when compared to any  
370 BF, Owen *et al.* reported that “the difference in mean BMI appeared somewhat smaller  
371 between 20 studies in which initial feeding groups were definitely exclusive (-0.06; 95% CI: -  
372 0.09, -0.04) and 12 studies that did not report whether feeding was exclusive (-0.13; 95% CI:  
373 -0.18, -0.08). However, this difference was not statistically significant (P=0.45).”<sup>19</sup>

374

375 Included amongst the reviews was a 2012 systematic review and meta-analysis by  
376 Gale *et al.*<sup>15</sup> (moderate quality), which also investigated the contemporary  
377 (immediate) effect of BF or formula feeding on the body composition of healthy, term  
378 infants. The authors concluded that compared to BF, formula feeding was associated  
379 with a transient lower fat mass and a higher fat-free mass from three to six months of  
380 age.

381

382 In summary, there is no conclusive evidence that exclusive BF has a stronger  
383 protective effect on the later risk of overweight and obesity than predominant or  
384 partial BF.

385

386

### 387 INFANT FORMULA

388 Eight systematic reviews assessed the effects of different components of infant  
389 formula feeding on BMI, overweight, obesity, or body composition (**Table S2**),<sup>28,29,30,</sup>

390 31,32,33,34,35 including two<sup>30,34</sup> which addressed only the immediate consequences. All  
391 reviews included exclusively or mainly randomized controlled trials (RCTs).

392

393 Variations in terms of assessed components of infant formulas and selected outcomes  
394 were observed between the included reviews. Based on the AMSTAR assessment  
395 (Table S3), only one of the reviews was of high quality;<sup>29</sup> four reviews were classified  
396 as being of moderate quality,<sup>28,30,31,33</sup> and two, of low quality.<sup>32,35</sup>

397

#### 398 • Protein content

##### 399 Body composition

400 Both a review by *Patro-Golqab et al.* 2016<sup>29</sup> (high quality) and a systematic review by  
401 *Abrams et al.* 2015<sup>28</sup> (moderate quality) identified data only on the immediate  
402 consequences of lowering the protein composition of infant formula feeding and  
403 concluded that the evidence was insufficient to determine whether reducing the  
404 protein content in infant formula influences infant body fat composition.

405

##### 406 Body mass index, overweight, obesity

407 A systematic review by *Patro-Golqab et al.* 2016<sup>29</sup> identified four publications (two  
408 RCTs) that evaluated both immediate and later effects of different protein contents in  
409 infant formulae on BMI. No significant differences were found for mean BMI and  
410 BMI-z-score below six months of life. Starting from 12 months of age, one RCT (the  
411 CHOP Study) with a large sample size reported data on mean BMI and BMI-z-scores  
412 at later ages. BMI was significantly lower in the lower-protein formula group  
413 compared with the higher-protein formula group at all time points (i.e., at six, 12,  
414 and 24 months and at six years). Similarly, CHOP was the only study to report on the  
415 protein content of infant formula and the risk of becoming obese and found a  
416 markedly reduced obesity prevalence in the lower-protein formula group (1.77 and  
417 2.2 g protein 100 kcal<sup>-1</sup> in infant and follow-on formulae, respectively) at the age of  
418 six compared with the higher-protein formula group (2.9 and 4.4 g protein 100 kcal<sup>-1</sup>,  
419 respectively) (one RCT  $n=448$ , unadjusted Relative Risk (RR) 0.44, 95% CI: 0.21 to  
420 0.91; adjusted RR 0.35, 95% CI: 0.15, 0.82).<sup>36</sup>

421

422 A 2015 review by *Abrams et al.*<sup>28</sup> also referred to the findings of the CHOP study with  
423 respect to BMI and obesity risk. Here, an additional RCT was included, reporting  
424 that the BMI at 24 months of age was lower in infants of overweight mothers fed  
425 lower-protein formula compared to controls.<sup>37</sup>

426

427 In summary, lowering the protein content of infant formula is a promising  
428 intervention to reduce the risk of later overweight and obesity in children, but more  
429 studies replicating the effects on long-term health outcomes are needed.

430

- 431 • **Addition of selected bacteria or non-digestible carbohydrates to infant**  
432 **formulae**

#### 433 **Body composition and BMI**

434 No reviews relevant to longer-term childhood BMI or body composition effects were  
435 identified. A systematic review by *Szajewska & Chmielewska* 2013<sup>30</sup> (moderate quality)  
436 investigated immediate effects of infant formula supplementation with different  
437 strains of bacteria, finding no significant difference in BMI between groups.  
438 Similarly, supplementation with inulin-type-fructans was summarized by *Liber &*  
439 *Szajewska*<sup>34</sup> (moderate quality), but no studies that assessed BMI were identified.  
440 None of the included trials reported on body composition.

441

442 In summary, there is no evidence to demonstrate long-term (or immediate) effects of  
443 infant formula supplemented with selected so-called “probiotic” bacteria or non-  
444 digestible carbohydrates on BMI.

445

- 446 • **Infant formula long-chain polyunsaturated fatty acids (LCPUFA) content**

#### 447 **Body composition and BMI**

448 A 2012 systematic review by *Campoy et al.*<sup>31</sup> (moderate quality) found no RCTs that  
449 assessed BMI. Body composition was not an outcome of interest in this systematic  
450 review.



451 A 2012 review by *Rodriguez et al.*<sup>32</sup> (low quality) assessed the effects of n-3 LCPUFA  
452 intake, during pregnancy and postnatally, on infants' and young children's body  
453 composition. Six RCTS (four conducted in preterm and two, in term infants) focused  
454 on infant formulae supplemented with n-3 LCPUFA. The first of the two RCTs in  
455 term infants (classified as of moderate quality) showed, compared to an  
456 unsupplemented formula group, no effect of supplementation of infant formula with  
457 docosahexaenoic acid (DHA) or both DHA and arachidonic acid from birth to 17  
458 weeks of age on body composition assessed at the age of 12 months. In the second  
459 RCT, in which the intervention was introduced from the first one to five days of life  
460 until the end of the second postnatal month, and the children were studied at 9 years  
461 of age, a similar lack of an effect on BMI and overweight risk in all of the study  
462 groups (LCPUFA-supplemented formula group, unsupplemented formula group,  
463 and breastfed group) was observed. However, the authors classified this study as  
464 being at high risk of bias. This was confirmed by the later review of *Voortman et al.*<sup>33</sup>  
465 (moderate quality) evaluating the effects of PUFA dietary intake and blood levels  
466 during pregnancy, lactation, or early childhood on obesity and other cardio-  
467 metabolic outcomes.

468

469 In summary, there is no evidence that consumption of LCPUFA-supplemented infant  
470 formula reduces the risk of later obesity.

471

## 472 • Soy-based infant formula

### 473 **Body mass index**

474 A 2002 systematic review by *Mendez et al.* (low quality) assessed growth of infants  
475 fed soy-based formula.<sup>35</sup> Based on the results of one retrospective cohort study, there  
476 was no difference in BMI assessed in young adults who were participants of infant  
477 feeding trials and fed soy-based formula compared to cow's milk-based formula  
478 during infancy.

479

480 In summary, there is no evidence that consumption of soy-based formula reduces the  
481 risk of later overweight or obesity.

482

483

484 **COMPLEMENTARY FEEDING**

485 Five systematic reviews reported on various timings of complementary feeding (CF)  
486 introduction,<sup>20,38,39,40,41</sup> and one systematic review reported on the effects of types of  
487 foods introduced during the CF period,<sup>42</sup> both addressing immediate and later  
488 effects.

489

490 • **Timing of complementary feeding introduction**

491 **Body mass index and overweight, obesity**

492 A 2015 systematic review by *Qasem et al.*<sup>40</sup> (moderate quality) aimed to summarize  
493 the influence of CF introduction at four months versus six months of age, but no  
494 significant differences between groups in BMI at six months of age were found.

495

496 A 2013 review by *Pearce & colleagues*<sup>39</sup> (moderate quality) is an update of the 2011  
497 systematic review by *Moorcroft et al.*<sup>38</sup> (moderate quality) in which the majority of  
498 studies showed no clear association between the age of introduction of solid foods  
499 and obesity during infancy and childhood. This update applied different inclusion  
500 criteria (i.e., incorporating populations from developing countries, but also limiting  
501 the lower mean age of children when outcomes were assessed to four years of age).  
502 Of the 23 included, 21 studies assessed the relationship between the timing of CF and  
503 later childhood BMI (measured from two to 19 years of age). No significant  
504 association was found in 13 studies, and in another three studies, the observed effect  
505 was no longer significant when adjusted analysis was performed. However, it was  
506 noted that there is a possibility that very early introduction of solids may have an  
507 impact on BMI, based on results from two of four identified studies that assessed  
508 very early introduction of CF (at three and less than three months). The authors  
509 concluded that *'there is no clear association between age of introduction of complementary*  
510 *feeding and childhood overweight or obesity, but some evidence suggests that very early*  
511 *introduction (at or before 4 months), rather than at four to six months or more than six*

512 months, may increase the risk of childhood overweight' measured at four to 12 years of  
513 age.

514

515 A 2012 systematic review by *Weng et al.*<sup>20</sup> (moderate quality) included prospective  
516 observational studies following up children from birth for at least two years to  
517 determine risk factors for childhood obesity. Among 30 included studies, four  
518 investigated the relationship between the earlier introduction of solid foods and  
519 childhood overweight at three (two studies), ten, and 11 years of age. There was  
520 some evidence supporting early introduction of solid foods as a risk factor for later  
521 overweight, but this was limited to formula-fed infants only. One of the two studies  
522 conducted in formula-fed infants found that compared with infants given solid foods  
523 after four months, infants given solid foods before four months were 1.12 times (95%  
524 CI: 1.02 to 1.23) more likely to be overweight at three years of age. The second study  
525 found that, compared with infants who were given solid foods between four and five  
526 months of age, infants given solid foods before four months were 6.3 times (95% CI:  
527 2.3 to 16.9) more likely to be overweight at three years of age. However, this  
528 relationship was not significant in two studies of breastfed infants. A 2001 review by  
529 *Lanigan et al.*<sup>41</sup> (low quality) included no additional studies compared to those  
530 described above.

531

### 532 **Adiposity**

533 A review by *Qasem et al.* 2015<sup>40</sup> (moderate quality) found no difference in fat mass  
534 between groups that received CF at four months versus six months of age, when  
535 studied at six months of age. In contrast, an earlier review by *Lanigan et al.* 2001<sup>41</sup>  
536 (low quality) found in two studies an increased fat mass at follow-up in seven-year-  
537 old children who had CF introduced before 15 weeks compared with six-year-old  
538 children who had CF introduced after five months. However, two of the remaining  
539 systematic reviews (both of moderate quality) found no clear association between the  
540 timing of CF introduction and measures of adiposity such as skinfold thicknesses, fat  
541 mass, and percentage fat mass measured by DXA and/or bioelectrical impedance.<sup>38,39</sup>

542 In conclusion, there is no consistent evidence of effects of the timing of introducing  
543 CF and later adiposity risk.

544 In summary, there is no consistent evidence of an association between the earlier  
545 introduction of CF before 15 weeks/four months and later childhood adiposity.

546

547 • **Types of complementary food**

548 **BMI, childhood obesity**

549 Only one systematic review by *Pearce & Langley-Evans 2013*<sup>42</sup> (moderate quality)  
550 analyzed whether the risk of subsequent overweight or obesity was affected by the  
551 type of CF introduced during infancy. Ten observational studies were included. The  
552 authors assessed different types of foods/food groups and found no association  
553 between the types of food given and childhood obesity in three out of four studies.  
554 One study found that delaying the age at which introduction of solid and semi-solid  
555 foods were introduced (bread and biscuits mixed with milk) had an inverse  
556 association with the BMI z-score at ten and 11 years of age, after adjustments. One of  
557 the included studies analyzed the association between adherence to a specific diet  
558 during infancy and BMI at four years of age. Neither fat mass nor BMI changes were  
559 associated with CF of 'a diet based on fruit, vegetables, meat, fish and home-  
560 prepared foods'. Evaluation of specific macronutrient's effects in regard to the CF  
561 period, together with quality assessment of the included studies, is presented  
562 elsewhere in this review.

563

564 In summary, there is no evidence to suggest associations between certain CF types or  
565 patterns and subsequent childhood overweight or obesity.

566

567

568 **PROTEIN INTAKE IN EARLY CHILDHOOD**

569 *Pearce & Langley-Evans 2013*<sup>42</sup> (moderate quality) also investigated the effects of  
570 protein (total protein content or type of protein) consumed during the CF period by  
571 infants on the risk of overweight or obesity and body composition in childhood.

572 Based on conflicting data from four cohort studies, the authors concluded that “*Some*  
573 *association was found between high protein intakes at 2–12 months of age and higher body*  
574 *mass index (BMI) or body fatness in childhood, but was not the case in all studies.*”

575

576 *Hornell et al. 2013*<sup>43</sup> (moderate quality) assessed the effects of different levels of  
577 protein intake (and different sources of protein) during infancy and childhood on  
578 different health outcomes, including BMI and body composition, in a Nordic setting.  
579 For the purpose of a subanalysis limited to the effects of early protein intake, the  
580 authors included 13 studies (two clinical trials, nine cohort studies, and two cross-  
581 sectional studies) in which the association of protein intake in children from 0 to  
582 approximately 3 years of age (only in 2 studies the age range was from 1 to 5 years)  
583 with BMI, overweight /obesity, or body composition (up to ten years of age) was  
584 evaluated. They concluded that higher protein intake during the first years of life is  
585 positively associated with increased growth and higher BMI later in life. The  
586 evidence was classified by the authors as convincing (grade one), when taking into  
587 account the results of the studies and evidence quality assessment. It needs to be  
588 emphasized, however, that this review incorporated data on the effects of protein  
589 intake and protein content in infant formula but used these terms synonymously.  
590 The evidence (data from four cohort studies and one cross-sectional study) was  
591 described by the authors as “limited-inconclusive (grade 4)” considering the  
592 conflicting results of the identified studies with respect to the effects of protein intake  
593 in early childhood on later body fat.

594

595 These two reviews varied greatly in terms of applied search strategy and eligibility  
596 criteria, which may explain differences in study selection and the important  
597 discrepancy in obtained results regarding BMI and obesity risk.

598

599 In summary, there is inconsistent evidence of an association between a higher dietary  
600 protein intake in early childhood beyond infancy and later childhood overweight or  
601 obesity.

602

603 FAT INTAKE IN EARLY CHILDHOOD

604 • **Total fat intake**

605 **BMI and body composition**

606 A 2014 Cochrane review (high quality) assessed the effects of fat intake in infancy on  
607 childhood outcomes of interest.<sup>44</sup> Four observational studies conducted in children  
608 aged up to three years were included. In one cohort (two analyses), the authors  
609 addressed associations of dietary fat intake at different time points (including second  
610 and third year of life) with percentage body fat at 70 months and with BMI at eight  
611 years of age. A direct relationship of fat intake with BMI or BMI change, as well as  
612 with the percentage of body fat, was noted. However, analyses of the other studies  
613 found no association, or even an inverse association to that expected. In one, greater  
614 total fat intake at two years was related to a lower percentage of subscapular skinfold  
615 and fat mass after 18 years of follow-up (but not BMI or other skinfolds). The authors  
616 concluded that there was no clear association between lower total fat intake and later  
617 BMI and/or body composition.

618

619 In summary, there is no conclusive evidence of a relationship between fat intake in  
620 the first years of life and childhood BMI or early adulthood adiposity.

621

622 • **Polyunsaturated fatty acid intake**

623 **BMI, body composition, and obesity**

624 A 2015 review by *Voortman et al.*<sup>33</sup> (moderate quality) assessed the influence of the  
625 intake and status of LCPUFA in infancy on later obesity (including effects on BMI  
626 and body fat). Eight interventional and observational studies conducted during early  
627 childhood that assessed different outcomes of interest were included. Three of the  
628 included interventional studies were performed in term infants and assessed  
629 different forms of PUFA intake (fish oils, dietary supplements), with different  
630 comparisons (placebo, other fats). Two reported no difference in BMI or body fat  
631 percentage immediately after the intervention, and another showed no long-term  
632 effect of the intervention on BMI at eight years (interventions starting from six  
633 months to five years). Five of the included cohort studies evaluated the intake or

634 levels of PUFA at various time-points (from birth until five years of age). Long-term  
635 effects were assessed after one to ten years of follow-up and showed conflicting  
636 evidence. In three studies, no consistent effects were noted. In one study, a lower  
637 obesity risk at four years was found (dietary intake of PUFA evaluated at 12 to 19  
638 months). In contrast, in another study, a higher BMI was found at ten years of age in  
639 a sub-group with higher n-3 and lower n-6 fatty acids levels at birth (in cord blood).  
640 The authors concluded that there was insufficient evidence to suggest an effect of  
641 polyunsaturated fatty acid intake in early childhood on later overweight or obesity.  
642 A 2014 review by *Koletzko et al.*<sup>45</sup> (low quality) included no additional studies  
643 compared to those described above.

644 In summary, there is no conclusive evidence that PUFA intake in early childhood  
645 influences long-term risk of overweight, obesity, or body fat content.

646

#### 647 **SUGARS AND SUGAR-SWEETENED BEVERAGES**

648 A total of seven systematic reviews<sup>46,47,48,49,50,51,52</sup> and one systematic review of  
649 systematic reviews<sup>53</sup> evaluated later as well as more immediate effects of sugar-  
650 sweetened beverages (SSB) and dietary sugar intake on childhood overweight and  
651 obesity. In the age group up to three years, a single RCT and different types of  
652 observational studies were included. The majority of the reviews were of low  
653 quality,<sup>46,47,48,49,50</sup> and two, of high quality.<sup>51,52</sup> Two reviews<sup>48,51</sup> (including one of high  
654 quality)<sup>51</sup> included our population of interest in the inclusion criteria; however, none  
655 identified any studies of exposures in children aged up to three years, and they are  
656 not described in detail.

657

#### 658 **Childhood BMI**

659 In a 2013 review by *Perez-Morales et al.*<sup>47</sup> (low quality), three out of seven  
660 longitudinal studies evaluating influences of exposure up to the age of three years  
661 focused on SSB intake. The authors concluded that there is '*a trend showing that high*  
662 *consumption of SSB is associated to higher BMI, waist circumference, and overweight later in*  
663 *childhood*'. In only one study (out of three related to our focus of interest), regular  
664 consumers of SSB at two years compared with 'non-consumers' had a higher risk of

665 overweight at 4.5 years (OR 2.4; 95%CI: 1.11 to 5.05) independent of the overall  
666 nutritional content of the diet.<sup>54</sup> In another study, no statistically significant  
667 association was noted between consumption of sweet drinks at the age of two to  
668 three years and development of overweight one year later among children who were  
669 non-overweight at baseline, however, a significant difference was found in children  
670 who were already at risk for overweight at baseline (BMI 85<sup>th</sup> to <95<sup>th</sup> percentile).<sup>55</sup>  
671 Similarly, increases in added sugar intake from SSB between the ages of one and two  
672 years were not associated with later BMI at the age of seven years in another study.<sup>56</sup>

673

674 In a systematic review by *Osei-Assibey et al.* 2012<sup>49</sup> (low quality), only two studies  
675 conducted in children aged up to three years were identified. One RCT, focusing on  
676 the high risk for obesity in a population of American Indians/Alaskan Natives,<sup>57</sup>  
677 showed that combined community and family interventions to promote  
678 breastfeeding (at visits before birth) and a reduction in the consumption of SSB (at  
679 visits within the first three months), rather than a community-alone intervention,  
680 decreased the BMI z-score rise in toddlers at the age of two years. Among  
681 longitudinal studies, only one was conducted in children aged two to three years,  
682 reported above,<sup>55</sup> which was also included in other systematic reviews.<sup>46,50</sup>

683

#### 684 **Childhood overweight/obesity**

685 A systematic review and meta-analysis by *Te Morenga et al.* 2012<sup>52</sup> (high quality)  
686 evaluated the influence of dietary sugar intake on childhood overweight and obesity  
687 after one year of follow-up. Among the 21 included studies, six reported children  
688 who were recruited under the age of three years. The authors found an association  
689 between one daily serving intake of SSB at baseline (versus children consuming none  
690 or very little) and odds of being overweight at follow-up (OR 1.55; 95%CI: 1.32 to  
691 1.82). However, this result should be treated with caution, as different  
692 populations/comparisons (including adolescents, obese children) were included and  
693 there may be effects of lasting dietary patterns rather than of early programming.  
694 Similar findings were reported in a systematic review of systematic reviews by *Keller*  
695 *et al.*<sup>53</sup>



696

697 Additionally, in a systematic review by *Gibson*<sup>46</sup> (low quality), one cross-sectional  
698 study showed a positive association between soda consumption and overweight  
699 amongst children who were two years of age.

700

701 In summary, there is inconsistent evidence to suggest an association between SSB  
702 intake in early childhood and long-term overweight and obesity; current diet is likely  
703 to be a major confounder.

704

705

### 706 ENERGY

707 *Pearce & Langley-Evans* 2013<sup>42</sup> reported one cohort study that focused on energy  
708 intake at four months of age and its influence on BMI; this study found a linear  
709 association between energy intake and higher BMI at one, two, three, and five years  
710 of age in formula-fed or mixed-fed infants only. Each 420 kJ per day increase in  
711 energy at four months led to a increase in risk of BMI >85th percentile with  
712 borderline significance (OR 1.25; 95% CI: 1.00 to 1.55). Higher energy intake at four  
713 months was also positively associated with rapid weight gain, which independently  
714 predicted the risk of obesity in children.<sup>42</sup> The quality of the identified study,  
715 assessed with the use of Newcastle-Ottawa scale, was quite high, although no  
716 adjustment for dietary intake at time of measurement (age one, two, three, and five  
717 years) was reported. Based on these findings, the authors stated that “*Higher energy*  
718 *intake during complementary feeding was associated with higher BMI in childhood*”.  
719 However, they also emphasized that considering the limited body of evidence (one  
720 single study), the findings were inconclusive.

721

722 In summary, there is limited evidence that total energy intake in early childhood is  
723 associated with later higher BMI. However, confirmation of this association by  
724 controlled intervention studies is not available.

725

726

727 **DAIRY FOOD INTAKE**

728 No reviews were found that addressed the effect of exposure to milk or dairy  
729 products in early life on later BMI or body composition in children other than the  
730 review by *Pearce & Langley-Evans*<sup>42</sup> which concluded, when referring to long-term  
731 consequences of different protein intakes in infancy, that “*particularly dairy protein, in*  
732 *infancy could be associated with an increase in BMI and body fatness, but further research is*  
733 *needed to establish the nature of the relationship.*” In relation to immediate effects, a  
734 recent review by *Dror et al.*<sup>58</sup> (moderate quality) found no significant association  
735 between total dairy or total milk intake and BMI z-score at two years or incident  
736 overweight at three years, in line with a previous 2011 review on the relationship  
737 between dairy consumption and overweight/obesity in children and adults.<sup>59</sup>

738  
739 In summary, there is inconsistent evidence of an association of dairy consumption in  
740 early childhood with increased later overweight and obesity, but there is a lack of  
741 relevant controlled intervention studies.

742

743 **FRUIT and VEGETABLE INTAKE**

744 No reviews were found that addressed associations between dietary intake of fruits  
745 and vegetables in early childhood on later body composition, overweight, and  
746 obesity.

747 In a review by *Kaiser et al.* 2014<sup>60</sup> (moderate quality) that aimed to summarize the  
748 evidence on ‘*the effectiveness of the general recommendation to eat more fruits and*  
749 *vegetables for weight loss or the prevention of weight gain*’, no studies in children were  
750 identified.

751

752 In summary, there is no evidence that the dietary intake of fruits and vegetables in  
753 early childhood affects later body composition, overweight, and obesity.

754

755

756 **ADHERENCE TO DIETARY GUIDELINES**

757 The influence of adherence to dietary guidelines was also addressed by *Pearce &*  
758 *Langley-Evans*.<sup>42</sup> Based on the results of one identified study, no association was  
759 found between the Infant Guideline Score (IGS, based on dietary patterns) and later  
760 childhood BMI, fat mass, or fat-mass index. Positive associations between increasing  
761 IGS and both lean mass and the lean mass index were observed in four-year-old  
762 children. The overall quality of this study was moderate, and no firm conclusions can  
763 be drawn from a single report.

764

765 In summary, there is insufficient evidence of any effects of adherence to dietary  
766 guidelines in early childhood on later body composition, overweight, and obesity.

767

## 768 **DISCUSSION**

### 769 **Summary of main findings**

770 The aim of this systematic review of systematic reviews was to examine existing  
771 evidence on different nutritional interventions or exposures in infants and children  
772 and their effects on later health, specifically outcomes related to overweight and  
773 obesity. We wished to address the 'early life programming' hypothesis, which  
774 suggests that there are periods of developmental vulnerability to nutritional  
775 exposures when suboptimal nutrition may lead to persistent phenotypic changes in  
776 later life and increased risk of obesity.<sup>6,7</sup> To achieve this goal, in reviewing the  
777 literature we attempted to distinguish immediate effects from later effects of early  
778 nutrition. However, there is no clearly defined cut-off time point to indicate the  
779 optimal time for assessment of the phenotypic effect of programming either in  
780 relation to the interval following the exposure or the age of the offspring. Moreover,  
781 many of the selected reviews included studies on both immediate and longer-term  
782 effects of the nutritional exposures, making conclusions sometimes difficult to be  
783 formulated. Our approach was to identify the age of participants during the  
784 intervention and outcome assessment, while attempting to arbitrarily classify  
785 observed effects as immediate or later. On this basis, we found no strong evidence  
786 that any of the nutritional interventions or exposures in children aged up to three  
787 years consistently reduces the risk of overweight/obesity or increased adiposity.

788 There was, however, weak evidence that some of these interventions/exposures may  
789 be associated with a reduced risk of overweight/obesity. A consistent association of  
790 breastfeeding with a modest reduction in the risk of later overweight and obesity in  
791 childhood and adulthood was found (the odds decreased by 13% based on high-  
792 quality studies), but residual confounding cannot be excluded. Lowering the protein  
793 content of infant formula is a promising intervention to reduce the risk of later  
794 overweight and obesity in children. There is no consistent evidence of an association  
795 of the age of introducing complementary foods, sugar-sweetened beverage, or  
796 energy intake in early childhood, with later overweight/obesity, but there are some  
797 indications of an association of protein intake during the complementary feeding  
798 period with later overweight/obesity.

799  
800

#### 801 **Strengths and limitations of this review**

802 This review summarizes evidence from a number of systematic reviews of different  
803 nutritional interventions for the same problem, thus, it differs from systematic  
804 reviews that summarize original studies. Our search strategy was developed to  
805 ensure a thorough literature search, with no restrictions by language. All analyses  
806 were defined a priori. Considering that for some interventions (e.g., breastfeeding),  
807 RCTs would have been unethical, systematic reviews of non-RCTs were included.  
808 However, our review might not be comprehensive. Moreover, reviews were included  
809 only if our population and outcomes of interest were clearly identified in the  
810 abstract. If not, these systematic reviews might have been omitted.

811

812 The majority of the included reviews were published between 2010 and 2015. The  
813 inclusion of older systematic reviews, which have not been updated, may be  
814 challenged. However, for completeness, we reviewed all available systematic  
815 reviews, as small differences in search strategies in the included reviews might have  
816 resulted in substantial differences in the set of studies identified. As a consequence,  
817 often the evidence from included reviews is overlapping. Nonetheless, whenever

818 possible, we aimed to base our conclusions on the most recent and robust reviews to  
819 avoid overestimating the effect.

820

821 Only some of the reviews included in our review were of high methodological  
822 quality based on the AMSTAR assessment. We acknowledge that originally this tool  
823 was developed to assess the reviews of RCTs only<sup>61</sup> and that other tools may be  
824 considered (including the newly developed ROBIS tool).<sup>62</sup> However, all of the  
825 assessed elements apply also to systematic reviews of observational studies, and this  
826 tool had been previously used by different authors of reviews of observational  
827 studies.<sup>24,53</sup>

828

829 The conclusions of the original systematic reviews were often limited by the small  
830 number of included trials and/or participants and/or by the heterogeneity of the  
831 studies included. Except for the Cochrane reviews, which consistently used the  
832 Cochrane Risk of Bias tool, in the other original systematic reviews, the risk of bias in  
833 the included studies was not always assessed. When evaluated, often the included  
834 studies were not methodologically rigorous.

835

## 836 **Conclusions**

837 Rigorous testing of the 'early life programming' hypothesis requires clarity on both  
838 the timing of an exposure and outcome assessment in order to distinguish immediate  
839 consequences of dietary interventions from longer-term and potentially programmed  
840 effects. More high quality, controlled interventional studies are needed to address  
841 specific relationships between some nutritional components in early life and later  
842 risk of adiposity, ranging from protein, fat, and SSB intake to overall diet quality as  
843 well as the consumption of different type of foods such as dairy products or fruits  
844 and vegetables. In addition, further research is needed to identify the most effective  
845 strategies to implement particular dietary recommendations.

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**Contributors**

All authors contributed to formulating the research question and designing the study. The first draft of the protocol was prepared by BMZ and BPG and further discussed by all authors. BPG, BMZ, MK, and SK searched specified data sources, selected articles, and extracted all necessary data. BPG and BMZ analyzed the data. BPG and BMZ wrote the first draft of the manuscript. All authors revised and/or commented on drafts. All authors accepted the final version of the manuscript.

**SUPPLEMENTARY MATERIALS**

**RESULTS** – description and methodological quality of included reviews, and the risk of bias of included studies.  
**Table S1.** Search strategy (an example for Ovid MEDLINE) used to identify potentially eligible reviews.  
**Table S2.** Characteristics of included reviews.  
**Table S3.** Quality assessment of the reviews.  
**Figure S1.** Flow diagram of the reviews identification and selection process.

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