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# NUTRITION RESEARCH REVIEWS



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## **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review**

Journal:	<i>Nutrition Research Reviews</i>
Manuscript ID	NRR-20-032
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Date Submitted by the Author:	05-May-2020
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## REVIEW PROPOSAL FORM

Has your manuscript been solicited by a member of the Editorial Board? Yes / No

If yes, by whom?

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Title of proposed review:

**Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review**

**Please provide the following information**

A description of the content of the proposed review:

### 1. BACKGROUND (MAX 100 WORDS)

Based on the 2018 Global Nutrition Report, concurrent stunting and wasting are internationally reported in 15.95 million children under 60 months of life, while combined overweight and stunting in 8.3 million children.

The impact of severe undernutrition on cognitive neurodevelopment in later life is well documented. Questions remain on whether there is still an opportunity to minimize long-term impact on human capital in these children and whether overnutrition also impacts neurodevelopment and cognition.

This narrative review aims to document the impact of under-and overnutrition in children aged 0-60 months with a focus on cognitive neurodevelopment in later life.

## 2. CONTENT OF THE MAIN REVIEW (MAX 300 WORDS)

A literature search was performed using PubMed and Cochrane database for publications from 01 January 2009 to 31 October 2019 using a systematic review approach. After review of the full-texts and cross-references from eligible narrative reviews, a total of 26 articles were graded for its quality and analysed for qualitative synthesis.

Retrieved literature emphasizes the importance of improvements in linear growth and the neurocognitive development during the first 24 months of age. There is also a need to monitor weight, length and head circumference during the first 24 months of age as the effects of length-for-age z-scores (LAZ) and height-for-age z-scores (HAZ) were associated with various elements of cognitive function such as attention span, time to proper walking, mathematics and language abilities in early life; and overage schooling, income and choice of partners/age of marriage in later life. The impact of undernutrition on social-temperament is still conflicting.

The potential window of opportunity to rescue neurodevelopment and cognition seems to be present among undernourished children who recovered at 8 years of age. However, their academic achievement was still lower than those who had never been stunted. This rescue could be due to the late period of cortex development and the on-going synaptogenesis at the age of 8 years.

Based on limited studies, the impact of overnutrition during early childhood seems to be confined to gross motor skills and executive control in contrast to the wider impact of undernutrition. Socio-economic conditions, together with maternal, paternal and child characteristics, influence the impact of under- and overnutrition on neurodevelopment and cognition.

## 3. MAIN CONCLUSIONS AND IMPLICATIONS (MAX 100 WORDS)

Both under- and overnutrition during the first 60 months of post-natal life affects the developmental trajectories of children in later life. Given the Global Nutrition Targets for 2025, intervention programs should aim to include reduction of childhood obesity and provide adequate socio-economic stimulations as well as nutrition supplementation for catch-up growth among under-nourished children potentially up to the age of 8 years. These interventions should involve nutritionists, pediatricians, and behavioral specialists in a collaborative multidisciplinary team in order to ensure successful and comprehensive outcomes in terms of growth and cognitive neurodevelopment.

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*A statement in support of the subject of the review:*

Please provide a statement which explains the relevance and likely interest of the review to the nutritional science community (MAX 200 WORDS).

With the increasing incidence of double-malnutrition problems (over- and undernutrition) in children especially in developing countries, we believe that this review could support the learnings from recently published literature to further guide policy makers and healthcare practitioners to put more focus on cognitive aspects as a result of growth deviations in early life.

*A statement about the scientific authority of the review:*

This should include the publication track record of the authors and the number of articles which they have published on the topic of the review (MAX 200 WORDS).

All authors have solid track records in the field of over-and under-nutrition among children 0-60 months of age. In total, the number of published articles in peer-reviewed journals from all authors are around 20 on undernutrition; and around 40 on overnutrition. Some of the authors also have publications in various other domains such as, vitamin D, adolescents health, neurocognition, quality of child's development and behaviour.

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### Cover Letter: NRR-20-032.R1



May 19, 2020

To:  
Prof. Christine Edwards  
Editor in Chief  
Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review"

Dear Prof. Edwards

We would like to thank you for accepting our proposal and giving us the opportunity to submit the above-mentioned manuscript to Nutrition Research Reviews. We believe that this manuscript fits to the aim of the journal to provide updated information based on recently available literature on the impact of nutrition on later health to allow swift actions from relevant stakeholders.

In this review, we would like to emphasize not only on the impact of undernutrition in early life on cognitive development but also on the impact of overnutrition. With increasing incidence of double-malnutrition

Close

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Submitting Author: Muhardi, Leilani

[Cover Letter](#)

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Submitting Author: Muhardi, Leilani

[Cover Letter](#)

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# NUTRITION RESEARCH REVIEWS



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## **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review**

Journal:	<i>Nutrition Research Reviews</i>
Manuscript ID	NRR-20-032.R1
Manuscript Type:	Review
Date Submitted by the Author:	21-May-2020
Complete List of Authors:	Suryawan, Ahmad; Airlangga University, Department of Child Health JALALUDIN, MUHAMMAD ; University of Malaya, Department of Pediatrics Koon, Poh ; Universiti Kebangsaan Malaysia, Department: Nutritional Sciences Programme, Centre for Community Health Studies, Faculty of Health Sciences Sanusi, Rasaki; University of Ibadan, College of Medicine TAN, MING HUI ; Singapore Institute of Technology, Dietetics and Nutrition Programme, Health and Social Sciences cluster Geurts, Jan; Koninklijke FrieslandCampina NV Innovation Centre Wageningen Muhardi, Leilani; FrieslandCampina AMEA, Medical Affairs
Keywords:	double burden malnutrition, cognitive neurodevelopment, nutrition intervention, window of opportunity

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1 ***Narrative Review***

2

3 **Malnutrition in early life and its neurodevelopmental and cognitive**  
4 **consequences: A narrative review**

5

6 *Running title: Malnutrition and cognitive developmental consequences*

7

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33 **Keywords:** double burden malnutrition; cognitive neurodevelopment; nutrition intervention;  
34 window of opportunity

35

**36 Word count:**

37 250 Words Abstract, 3680 words in Main Text (excluding tables, figures and references), 4 Tables,  
38 2 Figures, 38 References

39

**40 Abstract**

41 While the global burden of severe undernutrition on impairment of children's development is quite  
42 well-reported, the impact of overnutrition on cognitive neurodevelopment is still unclear.  
43 Concurrent stunting and overweight were reported in 8.3 million children based on Global Nutrition  
44 Report in 2018. This narrative review aims to document the impact of mild-to-severe under-and  
45 overnutrition in children aged 0-60 months, with a focus on cognitive neurodevelopment aspects in  
46 early, mid and later life. A literature search was performed using PubMed and Cochrane database  
47 for publications from 01 January 2009 to 31 October 2019. Ninety one articles were originally  
48 identified through the search strategy. After review of the full-texts and cross-references from  
49 eligible narrative reviews, a total of 26 articles were graded for quality assessment and analysed for  
50 qualitative synthesis. Improvements of linear growth and the neurocognitive development during  
51 the first 24 months of age is important among undernourished children. The potential window of  
52 opportunity to rescue neurodevelopment and cognition appears to extend up to 8 years of age. Based  
53 on limited studies, there seems to be no influence of undernutrition on social-temperament; also the  
54 impact of overnutrition during early childhood seems to be limited to attention, gross motor skills  
55 and executive control in contrast to a wider impact of undernutrition. Socio-economic conditions;  
56 maternal, paternal and child characteristics influence the impact of under- and overnutrition on  
57 neurodevelopment and cognition. In conclusion, under- and overnutrition during the first 60 months  
58 of life affects different aspects of the cognitive neurodevelopmental trajectories in later life.

59

**60 INTRODUCTION**

61 Malnutrition in children includes undernutrition (wasting or low weight-for-height,  
62 stunting or low height-for-age, and underweight or low weight-for-age), micronutrient  
63 deficiencies, and overweight/obesity (1). Based on the recent 2020 Global Nutrition report,  
64 for children aged under 60 months of life, the number of stunted children worldwide has  
65 decreased from 165.8 million in 2012 to 149.0 million in 2018, while the number of

66 overweight children has increased to 40.1 million in 2018 (1). It is also reported that  
67 stunting and overweight coexisting in same individual in 10 out of 111 countries.  
68 Concurrent stunting and wasting were reported in 15.95 million children of the same age  
69 category, while overweight stunted in 8.3 million children internationally in 2018 (2).

70 Malnutrition leads to economic, social, and medical issues for individuals and their  
71 families, for the community and at national levels (2). More importantly, the global burden  
72 of severe undernutrition is serious as it impairs children's development in the short  
73 (delayed cognitive, behavioural and motor development), medium (lower IQ and school /  
74 academic achievement) and long term (human capital) mostly in low and middle-income  
75 countries (3-6). In addition, it appears to still be unclear whether overnutrition impacts  
76 neurodevelopment and cognition or whether neurodevelopmental incapability influences  
77 overnutrition.

78 Although recent data showed that the incidence of stunting has reduced over the  
79 last decade (1) questions remain on whether there is still an opportunity to minimize long  
80 term impact on human capital in these children via nutritional and non-nutritional  
81 interventions. It is largely unclear whether these interventions should be targeted at  
82 specific aspects of neurodevelopment and cognition taking into consideration the timing of  
83 malnutrition with the timing of neurodevelopment in early childhood. There is also a need  
84 to improve our understanding on which aspects of neurodevelopment and cognition are  
85 affected in overweight and obese children in order to design specific intervention for these  
86 populations.

87 Building on the above, this narrative review aims to document the impact of under-  
88 and overnutrition as a proxy for suboptimal growth in children aged 0-60 months with a  
89 focus on developmental-related aspects (cognition, behavioural, motor and emotional  
90 development) in early, mid and later life.

91

## 92      **METHODS**

93            Literature published from 01 January 2009 to 31 October 2019 in PubMed and  
94      Cochrane database was retrieved using formulated search terms. Identification of a  
95      research question and inclusion /exclusion criteria, selection of studies and data collection  
96      and qualitative analysis were conducted following certain aspects of PRISMA 2019  
97      guidance for systematic reviews (Supplementary table 1). Simple grading of controlling  
98      study biases was conducted using certain elements of PRISMA 2019 guidelines for  
99      systematic review and meta-analysis, JADAD criteria for randomized controlled (RCT)  
100     studies, Newcastle Ottawa scale for cohort studies, and National Lung and Blood Institute  
101     (NLBI) criteria for observational cross-sectional studies. No extracting of individual data  
102     from individual studies included in meta-analyses and systematic-reviews and no  
103     synthesizing findings quantitatively or pooling numerical data were conducted. References  
104     of relevant narrative reviews (cross-references) were also examined to search for further  
105     studies that met the inclusion criteria.

### 106      **Data collection, extraction and analysis**

107     The PICO elements of the research question were defined as follows: the population of  
108     interest (P) included children aged 0-60 months; the intervention (I) was any observational  
109     procedure, nutrition supplementation, maternal education, or hygiene education compared  
110     (C) to nothing, placebo or any comparator that permits to attributes the effect to the  
111     intervention; and the outcome (O) was suboptimal child development (cognitive,  
112     behavioural, motor and emotional development). The title and abstract of each article  
113     retrieved by the search strategy were screened for inclusion criteria by all authors. Values  
114     that matched between the reviewers were used to create the clean database. Any values  
115     that did not result in a match, were reviewed and resolved through discussions among all  
116     the authors. Afterwards, two authors (JG and LM) independently extracted data from the  
117     identified full-text articles. Data extraction tables incorporated eligible full-texts from



118 original articles, meta-analyses and systematic reviews and from eligible references from  
119 retrieved narrative review to allow extraction of significant information for qualitative  
120 synthesis.

121

## 122 **RESULTS AND DISCUSSION**

### 123 ***Descriptive summary of included studies***

124 From the 91 articles originally identified through the search strategy, 26 full-text  
125 articles were selected after review of cross-references in eligible narrative reviews, and  
126 after a review of all the full-texts and grading for quality assessment (Figure 1).

127 Information was categorized based on the type of study and nutrition status of the  
128 children (Table 1 and Table 2). Information was extracted from 14 observational studies  
129 (undernutrition (n=8 articles); normonutrition (n=5 articles) and overnutrition (n=1 articles);  
130 4 intervention studies (undernutrition (n=2 articles) and normonutrition (n=2 articles); 4  
131 systematic reviews (undernutrition (n=1 article); normonutrition (n=2 articles) and  
132 overnutrition (n=2 articles) ) and 4 meta-analysis all on undernutrition. All publications on  
133 normo- and undernourished children were reporting on studies conducted in low- to  
134 middle-income countries, while all articles on over-nourished children were reporting data  
135 from high-income countries. Three meta-analyses and two intervention studies were  
136 retrieved for intervention studies on undernutrition. No interventional studies were retrieved  
137 on over-nourished children. Around 85% (n=22) of the retrieved literature had good quality  
138 in controlling their bias (Table 1 and 2).

139 To the best of our knowledge, this review complements previous meta-analyses  
140 and systematic reviews (4-6) and include a wider spectrum of sub-optimal growth (severe,  
141 moderate to mild undernutrition such as wasting, underweight and stunting; and  
142 overnutrition) during the first 60 months of life on various neurodevelopment aspects  
143 (cognition, motor development, temperament, socio-economy, academic achievement)

144 from school age to adulthood (Figure 2). It also covers both observational and  
145 interventional studies with nutrition- and non-nutrition related interventions and outcomes  
146 of interest.

147  
148 ***The importance of monitoring weight, length and head circumference during the***  
149 ***first 24 months of age.***

150  
151 Across the retrieved studies, effects of length-for-age z-scores (LAZ) and height-  
152 for-age z-scores (HAZ) were associated with various elements of cognitive function such  
153 as attention span, time to proper walking, mathematics and language abilities in early life;  
154 and overage schooling, income and choice of partners/age of marriage in later life (Table  
155 1). It was reported that healthy infants in the highest quartile of neonatal weight, length,  
156 and head circumference gain during the first 4 weeks of life had a higher IQ score at 6  
157 years of age as compared to those in the lowest quartile (7).

158 HAZ at 6 months among under-nourished children was positively associated with  
159 cognitive function at 11 years of age (8). Cognitive impairment associated with poverty and  
160 undernutrition is already visible at 7 months of age and worsens up to 64 months when it  
161 becomes more significant (8). In contrast, a longitudinal study among children in the  
162 Philippines, which was not retrieved as it is not within the timeframe of this review,  
163 proposes that malnutrition in the second year of life is more harmful than malnutrition  
164 before 12 months of age (30). HAZ at 4-6 years of age among healthy Malaysian children  
165 was significantly related to their cognitive functions (9).

166 The impact of undernutrition on social-temperament seems to be conflicting. Two  
167 meta-analysis retrieving data from lower and middle-income countries stating no influence  
168 of undernutrition on the child's temperament (4, 6). However one study among Bangladeshi  
169 children aged 6-24 months reported that underweight (weight-for-age z score < 2 SD)

170 children were less sociable, less attentive, more fearful and have more negative emotional  
171 traits as compared to the healthy children (10). A recently published systematic cum  
172 review-meta analysis reported a positive effect of nutrition interventions on social-  
173 temperament among stunted children especially in low- and middle-income countries (5).

174 In later life, these anthropometric deficits were translated into other effects such as  
175 overage schooling or less schooling (11), lower-income or living in poverty, choice of  
176 partners in terms of age and schooling difference, lower age at first child's birth, and a  
177 higher number of pregnancies and children (12).

178  
179 ***Improvements in linear growth and potential window of opportunity to rescue***  
180 ***neurodevelopment and cognitive abilities***

181  
182 This review further strengthens the importance of the first 1000 days of life as a  
183 window of opportunity for cognitive development. It was reported that HAZ velocity  
184 between 6 and 24 months among under-nourished children was positively associated with  
185 cognitive function (13) and that every 1-unit increase in HAZ below the age of 24 months  
186 is associated with a higher increment in motor, communication and cognitive ability scores  
187 at 26 to 80 months of age as compared to 1 unit increase in HAZ after 24 months of age  
188 (4, 11).

189 It appears that the window to rescue neurodevelopmental deficits is still possible up  
190 until 8 years of age provided that the stunting problem has been addressed. Based on data  
191 from the Young Lives cohort in Ethiopia, India, Peru, Cambodia, and Vietnam, the authors  
192 showed that children who were in the recovered group (stunted at 12 months of age but  
193 not stunted at 8 years of age) had better academic achievement (mathematics scores,  
194 receptive vocabulary scores, and reading-comprehension scores) compared to those who  
195 were persistently stunted (11). However, their academic achievement was still lower than

196 those who had never been stunted. This finding is consistent with the finding from a cohort  
197 in Malawi which reported that those who had recovered from stunting had better academic  
198 achievements at 11 years of age as compared to those who were persistently stunted from  
199 age 4 to 8 years (14). The possibility of a rescue time period beyond 2 years of life could  
200 be due to the late period of cortex development and the on-going synaptogenesis until a  
201 later age (3).

202 Interestingly, there are contradictory findings on the extent to which subsequent  
203 'catch-up' growth and 'catch-up' cognitive functioning are associated with stunting in  
204 children. In a very recent study, it was reported that children who were stunted at 24  
205 months of life and experienced catch-up growth often did worse on cognitive tests at 4-5  
206 years of age than children who were never stunted, and almost as poorly as children who  
207 remain stunted (15). It is important to note that the exact definition of 'catch-up' plays an  
208 important role in this observation. Desmond and Casale (2017) formulated five definitions  
209 for it, ranging from lenient to strict (I: increase in HAZ, II: recovery from stunting (HAZ at  
210 5y>-2), III: decrease in height for age difference, IV: recovery from stunting and decrease  
211 in height-for-age deficit, and V: recovery from stunting (HAZ at 5y>-2) + HAZ at 5y >-1  
212 ('normal' range)). The reported observation above is based on definition I-IV of 'catch-up'.  
213 Thus, the definition of 'catch-up' growth should be carefully defined in order to determine  
214 the optimal goal for catch-up growth with the aim to rescue neurodevelopment and  
215 cognitive ability in later life.

216  
217 ***The importance of interventions in improving cognitive outcomes among***  
218 ***undernourished children***

219  
220 There were 7 retrieved publications assessing the effectiveness of intervention  
221 studies in improving cognitive outcomes among undernourished children which consists of

222 3 randomized controlled trial, 2 systematic reviews and 2 meta-analysis. The overall quality  
223 of these studies is good at controlling the study's bias (Table 2).

224 From one intervention study in undernourished (16) and one in normo-nourished  
225 children (17), it appears that the effect of the vitamin/nutrition intervention on rescuing the  
226 neurodevelopment and cognitive deficits is more pronounced in stunted children than in  
227 normo-nourished ones. Stunted children with high levels of plasma homocysteine and  
228 those who were aged less than 24 months at the end of the follow-up had the highest  
229 impact in gross motor and problem-solving functioning skills after being supplemented with  
230 vitamin B12 on daily basis (16). No additional benefits in growth or cognitive performance  
231 with daily multi-micronutrient supplements (iron, zinc) were reported in 422 healthy  
232 children aged 12 to 24 months of life (17). It should be noted however that these studies  
233 were different in types of intervention (oral food supplement high in iron and zinc vs vitamin  
234 12 and folic acid supplementation) and age of enrolment (younger than 2.5 months of age  
235 vs 6 months of age and older) regardless of the similar intervention duration of 6-months.

236 In contrast, an intervention study combining multiple micronutrient intervention with  
237 and without responsive stimulation for around 20 months among 1486 mother-children  
238 pairs in Pakistan reported that children exposed to 'enhanced' nutrition had significantly  
239 higher development scores (cognitive, language, and social-emotional scales) at 12  
240 months of age than the control group (18). Another group of children who received  
241 responsive stimulation had significantly higher development scores on the cognitive,  
242 language, and motor scales at 12 and 24 months of age, and on the social-emotional scale  
243 at 12 months of age, than control. In comparison, the treatment effect on cognition,  
244 language and motor development at 24 months were moderate-to-large for responsive  
245 stimulation, and were low to moderate for enhanced nutrition group the study (18).

246 It seems that either nutrition or parent-based responsive learning intervention affect  
247 neurodevelopment and cognition. This is quite consistent with the recently published

248 systematic review and meta-analysis which assessed the nutrition and responsive learning  
249 interventions on neurodevelopmental development of children 0-60 months of age (5).  
250 Based on the 75 retrieved studies from various databases until June 2019, it was reported  
251 that the effect size of nutritional supplementation was significantly associated with effect  
252 size on cognitive and motor scores. However, the pooled effect of these supplementations  
253 is one fourth smaller than the pooled effect size of responsive care and learning  
254 opportunities on cognitive, language, and motor scales. The authors of the review also  
255 suggested that postnatal multiple nutrient supplementations can affect linear growth,  
256 cognitive development and socio-temperament; but multiple micronutrient  
257 supplementations combine with responsive care and learning opportunities affect only  
258 cognitive development but not linear growth (5).

259 No retrieved studies assessed the direct relationship between food intake, including  
260 protein intake, nutritional status, in particular linear growth, and cognitive function; as most  
261 of the studies link nutrition interventions directly to the cognitive outcomes.

262

### 263 ***The impact of overnutrition on neurodevelopment and cognition***

264 Only one cross-sectional study and two systematic reviews were retrieved that  
265 describe the impact of overnutrition on cognitive neurodevelopmental aspects (19-21)  
266 (Table 1).

267 All studies seem to point towards a more limited impact of overnutrition on aspects  
268 of neurodevelopment and cognition in the studied affluent populations, in contrast with  
269 those describing the impact of undernutrition. All retrieved literature demonstrated that  
270 attention, executive control (inhibitory control, working memory, reward sensitivity,  
271 impulsivity) and gross motor skills are the most affected areas. A study among overweight  
272 Italian children showed poorer gross motor skill performance than their normal weight  
273 peers (19) while both systematic reviews reported poorer executive control, more difficulty

274 with inhibition and less effective inhibition strategies in overweight children compared to  
275 healthy weight children (20, 21). In addition, a poorer performance of inhibitory control  
276 among children with higher BMI at 2-5 years of age was associated with a much higher  
277 BMI at a later age (5.5-15 years of age) (20). This latter finding suggests directionality in  
278 the association between obesity and executive function. Children with lower executive  
279 function are speculated to have lower self-regulation of caloric intake and engaging in  
280 physical activity, which leads to overweight or obesity. This was also reported by Hayes et  
281 al (2018) who showed that low executive function stimulates excess adiposity leading to  
282 exacerbating decrements in executive function in childhood (22). On the other hand,  
283 studies showed that obesity/early life adiposity reduces executive function via several  
284 biological mechanisms. Pro-inflammatory cytokines produced by the adipose tissue can  
285 stimulate inflammatory pathways in all age categories leading to cognitive development  
286 deficits (21) and dysregulation of appetite-regulating hormones could further harm their  
287 cognitive skills (21).

288 In addition, poor gross motor skills, which is correlated with less physical activity (20) and  
289 reduced capability in providing attention (20, 21), should be taken into consideration when  
290 designing intervention programs for these children.

291

292 ***Factors influencing the impact of suboptimal growth on neurodevelopment and***  
293 ***cognition***

294 From the retrieved literature, the influencing factors were further classified into  
295 maternal and paternal factors, child's characteristics and health condition, and socio-  
296 economic condition (Table 3). Several maternal parameters during pregnancy, such as  
297 maternal weight gain and smoking, have been consistently reported to influence the impact  
298 of suboptimal growth on cognitive neurodevelopment in addition to low birth weight and

299 stunting at birth; suggesting the importance of prenatal nutrition and maternal health for  
300 later life (8, 10, 15, 23, 24).

301 The influence of sex on suboptimal growth and cognitive neuro-development seems  
302 quite conflicting from the retrieved literature. Normo- and undernourished girls had slightly  
303 higher scores of intelligence (7), social maturity (15), and manageability (10) than boys of  
304 the same nutritional status while opposite findings were reported by Mohd Nasir MT et al.  
305 in normo-nourished children (9).

306 Among under-nourished children particularly, the literature reported that parents  
307 with a low level of nutritional knowledge, those who perceived less responsibility in the  
308 feeding task, or those who were less restrictive towards access to unhealthy foods had  
309 children who experienced suboptimal growth and suffered from impaired cognitive  
310 development (4, 9). From this perspective, diet quality demonstrated to be a positive  
311 predictor of improved cognitive outcomes in children (4, 9). For instance, food fortified with  
312 calcium, iron, zinc, vitamins B2, and proteins is associated with improved cognitive  
313 outcomes because of the probable role of these nutrients in early brain development (5,  
314 18). By contrast, a lack of dietary protein may delay or inhibit brain and cognitive  
315 development (4, 25). On that note, recent evidence proposed supplementation of animal  
316 protein, in particular milk, as an essential component in a child's diet in order to prevent  
317 undernutrition and improved cognition (26-28).

318 The influence of a proxy indicator for socio-economic factors using Home  
319 Observation for Measurement of the Environment (HOME) was reported in several studies  
320 among undernourished children to influence the impact of under-and overnutrition on  
321 neurodevelopment and cognition (4, 7, 18, 23, 24, 29, 30). This score was developed to  
322 measure responsiveness and stimulation of the home environment which consists of  
323 several questions including possession of books and toys ownership at home. Among  
324 overweight children, socioeconomic status was the only influencing factor reported with



325 those in lower socio-economic situations had a lower motor skill functioning than their  
326 counterparts with higher socioeconomic status (19) .

327           This review has several limitations. First, chronic illnesses and hospital  
328 malnutrition were excluded although they could have a similar impact on overall  
329 developmental aspects. A second limitation is that the statistical significance of pooled  
330 effects of all studies combined was not conducted since the review is narrative and not  
331 systematic. Furthermore, it is likely that some relevant literature was missed as the search  
332 was limited to peer-reviewed research published within the past decade. There may be  
333 value in additionally reviewing reports outside the peer-reviewed literature to address  
334 potential publication bias and evaluating patterns over a longer period of time.

335 As for the strengths, this narrative review approach provides comprehensive and updated  
336 scientific evidence for healthcare professionals and policymakers in a relatively shorter  
337 time. It is hopeful that this synthesized evidence will allow them to plan and execute  
338 necessary intervention programs for preventing and managing suboptimal growth with a  
339 focus on achieving optimal cognitive potential in young children. In addition, the review  
340 was conducted using methodological approaches similar to systematic reviews albeit  
341 without grading of scientific evidence that would allow more accuracy in literature  
342 screening and less bias. A cross-referencing of eligible studies from retrieved narrative  
343 reviews allowed further completion of the evidence and enabled the retrieval of information  
344 of not only the populations that experience under- and overnutrition but also in the normal  
345 population which identified children with faltering growth. It also enabled the retrieval of  
346 studies from various geographical areas (low- to high-income studies) as well as studies  
347 with various developmental deficits.

348           Consideration for future research and actions:

349 1) More studies should be conducted on the impact of nutritional/behavioural intervention  
350 on overweight/obesity in early life on neurodevelopment and cognition especially in low-

351 income countries as all the current retrieved literature were from high-income countries.  
352 Overnutrition in childhood is on the rise and can co-exist with undernutrition within the  
353 same population, for example in India and Indonesia. Around 46.6 and 36.6 million children  
354 under five are stunted and more than 1 million children in the same age group are  
355 overweight in India and Indonesia respectively. This amounts to almost a total of 90 million  
356 Indian and Indonesian children who are at risk of sub-optimal neurodevelopment and  
357 cognitive function (2). Thus an increase in childhood obesity prevalence may have adverse  
358 long-term consequences on human capital in these countries, in addition to those from  
359 under-nutrition.

360 2) Intervention studies for both under- and overnutrition must assess the association  
361 between these nutritional statuses and cognitive neurodevelopment as most interventions  
362 usually focus only on providing nutrients related to brain development and not for optimal  
363 growth and vice-versa as also suggested by Prado et al (5). For example, several studies  
364 and systematic reviews recently published assessed the impact of animal-based food  
365 supplementations or milk interventions on growth among stunted children or only on  
366 cognitive neurodevelopment but not on both aspects simultaneously (26, 27).

367 3) Any program or intervention for growth monitoring in the community or in hospital  
368 settings should engage the involvement of nutritionists, paediatricians, and behavioural  
369 specialists in a collaborative multidisciplinary team. They have a double duty actions to  
370 think about both sides of malnutrition when planning and implementing intervention  
371 programmes (31). These actions taken should be able to tackle both under-nutrition and  
372 over-nutrition at the same time – not just either or in order to ensure successful and  
373 comprehensive outcomes in terms of growth and cognitive neurodevelopment.

## 374 **CONCLUSIONS**

375 Both under- and overnutrition during the first 60 months of post-natal life affect the  
376 developmental trajectories of children in later life. Weight and length/height need to be

377 monitored even beyond 60 months of life to enable early recognition of growth deviations  
378 and to allow appropriate and timely interventions to attenuate the negative  
379 neurodevelopmental and cognitive impacts. Given the Global Nutrition Targets for 2025  
380 (32), intervention programs should aim to include reduction of childhood obesity and  
381 adequate socio-economic stimulations as well as nutrition supplementation for catch-up  
382 growth among under-nourished children potentially up to the age of 8 years given the  
383 possibility of improving cognitive achievement especially in those recovered from stunting.  
384 These specific and targeted interventions might be key to safeguard future human capital  
385 especially in countries with a high incidence of stunting and overweight.

386

387

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398

399 **Authors' contribution**

400 All authors were involved in setting the concept, objective and selection criteria for the  
401 review. All authors were also involved in the selection of eligible articles based on titles  
402 and abstract. LM and JG further selected the eligible articles based on full texts. All authors  
403 provided agreement on the final included articles. All authors participated in data  
404 extraction, synthesis and interpretation. All authors provided input and agreed on the final  
405 version of the manuscript.

406

407 **Competing interests**

408 Leilani Muhandi, Verena Tan and Jan Geurts are employees of FrieslandCampina at the  
409 time of the manuscript's development.

410

411 **Consent for publication**

412 Not applicable.

413

414 **Ethics approval and consent to participate**

415 Not applicable.

416

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418

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**FW: Nutrition Research Reviews NRR-20-032.R1: Decision on Manuscript**

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Wed, Aug 19, 2020 at 8:28 AM

To: ahmad suryawan <suryawan.ahmad@gmail.com>, Verena Tan Ming Hui <Verena.Tan@singaporetech.edu.sg>, "Geurts, J.M.W. (Jan)" <Jan.Geurts@frieslandcampina.com>, Rasaki Sanusi <sanusiadegoke2003@gmail.com>, Universiti Kebangsaan Malaysia <pbkoon@ukm.edu.my>, Muhammad Yazid Jalaludin <yazidj@ummc.edu.my>  
Cc: "Kudla, U. (Urszula)" <Urszula.Kudla@frieslandcampina.com>

Dear Authors,

Please find the decision on the manuscript below as shared by Prof. Yazid. Although it still requires major revision, I think we past the 2<sup>nd</sup> milestones. Congratulations to all of us!

I would like to propose the following as next steps:

<b>Action Plans</b>	<b>PIC</b>	<b>Time line</b>
Share feedback on the reviewers' comment to Leilani	All authors	Aug 19-24
Revise manuscript and prepare letter to reviewers	Leilani	Aug 24- Sept 2
Review revised manuscript and letter to reviewers	All authors	Sept 3-9
Language editing/ proof-read	External party	Sept 10-20
Review revised manuscript after proof read	All authors	Sept 21-26
Submission to journal	Leilani	Sept 27-28

Thank you for all your patience and support; looking forward to hear from you soon.

Kind regards,

Leilani

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**From:** Muhammad Yazid Jalaludin <[yazidj@ummc.edu.my](mailto:yazidj@ummc.edu.my)>  
**Sent:** Tuesday, August 18, 2020 9:05 PM  
**To:** Muhardi, L.M. (Leilani) <[leilani.muhardi@frieslandcampina.com](mailto:leilani.muhardi@frieslandcampina.com)>  
**Subject:** Fwd: Nutrition Research Reviews NRR-20-032.R1: Decision on Manuscript

Dear Dr Leilani,

Decision: Major Revision.

Sent from my iPhone

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18-Aug-2020

\*\*A copy of this decision email has also been sent to the reviewers\*\*  
\*\*Please ensure that all co-authors are made aware of the content of this email\*\*

Dear Prof. JALALUDIN,

Manuscript ID NRR-20-032.R1 entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review" which you submitted to Nutrition Research Reviews, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter. While the reviewer(s) recognise the potential of your manuscript as a valuable contribution to the journal, they also suggest some major revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript. To start your revision now, click the link below:

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If English language editing has been requested in the below comments, we list a number of third-party services specialising in language editing and/or translation. Use of any of these services is voluntary, and at your own expense.

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Because we are trying to facilitate timely publication of manuscripts submitted to Nutrition Research Reviews, your revised manuscript should be uploaded as soon as possible. We expect to receive your revision by 17-Nov-2020. If it is not possible for you to submit your revision by this date, please contact the Editorial Office to rearrange the due date. Otherwise we may have to consider your paper as a new submission. Once again, thank you for submitting your manuscript to Nutrition Research Reviews and I look forward to receiving your revision.

Sincerely,  
Prof. Christine Edwards  
Editor-in-Chief, Nutrition Research Reviews  
[christine.edwards@glasgow.ac.uk](mailto:christine.edwards@glasgow.ac.uk)

Editor

Comments to the Author:

Could the authors please ensure that this remains a narrative review and doesn't switch to a systematic review

Reviewer: 1

Comments to the Author

This is a very general narrative review and literature search looking for both under and over nutrition and its affect on neurodevelopment and cognition is quite wide. I wonder if it might have been better to stick to one or the other and that the scope becomes very broad and difficult to manoeuvre in one article without really paying attention to the subtleties of any of the literature. The arguments and understandings of why many papers may have not come up with results or what it was that influenced the information retrieved is really limited and therefore does not add a lot to the literature that was already there in terms of critical appraisal.

The article is described as a narrative review and then is written up as though it was a systematic review but not quite done like that – this is a little confusing for the reader!

Abstract:

Not sure what this sentence really means; "Improvements in linear growth and the neurocognitive development during the first 24 months of age is important among undernourished children". Maybe the authors mean something like; "Research demonstrates the importance of the relationship between linear growth and neurocognition in children less than 24 months; particularly in those underweight" (or something like this)? Not very clear as to what the real meaning of the sentence is.

Again with this sentence; "also the impact of overnutrition during early childhood seems to be limited to attention, gross motor skills and executive control..." – should this not read; "The impacts of overnutrition during early childhood have mainly concentrated on outcomes relating to attention, gross motor skills and executive control.."

These last sentences are very generic and nothing "new"; "Socio-economic conditions; maternal, paternal and child characteristics influence the impact of under- and overnutrition on neurodevelopment and cognition. In conclusion, under- and overnutrition during the first 60 months of life affects different aspects of the

cognitive neurodevelopmental trajectories in later life.” It might be helpful if the authors could provide a little more specifics within their conclusions in these two sentences.

Line 158 \_ “HAZ in undernourished children” – could the authors define what they mean by “undernourished”? Do they mean underweight, or wasted? A clear definition is required.

Line 166 “The impact of undernutrition on social temperament seems to be conflicting” – do the authors mean; “Evidence of the impact of undernutrition (as defined as...) on social temperament is very variable in the studies identified”

In places, the authors state information but there is no criticism as to why it might be that there is limited evidence across studies e.g. lines 166 – 173. This makes the article confusing to read – maybe if the authors could state things to take into account some of the issues as they write, it might help. For example; “Although one meta-analysis has demonstrated no effect of undernutrition on children’s temperament, some more recent and detailed studies have demonstrated some effect”. “Those studies which have investigated interventions have demonstrated some effect of socio-emotional outcomes from the intervention...” Maybe mentioning in what way the socio-emotional outcome was affected (what was measured) would be helpful.

Again on line 174, the authors mention that “in later life, these anthropometric deficits (what does this mean??) were translated into other effects such as overage schooling (not sure what this means) or ????? This is really unclear and it might be best to be clearer as to what the authors mean e.g. “In later life, studies we reviewed demonstrated that low height for age z scores correlated highly with children completing less years of school or not progressing to higher years....” Or something along those lines.

Line 199 - “The possibility of rescue time period beyond 2 years of life could be due to the late period of cortex development and the ongoing synaptogenesis....” Could the authors make clear what they mean here – again it is just not clear whether the late period of cortex development and ongoing synaptogenesis that they mean is beyond 2 years or not beyond 2 years?

Lines 202 – 215 are much easier to read and have much more of a clear explanation and definition within them.

Line 232 – “that these studies were different in types of intervention (oral food supplement high in...”. These statements here are very general and unclear to the reader. Could they be made much more specific so they are clearer to the reader?

Line 246; “It seems that either nutrition or parent-based responsive learning intervention affect neurodevelopment and cognition”. The authors here make this general statement but for the reader, there is no clarity as to what the authors mean and in what way. This is all really important as these articles are very different and are looking at interventions that improve responsiveness is very different than those which affect nutrition. This is not very clear from the statements.

#### Grammar:

Throughout there are a lot of issues with the grammar – I have picked up on some but there are many more and the team would need to go through these with a native English speaker and review. Plurals seem to be a particular issue e.g. “meta-analyses” rather than “meta-analysis” and ensuring that “s” is put on the end of words. It is therefore quite confusing to read in places.

“focus on cognitive neurodevelopment aspects” – maybe should read “with a focus on the cognitive and neurodevelopmental outcomes...”

Line 66 “It is also reported that stunting and overweight coexisting..” maybe reads better as; “stunting and overweight coexists..”

Line 76 – “neurodevelopment incapability”.. What does this mean? Use a different term.

Line 85 – “specific interventions” not “specific intervention”

Line 140 “include” rather than “includes”

Interesting that two of the authors are from Friesland Campina – a milk company. This is written in the funding section but is important to acknowledge as a conflict of interest possibly. The team also acknowledge “ContentEd Singapore” however it is unclear how they were involved and what they did. If they are a company who specialise in medical writing and editing, they need some support with grammar in their writing.

Reviewer: 2

#### Comments to the Author

This obviously is an important topic. I think the manuscript would benefit from greater clarity in a number of areas.

- 1) First, what is the really new question that the authors are trying to address in this review? Is it the critical window in which nutritional correction can address developmental deficits? Or the combination of stunting and overweight and the impact of this? At present, the message gets a little lost and the story is not clear.
- 2) Secondly, I think that (even though the journal is nutrition research reviews) the manuscript would benefit from definitions. For the purposes of this, what is meant by undernutrition, norm-nutrition and overnutrition? Is the last of these even appropriate? Don't many overweight / obese children suffer from malnutrition rather than over nutrition - e.g. poor balance or quality of nutrients?
- 3) The term normonutrition confused me, particularly as many of these studies were from low-income countries. Were the children really 'normonourished' - whatever this means?
- 4) The PICO statement is confusing. Is it really needed to be formulated in this way? What is an observational intervention? Does this mean that the study was simply an observational cohort - in which case no intervention? Observational intervention seems to me a contradictory phrase.
- 5) on page 3, it starts that stunting and overweight coexist in 'same individual in 10 out of 111 countries.' I don't understand what this is trying to say. Obviously, stunting and overweight coexist in some children in many more than 10 countries...? Could this please be clarified.
- 6) For me, the most interesting aspect is the critical window for addressing the impact of malnutrition. I thought this could be developed further and more clearly. Generally, the story and key message throughout does not come across as clearly as it could do.
- 7) the tables are not clear. More clarity around what the observational cohort was and what the interventions were would be helpful. For example, trying to understand the cohorts is challenging - observational study of healthy Ethiopian newborns with norm-nutrition...? Or of 2, 853 Bangladeshi singleton babies? Were these all of normal birthweight (defined how?) and what was the definition of norm-nutrition for them? It is difficult to interpret the meaning of the studies without greater clarity.

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## RESPONSE TO REVIEWERS

To:  
Prof. Christine Edwards  
Editor in Chief  
Nutrition Research Reviews

Re: Manuscript titled “Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review”

Thank you for in-principal acceptance of our manuscript entitled “Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review” in Nutrition Research Reviews. We really appreciate the inputs given by the two reviewers. We have revised the manuscript to the best of our capabilities to follow the suggestions of the reviewers as per below explanation.

We hope that the revised manuscript is satisfactory and it can be published soon. We look forward to having your favourable response.

Yours sincerely,

**Assoc Prof Dr Muhammad Yazid Jalaludin**  
Corresponding authors

*Reviewers' comments:*

This is a very general narrative review and literature search looking for both under and over nutrition and its effect on neurodevelopment and cognition is quite wide. I wonder if it might have been better to stick to one or the other and that the scope becomes very broad and difficult to manoeuvre in one article without really paying attention to the subtleties of any of the literature. The arguments and understandings of why many papers may have not come up with results or what it was that influenced the information retrieved is really limited and therefore does not add a lot to the literature that was already there in terms of critical appraisal.

The article is described as a narrative review and then is written up as though it was a systematic review but not quite done like that – this is a little confusing for the reader!

*Response to reviewer :*

As the concurrent problem of under- and over-nutrition exists in many countries across the world, we believe it will be beneficial to address the impact of both conditions on cognitive and neurodevelopment in one article. Also, we have added the definition of scoping review which quite closely fits the manuscript on the method section (line 89-106). We hope that this will differentiate the manuscript from a systematic review. In addition, general editing to the overall text has been made in italics in order to improve the clarity of the statements.

**Abstract:**

*Reviewer's comment:*

Not sure what this sentence really means; "Improvements in linear growth and the neurocognitive development during the first 24 months of age is important among undernourished children". Maybe the authors mean something like; "Research demonstrates the importance of the relationship between linear growth and neurocognition in children less than 24 months; particularly in those underweight" (or something like this)? Not very clear as to what the real meaning of the sentence is.

*Response to reviewer:*

Changes have been made to now line 45-46 to better clarify the real meaning of this sentence.

*Reviewer's comment:*

Again with this sentence; "also the impact of overnutrition during early childhood seems to be limited to attention, gross motor skills and executive control..." – should this not read; "The impacts of

overnutrition during early childhood have mainly concentrated on outcomes relating to attention, gross motor skills and executive control..”

*Response to reviewer:*

Changes have been made to now line 49--50 to better clarify the real meaning of the sentence.

*Reviewer’s comment:*

These last sentences are very generic and nothing “new”; “Socio-economic conditions; maternal, paternal and child characteristics influence the impact of under- and overnutrition on neurodevelopment and cognition. In conclusion, under- and overnutrition during the first 60 months of life affects different aspects of the cognitive neurodevelopmental trajectories in later life.” It might be helpful if the authors could provide a little more specifics within their conclusions in these two sentences.

*Response to reviewer:*

Changes have been made to provide more specific results and conclusion as stated in now line 50-57.

*Reviewer’s comment:*

Line 158 \_ “HAZ in undernourished children” – could the authors define what they mean by “undernourished”? Do they mean underweight, or wasted? A clear definition is required.

*Response to reviewer:*

Further clarification on HAZ has been added in line now 145-146 to include “ All HAZ categories at 6 months defined as mild/moderate/severe stunting (<-2 to -1.01) , at risk for stunting (-1 to -0.001), or normal ( $\geq 0$ ) were positively associated with cognitive function at 11 years of age.”

*Reviewer’s comment:*

Line 166 “The impact of undernutrition on social temperament seems to be conflicting” – do the authors mean; “Evidence of the impact of undernutrition (as defined as...) on social temperament is very variable in the studies identified”.

*Response to reviewer:*

Changes have been made on now line 155-156 to better clarify the real meaning of this sentence to: “Evidence of the impact of underweight and stunting on social temperament is largely variable across the identified studies.

*Reviewer's comment:*

In places, the authors state information but there is no criticism as to why it might be that there is limited evidence across studies e.g. lines 166 – 173. This makes the article confusing to read – maybe if the authors could state things to take into account some of the issues as they write, it might help. For example; “Although one meta-analysis has demonstrated no effect of undernutrition on children’s temperament, some more recent and detailed studies have demonstrated some effect”. “Those studies which have investigated interventions have demonstrated some effect of socio-emotional outcomes from the intervention...” Maybe mentioning in what way the socio-emotional outcome was affected (what was measured) would be helpful.

*Response to reviewer:*

Changes have been made on now line 156-160 to better clarify the real meaning of the sentence to: “Two meta-analysis that described data from lower and middle-income countries showed limited influence of undernutrition on a child’s attachment, emotionality, social competence and temperament [4, 6]. However, in a study among Bangladeshi children aged 6-24 months, it was reported that severely underweight children (weight-for-age z score, WAZ < -2 SD) were less sociable, less attentive, more fearful and had more negative emotional traits as compared to healthy, normo-nourished children [13]. “

*Reviewer's comment:*

Again on line 174, the authors mention that “in later life, these anthropometric deficits (what does this mean??) were translated into other effects such as overage schooling (not sure what this means) or ????? This is really unclear and it might be best to be clearer as to what the authors mean e.g. “In later life, studies we reviewed demonstrated that low height for age z scores correlated highly with children completing less years of school or not progressing to higher years...” Or something along those lines.

*Response to reviewer:*

Changes have been made on now line 167-171 to better clarify the real meaning of the sentence to: “ Low HAZ and WAZ correlated strongly with children needing a longer time to complete schooling or less schooling [14], and in later life with lower-income and living in less conducive environment such as having first child at a younger age and a higher number of pregnancies [15].  
”

*Reviewer's comment:*

Line 199 - "The possibility of rescue time period beyond 2 years of life could be due to the late period of cortex development and the ongoing synaptogenesis...." Could the authors make clear what they mean here – again it is just not clear whether the late period of cortex development and ongoing synaptogenesis that they mean is beyond 2 years or not beyond 2 years?

*Response to reviewer:*

Changes have been made on now line 183-184 to better clarify the real meaning of the sentence to: "Based on the above, it seems likely that the period in which neurocognitive deficits can be rescued by appropriate interventions extends well beyond the age of 2 years. This longer rescue period coincides with prefrontal cortex development until 8 years of age and on-going synaptogenesis at that age [3]"

*Reviewer's comment:*

Lines 202 – 215 are much easier to read and have much more of a clear explanation and definition within them.

*Response to reviewer:*

Noted. No changes are made.

*Reviewer's comment:*

Line 232 – "that these studies were different in types of intervention (oral food supplement high in...". These statements here are very general and unclear to the reader. Could they be made much more specific so they are clearer to the reader?

*Response to reviewer:*

We have deleted the confusing statement.

*Reviewer's comment:*

Line 246; "It seems that either nutrition or parent-based responsive learning intervention affect neurodevelopment and cognition". The authors here make this general statement but for the reader, there is no clarity as to what the authors mean and in what way. This is all really important as these articles are very different and are looking at interventions that improve responsiveness is very different than those which affect nutrition. This is not very clear from the statements.

*Response to reviewer:*

Changes have been made on now line 220-223 to better clarify the real meaning of the sentence to:



“Recent systematic review cum meta-analysis which assessed the impact of nutrition with or without stimulation reported parent-based responsive learning intervention, more than nutrition supplementation, appears to have better influence on neurodevelopment and cognition of children 0-60 months of age (5)”

*Reviewer’s comment:*

Grammar:

Throughout there are a lot of issues with the grammar – I have picked up on some but there are many more and the team would need to go through these with a native English speaker and review. Plurals seem to be a particular issue e.g. “meta-analyses” rather than “meta-analysis” and ensuring that “s” is put on the end of words. It is therefore quite confusing to read in places. “focus on cognitive neurodevelopment aspects” – maybe should read “with a focus on the cognitive and neurodevelopmental outcomes...”

*Response to reviewer:*

We have tried to improve the language accuracy and grammar in the revision.

*Reviewer’s comment:*

Line 66 “It is also reported that stunting and overweight coexisting..” maybe reads better as; “stunting and overweight coexists..”

*Response to reviewer:*

We have deleted the statement to avoid confusing.

*Reviewer’s comment:*

Line 76 – “neurodevelopment incapability”.. What does this mean? Use a different term.

*Response to reviewer:*

Change has been made on sentence on now-line 72 to:” neurodevelopmental deficits”

*Reviewer’s comment:*

Line 85 – “specific interventions” not “specific intervention”

*Response to reviewer:*

Change has been made on sentence on now line 80 to: ”specific interventions”

*Reviewer’s comment:*

Line 140 “include” rather than “includes”

*Response to reviewer:*

No changes is made on sentence on now line 132 as we consider it is grammatically correct.

*Reviewer's comment:*

Interesting that two of the authors are from Friesland Campina – a milk company. This is written in the funding section but is important to acknowledge as a conflict of interest possibly.

*Response to reviewer:*

We have amended the information on conflicting interest as follows: "Verena Tan was an employee of FrieslandCampina at the time of the manuscript's development. Leilani Muhandi and Jan Geurts are employees of FrieslandCampina at the time of the manuscript's development, submission and revision."

*Reviewer's comment:*

The team also acknowledge "ContentEd Singapore" however it is unclear how they were involved and what they did. If they are a company who specialise in medical writing and editing, they need some support with grammar in their writing.

*Response to reviewer:*

The acknowledgement has been revised to specify the involvement of Content Ed as follows: "FrieslandCampina supported retrieval of relevant publications and the development of the 1st manuscript draft by Content Ed Singapore"

Reviewer: 2

*Comments to the Author*

This obviously is an important topic. I think the manuscript would benefit from greater clarity in a number of areas.

*Reviewer's comment:*

1) First, what is the really new question that the authors are trying to address in this review? Is it the critical window in which nutritional correction can address developmental deficits? Or the combination of stunting and overweight and the impact of this? At present, the message gets a little lost and the story is not clear.

*Response to reviewer:*

Previously line 68-70 has been deleted to keep the focus on co-existing of under- and overnutrition in the same population. Further elaboration on research questions has been added on now line 91-95.

*Reviewer's comment:*

2) Secondly, I think that (even though the journal is nutrition research reviews) the manuscript would benefit from definitions. For the purposes of this, what is meant by undernutrition, norm-nutrition and overnutrition? Is the last of these even appropriate? Don't many overweight / obese children suffer from malnutrition rather than over nutrition - e.g. poor balance or quality of nutrients?

*Response to reviewer:*

Definition of under- and overnutrition has been added in the objective of the review on now line 85-89. The term normo-nutrition has been clearly defined on line 84.

*Reviewer's comment:*

3) The term normonutrition confused me, particularly as many of these studies were from low-income countries. Were the children really 'normonourished' - whatever this means?

*Response to reviewer:*

The term normo-nutrition has been clearly define on line 84.

*Reviewer's comment:*

4) The PICO statement is confusing. Is it really needed to be formulated in this way? What is an observational intervention? Does this mean that the study was simply an observational cohort - in which case no intervention? Observational intervention seems to me a contradictory phrase.

*Response to reviewer:*

We agree with the suggestions. The information on PICO has been removed.

*Reviewer's comment:*

5) on page 3, it starts that stunting and overweight coexist in 'same individual in 10 out of 111 countries.' I don't understand what this is trying to say. Obviously, stunting and overweight coexist in some children in many more than 10 countries...? Could this please be clarified.

*Response to reviewer:*

We agree with the suggestion. The statement " stunting and overweight coexist in 'same individual in 10 out of 111 countries..." has been removed from the text.

*Reviewer's comment:*

6) For me, the most interesting aspect is the critical window for addressing the impact of malnutrition. I thought this could be developed further and more clearly. Generally, the story and key message throughout does not come across as clearly as it could do.

*Response to reviewer:*

We agree with the suggestion. Changes have been made on now line 183-184 to better clarify the real meaning of the sentence to: "This opens the possibility of a rescue time period for neurodevelopmental and cognition beyond 2 years of life which coincides with pre-frontal cortex development until 8 years of age and on-going synaptogenesis at that age (3)."

*Reviewer's comment:*

7) the tables are not clear. More clarity around what the observational cohort was and what the interventions were would be helpful. For example, trying to understand the cohorts is challenging - observational study of healthy Ethiopian newborns with norm-nutrition...? Or of 2, 853 Bangladeshi singleton babies? Were these all of normal birthweight (defined how?) and what was the definition of norm-nutrition for them? It is difficult to interpret the meaning of the studies without greater clarity.

*Response to reviewer:*

Consistent terminology and detailed information have been added in the tables to improve clarity for better interpretation of the studies.

<b>3</b>	<b>Second revision (ID NRR-20 0.32.R2)</b> was submitted to Journal	<b>18 Sept 2020</b>
	Decision: Acceptable in principle (due date 09-Mar-2021)	

## Cover Letter: NRR-20-032.R2



Kuala Lumpur, September 18, 2020

To:  
Prof. Christine Edwards  
Editor in Chief  
Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review"

Thank you for in-principle acceptance of our manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review" in Nutrition Research Reviews. We really appreciate the inputs given by the two reviewers. We have revised the manuscript to the best of our capabilities to follow the suggestions of the reviewers as per below explanation.

We hope that the revised manuscript is satisfactory and that it can be published soon. We look forward to having your favourable response.

Yours sincerely,

Close

- Acceptable as received (31-May-2021)
- In Production

Contact Journal

032.R5 neurodevelopmental and cognitive consequences: A Scoping review

Submitting Author: Muhardi, Leilani

[Cover Letter](#)

EA: Sage, Alison    NRR-20-032.R4    Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review    31-Mar-2021    31-Mar-2021

- Acceptable in principle (12-May-2021)
- a revision has been submitted

Contact Journal

[View Submission](#)

Submitting Author: Muhardi, Leilani

[Cover Letter](#)

EA: Sage, Alison    NRR-20-032.R3    Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review    18-Dec-2020    18-Dec-2020



# NUTRITION RESEARCH REVIEWS



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## **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review**

Journal:	<i>Nutrition Research Reviews</i>
Manuscript ID	NRR-20-032.R2
Manuscript Type:	Review
Date Submitted by the Author:	18-Sep-2020
Complete List of Authors:	Suryawan, Ahmad; Airlangga University, Department of Child Health JALALUDIN, MUHAMMAD ; University of Malaya, Department of Pediatrics Koon, Poh ; Universiti Kebangsaan Malaysia, Department: Nutritional Sciences Programme, Centre for Community Health Studies (ReaCH), Faculty of Health Sciences Sanusi, Rasaki; University of Ibadan, College of Medicine TAN, MING HUI ; Singapore Institute of Technology, Dietetics and Nutrition Programme, Health and Social Sciences cluster Geurts, Jan; Koninklijke FrieslandCampina NV Innovation Centre Wageningen Muhardi, Leilani; FrieslandCampina AMEA, Medical Affairs
Keywords:	underweight, stunting, obesity, cognition, neurodevelopment

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Manuscripts

1 **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A**

2 ***Scoping review***

3

4 *Running title: Malnutrition and cognitive neurodevelopmental consequences*

5

6 Suryawan A<sup>1</sup>, Jalaludin MY<sup>2</sup>, B.K. Poh<sup>3</sup>, Rasaki Sanusi<sup>4</sup>, V.M.H. Tan<sup>5</sup>, J. Geurts<sup>6</sup>, Muhandi L<sup>7</sup>.

7

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30

31 249 Words Abstract, 3539 words in Main Text (excluding tables, figures and references), 4 Tables, 2

32 Figures, 41 References

33



## 34 Abstract

35 The negative impact of severe underweight and stunting, on cognitive neurodevelopment of  
36 children is documented and well-reported; however, the effect of overweight/obesity, is still unclear.  
37 Stunting and overweight affected 189 million children worldwide as reported in the Global Nutrition  
38 Report in 2018.

39 This *scoping* review aims to document the impact of mild/moderate and severe underweight,  
40 stunting, and overweight/obesity in children aged 0-60 months on neurodevelopmental and cognitive  
41 aspects across life stages. *Twenty-six articles were content-analyzed for qualitative synthesis from*  
42 *retrieved literature from PubMed and Cochrane databases published from 01 January 2009 to 31*  
43 *October 2019.*

44 *Growth in length and cognitive neurodevelopment in normo-nourished and stunted children*  
45 *under 24 months are found to be associated. Among stunted children, cognitive and neurodevelopmental*  
46 *deficits could still be potentially rescued if they can recover before 8 years of age. The rescue period*  
47 *coincides with on-going prefrontal cortex development and synaptogenesis. The impact of*  
48 *overweight/obesity on cognitive neurodevelopment appears to be limited and are related to attention,*  
49 *gross motor skills and executive control. Parental education level, birth weight/length, breastfeeding*  
50 *duration, sanitation level are some identifiable factors that modify the impact of under- and*  
51 *overnutrition on cognitive and neurodevelopment.*

52 *In conclusion, as underweight, stunting and overweight/obesity have impact on cognitive*  
53 *neurodevelopment, intervention programs should involve multidisciplinary teams. Programs should aim*  
54 *to supply adequate intakes for catch-up growth before the age of 8 years for those who are underweight*  
55 *or stunted, provide adequate socio-economic stimulation, and reduce childhood obesity, as measures to*  
56 *improve cognition and neurodevelopment.*

57 **Keywords:** children, underweight, stunting, overweight, obesity, malnutrition, undernutrition,  
58 overnutrition, cognition, neurodevelopment

59

## 60 INTRODUCTION

61 Malnutrition (wasting or low weight-for-height, stunting or low height-for-age, and underweight  
62 or low weight-for-age), micronutrient deficiencies and overweight/obesity are public health problems  
63 among children aged less than 60 months. However, while the number of stunted children worldwide  
64 has decreased recently, the number of overweight children has increased with the total number of  
65 affected children around 189 million [1].

66 Malnutrition leads to economic, social, and health issues for families, for the community and at  
67 national levels [2]. More importantly, *severe undernutrition in this case defined as severe stunting and*  
68 *underweight* impairs children's development in the short (delayed cognitive, behavioural and motor  
69 development), medium (lower IQ and school / academic achievement) and long term (human capital),  
70 mostly in low and middle-income countries [3-6]. It is still currently unclear whether overnutrition  
71 impacts neurodevelopment and cognition or *neurodevelopmental deficit* influences overnutrition or both.

72 Despite the reduction in stunting over the last decade [1], there still exist a need to understand if  
73 there are opportunities to mitigate the negative, long term impact of stunting on human capital  
74 interventions. It is also currently unclear if these interventions could be targeted at specific aspects of  
75 neurodevelopment and cognition, taking into consideration the timing of malnutrition with the timing of  
76 cognitive neurodevelopment in early childhood. More information is also needed to understand the  
77 aspects of neurodevelopment and cognition that are affected in overweight/obese children to design  
78 *specific interventions*.

79 This *scoping* review was therefore designed to extract from published literature on the impact of  
80 undernutrition (stunting defined as height for age z score (HAZ) <-2), underweight defined as weight  
81 for age z score (WAZ) <-2) and overnutrition (defined as overweight and obesity) in children aged 0-60  
82 months as compared to normo-nourished children (defined as not stunted, not wasted, not underweight,  
83 nor overweight/obese) on cognitive neurodevelopmental aspects (cognition, behavioural, motor and  
84 emotional development) in early, mid and later life.

85

## 86 **METHODS**

87 This review followed *the consistent approach of a scoping review* to compile findings from  
88 studies with different designs and methodologies to answer the stated critical research questions [7].  
89 These were the research questions formulated: (1) which developmental consequences are affected by  
90 over- and undernutrition during the first 60 months of life? (2) What other factors can modify these  
91 outcomes? (3) Which factors can mitigate the impact of over- and undernutrition on neurodevelopment  
92 and cognition? (4) is the effect on cognitive neurodevelopmental partly or fully reversible? and (5) what  
93 are the implications for intervention strategies?

94 Literature published from 01 January 2009 to 31 October 2019 in PubMed and Cochrane  
95 databases were retrieved using formulated search terms. The title and abstract of each article retrieved  
96 were screened based on inclusion criteria by all authors. A simple grading of controlling study biases  
97 using *JADAD* criteria for randomized controlled (RCT) studies, Newcastle Ottawa scale for cohort  
98 studies, and National Heart, Lung and Blood Institute (NHLBI) criteria for observational cross-sectional  
99 studies were then conducted by five authors (AS, MYJ, PBK, LM and JG) to select studies for further  
100 qualitative analyses (Table 1 and 2). References of relevant narrative reviews (cross-references) were  
101 also examined to search for further studies that met the inclusion criteria. JG and LM independently then  
102 extracted data from the identified full-text articles. Data extraction tables incorporated important  
103 information from eligible full-texts to allow the extraction of significant information for qualitative  
104 synthesis.

## 105 **RESULTS AND DISCUSSION**

### 106 *Descriptive summary of included studies*

107 From the 91 articles originally identified through the search strategy, 26 full-text articles were  
108 selected after a review of cross-references in eligible narrative reviews. Full text was used for  
109 information extraction and grading for quality assessment ([Figure 1](#)).

110 Information was categorized based on the type of study and nutritional status of the children  
111 (Table 1 and Table 2) as well as by factors influencing the impact of nutritional status on cognitive

112 neurodevelopment (Table 3). Information was extracted from 14 observational studies (undernutrition  
113 (n=8 articles); normo-nutrition (n=5 articles) and overnutrition (n=1 article); 4 intervention trials  
114 (undernutrition (n=2 articles) and normo-nutrition (n=2 articles)); 4 systematic reviews (undernutrition  
115 (n=1 article); normo-nutrition (n=2 articles) and overnutrition (n=2 articles)) and 4 meta-analysis (all on  
116 undernutrition). All publications on under- and normo-nourished children were conducted in low- to  
117 middle-income countries, while all articles about over-nourished children reported data from high-  
118 income countries. No intervention study was retrieved on overweight/obese children. About 85% (n=22)  
119 of the retrieved literature had good quality in controlling bias.

120 To the best of our knowledge, this review complements previous meta-analyses and systematic  
121 reviews [4-6] and includes a wider spectrum of sub-optimal nutritional status (mild/moderate to severe  
122 underweight and stunting; and overweight/obesity as markers of overnutrition) during the first 60 months  
123 of life on various neurodevelopment aspects (cognition, motor development, temperament, socio-  
124 economic status, academic achievement) that manifest from infancy, school age to adulthood (Figure 2).  
125 This review also *covers* observational longitudinal cohorts and interventional studies with nutrition- and  
126 non-nutrition related interventions on the outcomes of interest.

127

### 128 ***The importance of monitoring weight, length and head circumference during the first 24 months of*** 129 ***age***

130 From the reviewed studies, length-for-age z-scores (LAZ) and height-for-age z-scores (HAZ)  
131 (anthropometric measures of stunting in children) are associated with various elements of cognitive  
132 functioning, such as attention span, time taken to properly walk, mathematics and language abilities in  
133 early life; income and choice of partners/age of marriage in later life (Table 1). It was reported that  
134 healthy infants in the highest quartile of neonatal weight, length, and head circumference gain during  
135 the first 4 weeks of life had a higher IQ score at 6 years of age when compared to those in the lowest  
136 quartile [8].

137            *From a longitudinal study in the Philippines, all HAZ categories at 6 months (defined as*  
138 *mild/moderate/severe stunting ( $-2 \leq \text{HAZ} < -1.01$ ), at risk for stunting ( $-1 \leq \text{HAZ} < 0$ ) or normal height*  
139 *( $\text{HAZ} \geq 0$ )) were positively associated with cognitive function at 11 years of age. In addition, changes in*  
140 *HAZ from 6 to 24 months and changes in HAZ from 24 months to 11 years were also positively*  
141 *associated with cognitive ability at 11 years in the same study [9]. This is similar to the results among*  
142 *Bangladeshi children which reported cognitive impairment associated with poverty, birth condition and*  
143 *post-natal growth which started at 7 months of age and worsen up to 64 months when it became more*  
144 *significant [10]. While it was reported that stunting in the second year of life is more harmful than*  
145 *stunting before 12 months of age [11], HAZ at 4-6 years of age among healthy Malaysian children was*  
146 *reported to be significantly related to their cognitive functions [12].*

147            *Evidence for the impact of underweight and stunting on social skills development is largely*  
148 *variable across the identified studies. Two meta-analysis that described data from lower and middle-*  
149 *income countries showed limited influence of undernutrition on a child's attachment, emotionality,*  
150 *social competence and temperament [4, 6]. However, in a study among Bangladeshi children aged 6-*  
151 *24 months, it was reported that severely underweight children (weight-for-age z-score,  $\text{WAZ} < -2$ ) were*  
152 *less sociable, less attentive, more fearful and had more negative emotional traits as compared to normo-*  
153 *nourished children [13]. There is evidence therefore, that underweight and stunting have an impact on*  
154 *social skills development. Low HAZ and WAZ correlated strongly with children having less schooling*  
155 *or needing a longer time to complete schooling [14], and in later life, with lower-income and living in*  
156 *less conducive environment, such as having higher number of pregnancies and having the first child at*  
157 *a younger age [15].*

158

159 ***Improvements in linear growth and potential window of opportunity to rescue neurodevelopment and***  
160 ***cognitive abilities***

161            This review further strengthens the importance of the first 1000 days of life as a window of  
162 opportunity for rescuing neurocognitive deficits. It was reported that HAZ velocity between 6 and 24

163 months among under-nourished children is positively associated with cognitive function [9] and that  
164 every 1-unit increase in HAZ below the age of 24 months is associated with a higher increment in motor,  
165 communication and cognitive ability scores at 26 to 80 months of age as compared to a 1 unit increase  
166 in HAZ after 24 months of age [4, 14].

167 Data from the Young Lives cohort in Ethiopia, India, Peru, Cambodia, and Vietnam, indicated  
168 that children who were in the recovered group (stunted at 12 months of age but not stunted at 8 years of  
169 age) had better academic achievement (mathematics scores, receptive vocabulary scores, and reading  
170 comprehension scores) compared to those who stayed persistently stunted [14]. However, their academic  
171 achievement was still lower than those who had never been stunted. This finding is consistent with the  
172 finding from a cohort in Malawi which reported that those who had recovered from stunting had better  
173 academic achievements at 11 years of age as compared to those who were persistently stunted from age  
174 4 to 8 years [16]. Based on the above, it seems likely that the period in which neurocognitive deficits  
175 can be rescued by appropriate interventions if the child recovered from stunting well beyond 2 years of  
176 age up until 8 years of age, *which is in line with prefrontal cortex development and on-going*  
177 *synaptogenesis at that age* [3]. *Interestingly, Casale and colleagues (2014) reported that children who*  
178 *were stunted at 24 months of age and experienced catch-up growth, often did worse on cognitive tests*  
179 *at 4-5 years of age than children who were never stunted, and almost as poorly as children who had*  
180 *remained stunted* [17]. This appears to contradict previously stated findings from the Young Lives and  
181 Malawi cohorts. It is important to note, however, that the exact definition of ‘catch-up’ plays a critical  
182 role in this observation. Recently, five definitions was formulated for “catch-up growth”, ranging from  
183 lenient to strict (I: increase in HAZ, II: recovery from stunting (HAZ at 5 years  $>-2$ ), III: increase in  
184 height-for-age difference, IV: recovery from stunting and increase in height-for-age difference, and V:  
185 recovery from stunting with stricter cut-off point where HAZ falls within ‘normal’ range (HAZ at 5  
186 years  $>-1$ ) [18] . The reported observation above is based on definitions I-IV of ‘catch-up’. Thus, the  
187 term ‘catch-up’ should be carefully defined when determining the optimal goal for catch-up growth in  
188 order to rescue neurodevelopment, and consequently, cognitive ability in later life.

189 ***The importance of interventions in improving cognitive outcomes among undernourished children***

190 Seven publications assessed the effectiveness of intervention studies in improving cognitive  
191 outcomes among undernourished children. The publications covered 3 randomized controlled trials, 2  
192 systematic reviews and 2 meta-analyses. The overall quality of these studies was judged as good when  
193 considering the risk for bias (Table 2).

194 Stunted children with high levels of plasma homocysteine and those who were younger than 24  
195 months at the end of the follow-up period showed the biggest improvement in gross motor function and  
196 problem-solving functioning skills after being supplemented with vitamin B12 on a daily basis [19]. In  
197 contrast, the effect of the vitamin/nutrition intervention on rescuing or maintaining normal  
198 neurodevelopment and cognitive deficits in normo-nourished children remained inconclusive [5, 19, 20].  
199 No benefits in growth or cognitive performance were reported among 422 healthy children aged 12 to  
200 24 months receiving daily multi-micronutrient supplements (iron and zinc) [20]. Interestingly, in an  
201 intervention trial in which multiple micronutrient supplementations (vitamin B12 and folic acid) were  
202 combined with and without responsive stimulation for around 20 months among 1486 mother-child pairs  
203 in Pakistan it was found that children exposed to the combination, regardless of their nutrition status,  
204 had significantly higher developmental scores (cognitive, language, and social-emotional scales) at 12  
205 months than the control group [21]. Another group of children who received responsive stimulation had  
206 significantly higher development scores on the cognitive, language, and motor scales at 12 and 24  
207 months of age, and on the social-emotional scale at 12 months of age, than control. In comparison, the  
208 treatment effect on cognition, language and motor development at 24 months were moderate-to-large  
209 for responsive simulation, and were low to moderate for combined group [21].

210 *A recent systematic review cum meta-analysis which assessed the impact of nutrition with or*  
211 *without stimulation interventions concluded that parent-led responsive learning, more than nutrition*  
212 *supplementation, appears to have better influence on the neurodevelopment of children aged 0-60*  
213 *months [5]. This systematic review, which was based on 75 retrieved studies from various databases,*  
214 *reported that the pooled effect of these supplementations is one fourth smaller than the pooled effect size*

215 *of responsive care and learning opportunities on cognitive, language, and motor scales.* The review also  
216 suggested that postnatal multiple nutrient supplementations can improve linear growth, and to a smaller  
217 extent cognitive development and socio-temperament; while interventions promoting responsive care  
218 and learning opportunities affects only cognitive development but not linear growth [5].

219  
220 ***The impact of overweight/obesity on neurodevelopment and cognition***

221 Only one cross-sectional study and two systematic reviews were retrieved that describe the  
222 impact of overweight/obesity on cognitive neurodevelopmental aspects [22-24] (Table 1). All studies  
223 seem to point towards a more limited impact of overweight/obesity on aspects of neurodevelopment and  
224 cognition in the studied affluent populations, in contrast with those describing the impact of  
225 undernutrition. All retrieved literature demonstrated that attention, executive control (inhibitory control,  
226 working memory, reward sensitivity, impulsivity) and gross motor skills are the most affected areas.

227 A study among overweight Italian children showed poorer gross motor skills in the overweight  
228 children than their normal-weight peers [22] while other systematic reviews reported poorer executive  
229 control, more difficulty with inhibition in overweight children compared to healthy weight children [23,  
230 24]. There is a suggestion of directionality in the association between obesity and executive function.  
231 Children with lower executive function are speculated to have lower self-regulation of energy/caloric  
232 intake and decreased participation in physical activity, which leads to or potentiates overweight or  
233 obesity. It was also reported that low executive function stimulates excess adiposity leading to  
234 exacerbating decrements in executive function in childhood [25]. On the other hand, various studies  
235 showed that obesity/early life adiposity reduces executive function via several biological mechanisms.  
236 Pro-inflammatory cytokines produced by the adipose tissue can stimulate inflammatory pathways in all  
237 age categories leading to cognitive development deficits and dysregulation of appetite-regulating  
238 hormones could further harm cognitive skills [24]. *The limited affected cognitive neurodevelopmental*  
239 *areas reported in these affluent populations may be more diverse and pronounced in less-affluent*  
240 *societies.* In conclusion, poor gross motor skills, which are correlated with less physical activity [23]



241 and reduced attention span [23, 24], should be taken into consideration when designing intervention  
242 programs for these overweight/obese children.

243

### 244 ***Factors influencing the impact of suboptimal growth on neurodevelopment and cognition***

245 From the literature, the influencing factors identified were further classified into maternal and  
246 paternal factors, child's characteristics and health conditions, as well as socio-economic factors (Table  
247 3). Several pregnancy-related maternal parameters, such as maternal weight gain and smoking, have  
248 been consistently reported to increase the impact of suboptimal growth on cognitive neurodevelopment  
249 in addition to infant's condition at birth, such as low birth weight and short length at birth; suggesting  
250 the importance of prenatal nutrition and maternal health for later life [10, 13, 17, 26, 27].

251 The influence of sex on suboptimal growth and cognitive neuro-development seems quite  
252 conflicting in the literature; normo-nourished and undernourished girls had slightly higher scores of  
253 intelligence [8], social maturity [17], and manageability [13] than boys of the same nutritional status  
254 while the opposite findings were reported in normo-nourished children [12].

255 Particularly among under-nourished children, it appears that parents with a low level of  
256 nutritional knowledge, those who perceived less responsibility in the parenting task, or those who were  
257 less restrictive towards access to unhealthy foods, had children who experienced suboptimal growth and  
258 suffered from impaired cognitive development [4, 12]. Diet quality was demonstrated to be a positive  
259 predictor of improved cognitive outcomes in these children [4, 12]. For instance, food fortified with  
260 calcium, iron, zinc, vitamins B2, and proteins was associated with improved cognitive outcomes because  
261 of the probable role of these nutrients in early brain development [5, 21]. By contrast, a lack of dietary  
262 protein may delay or inhibit brain and cognitive development [4, 28]. On that note, recent evidence  
263 proposed supplementation of animal protein, in particular milk, as an essential component in a child's  
264 diet in order to prevent undernutrition and improve cognition [29-31].

265 The influence of the Home Observation for Measurement of the Environment (HOME)  
266 parameter as a proxy indicator for socio-economic factors, was reported in several studies among

267 undernourished children to be correlated with the impact of undernutrition and overweight/obesity on  
268 neurodevelopment and cognition [4, 8, 21, 26, 27, 32, 33]. This parameter was developed to measure  
269 responsiveness and stimulation of the home environment, which consists of several questions including  
270 questions about home ownership and the possession of books and toys. Among overweight children,  
271 socioeconomic status was the only influencing factor reported in the papers in this review. Those in  
272 lower socio-economic situations had lower motor skills than their counterparts with higher  
273 socioeconomic status [22] .

274 This review has several limitations. First, chronic illnesses and hospital malnutrition were  
275 excluded although they could have a similar impact on overall developmental aspects. A second  
276 limitation is that the statistical significance of pooled effects of all studies combined was not calculated  
277 as this review is a scoping one and not systematic. Furthermore, the search strategy may have missed  
278 some relevant papers due to limited peer-reviewed research published only in the past decade. To  
279 overcome this, reviewing reports outside the peer-reviewed literature (ie. grey literature) should be done  
280 in the future.

281 One of the strengths of this scoping review is that it expeditiously provides comprehensive and  
282 updated scientific evidence for healthcare professionals and policymakers. This synthesized evidence  
283 will hopefully allow key stakeholders to plan and execute necessary intervention programs for  
284 preventing and managing suboptimal growth with a focus on achieving optimal cognitive potential in  
285 young children. In addition, this scoping review was conducted using specific methodological  
286 approaches that would allow more accuracy in literature screening and less bias. A cross-referencing of  
287 eligible studies from retrieved narrative reviews allowed further completeness of the evidence and  
288 enabled the retrieval of information of not only the populations that experience undernutrition and  
289 overweight/obesity but also in the normal population which identified children with faltering growth. It  
290 also enabled the retrieval of studies from various geographical areas (low- to high-income studies) as  
291 well as studies on various developmental deficits. *Hitherto emphasis has been placed on the impact of*  
292 *malnutrition in children on morbidity and mortality, this review points to the quality of life that may be*

293 *affected by sub-optimal malnutrition on neurodevelopment and cognition. From public health*  
294 *perspectives, prevention of childhood malnutrition must be addressed not only by economic*  
295 *empowerment, but also through health promotion and education, as well as policy.*

296 ***Consideration for future research and actions:***

297 1) More studies should be conducted on the impact of nutritional/behavioural interventions in  
298 overweight/obese children on neurodevelopment and cognition especially in low-income countries as  
299 all the currently retrieved literature were from high-income countries. Overweight/obesity in childhood  
300 is on the rise and can co-exist with undernutrition within the same population, for example as seen in  
301 India and Indonesia. Around 46.6 and 36.6 million children under the age of five are stunted and more  
302 than 1 million children in the same age group are overweight in India and Indonesia respectively. This  
303 amounts to almost a total of 85 million Indian and Indonesian children who are at risk of sub-optimal  
304 neurodevelopment and cognitive function [2]. An increase in childhood obesity prevalence may have  
305 adverse long-term consequences on human capital in these countries, in addition to the negative  
306 consequences of under-nutrition.

307 2) Intervention studies for both undernutrition and overweight/obesity must assess the association  
308 between these nutritional status and cognitive neurodevelopment as most interventions usually focus  
309 only on providing nutrients related to brain development and not for optimal growth and vice-versa as  
310 also suggested by Prado et al [5]. For example, several studies and systematic reviews, recently  
311 published, assessed the impact of animal-based food supplementation or milk interventions on growth  
312 among stunted children or on only cognitive neurodevelopment but not on both aspects simultaneously  
313 [29, 30].

314 3) Any program or intervention for growth monitoring in community or hospital settings should engage  
315 nutritionists, general practitioners, paediatricians, and behavioural specialists in a collaborative  
316 multidisciplinary team. They have the dual-responsibility to consider both ends of the malnutrition  
317 spectrum when planning and implementing intervention programs [34]. Actions should be taken to

318 tackle both undernutrition and overweight/obesity concurrently – not just either one, to ensure successful  
319 and comprehensive outcomes in terms of childhood growth and cognitive neurodevelopment.

320

## 321 **CONCLUSION**

322 Both under- and overnutrition during the first 60 months of post-natal life affect the  
323 developmental trajectories of children in later life. Weight and length/height need to be monitored even  
324 beyond 24 months of life to enable early recognition of growth retardation/deviations and to allow  
325 appropriate and timely interventions to address the negative neurodevelopmental and cognitive impacts.  
326 Given the Global Nutrition Targets for 2025 [35], intervention programs involving a multidisciplinary  
327 team should aim to include reduction of childhood obesity and adequate socio-economic stimulations as  
328 well as nutrition supplementation for catch-up growth among under-nourished children. Nutrition and  
329 interventions can potentially rescue neurocognitive development up to the age of 8 years particularly in  
330 those recovering from stunting. These specific, targeted and simultaneous interventions may be key to  
331 safeguard future human capital especially in countries with high prevalence of stunting,  
332 overweight/obesity or both.

333

334

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345

346 **Authors' contribution**

347 All authors were involved in setting the concept, objective and selection criteria for the review. All  
348 authors were also involved in the selection of eligible articles based on titles and abstract. A simple  
349 grading of controlling study biases were then conducted by five authors (AS, MYJ, PBK, LM and JG).  
350 Afterwards, LM and JG selected the eligible articles based on full texts. All authors provided agreement  
351 on the final included articles. All authors participated in data extraction, synthesis and interpretation. All  
352 authors provided inputs and agreed on the final version of the manuscript.

353

354 **Competing interests**

355 Verena Tan was an employee of FrieslandCampina at the time of the manuscript's development. Leilani  
356 Muhardi and Jan Geurts are employees of FrieslandCampina at the time of the manuscript's  
357 development, submission and revision.

358

359 **Consent for publication**

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361

362 **Ethics approval and consent to participate**

363 Not applicable.

364

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For Peer Review





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Wed, Dec 2, 2020 at 11:04 AM

To: ahmad suryawan &lt;suryawan.ahmad@gmail.com&gt;, Verena Tan Ming Hui &lt;Verena.Tan@singaporetech.edu.sg&gt;, "Geurts, J.M.W. (Jan)" &lt;Jan.Geurts@frieslandcampina.com&gt;, Rasaki Sanusi &lt;sanusiadegoke2003@gmail.com&gt;, Universiti Kebangsaan Malaysia &lt;pbkoon@ukm.edu.my&gt;

Cc: yazidj &lt;yazidj@ummc.edu.my&gt;, "Kudla, U. (Urszula)" &lt;Urszula.Kudla@frieslandcampina.com&gt;

Dear Authors,

I am happy to share the decision from the journal as per below information from Prof. Yazid.

As such, would it be possible to propose below timeline:

- Leilani to provide revision and share to all authors – Dec 5
- Authors to review the revision and provide feedback – Dec 8
- Manuscript sent for language editing- Dec 9
- Ready to submit manuscript- Dec 12

Apology for the rush as I am planning to take some leave starting from Dec 15.

Thank you in advance for all your support and looking forward to hear from you all soon.

Kind regards,

Leilani

ACTION	STATUS	ID	TITLE	SUBMITTED	DECISIONED
<a href="#">create a revision</a>	EA: <a href="#">Sage, Alison</a>	NRR-20-032.R2	Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review	18-Sep-2020	01-Dec-2020
	<ul style="list-style-type: none"> <li>Acceptable in principle (01-Dec-2020)</li> <li>Due on: 31-Jan-2021</li> </ul>		<a href="#">View Submission</a>		
	<a href="#">view decision letter</a>				

**From:** Muhammad Yazid Jalaludin <[yazidj@ummc.edu.my](mailto:yazidj@ummc.edu.my)>  
**Sent:** Tuesday, December 1, 2020 11:30 PM  
**To:** Muhardi, L.M. (Leilani) <[leilani.muhardi@frieslandcampina.com](mailto:leilani.muhardi@frieslandcampina.com)>  
**Subject:** Fwd: Nutrition Research Reviews NRR-20-032.R2

Need for a minor revision and English language editing.

Thanks

Sent from my iPhone

Begin forwarded message:

**From:** Nutrition Research Reviews <[onbehalfof@manuscriptcentral.com](mailto:onbehalfof@manuscriptcentral.com)>  
**Date:** 1 December 2020 at 23:18:16 MYT  
**To:** [yazidj@ummc.edu.my](mailto:yazidj@ummc.edu.my)  
**Subject:** Nutrition Research Reviews NRR-20-032.R2  
**Reply-To:** [nrr.edoffice@cambridge.org](mailto:nrr.edoffice@cambridge.org)

01-Dec-2020

**\*\*A copy of this decision email has also been sent to the reviewers\*\***  
**\*\*Please ensure that all co-authors are made aware of the content of this email\*\***

Dear Prof. JALALUDIN,

Your manuscript "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review" has been evaluated and, while considered positively by the reviewers, some minor revisions are needed before a final decision can be made. The comments of the reviewer(s) who looked at your manuscript are included at the foot of this letter (if applicable). Please take these into account when preparing a revised version of the manuscript. Use the following link to create a revision now:

\*\*\* PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. \*\*\*

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If English language editing has been requested in the below comments, we list a number of third-party services specialising in language editing and/or translation. Use of any of these services is voluntary, and at your own expense.

<https://www.cambridge.org/core/services/authors/language-services>

Sincerely,  
Dr. Christine Edwards  
Editor-in-Chief, Nutrition Research Reviews  
[christine.edwards@glasgow.ac.uk](mailto:christine.edwards@glasgow.ac.uk)

Editor  
Comments to the Author:  
(There are no comments.)

Reviewer: 1

Comments to the Author

The manuscript is much improved. There are still minor issues with English language.

The only significant concern is that the conclusions do not directly align with the results. In the abstract and overall conclusion, it states that 'intervention programs should involve multidisciplinary teams' - I don't see this evidence in the results section. The abstract also states that programs should 'provide adequate socio-economic stimulation' - apart from not knowing what this means, there also is not evidence presented in the paper to support this conclusion. Similarly, it states programmes should reduce childhood obesity as measures to improve cognition and neurodevelopment. Again, the evidence for reduction in childhood obesity improving outcomes is not presented. The fact that overweight and obesity are associated with worse outcomes does not mean that reducing overweight and obesity will reverse that - there may be numerous confounders.

The conclusion must reflect the findings of the research.

Abstract - the sentence beginning "The rescue period coincides with..." is not needed in the abstract and can be deleted.  
Introduction, first page, define severe stunting and overweight here. Define overweight and obesity at the bottom of page 3.

Reviewer: 2

Comments to the Author

This paper is much better and clearer than it was. There are still some grammatical issues that need to be addressed and a fluent English speaker or a copy-editor might want to check these.

I am still not sure that a review which has such a large scope is as meaningful as one which decided to take one issue or another – but the authors do say that both undernutrition and overnutrition are issues globally and both may have an impact on cognition... just seems that you lose the detail with doing both of these. As the authors say; "the negative impact of

severe underweight or stunting is documented and well reported" The research on obesity and information as to what is out there and what might help move the research forward may be the most interesting e.g. what are the confounders/issues that might need to be addressed to do better research? I think at this stage though, having gone through the review once, it would be up to the editors if they wanted to limit the scope. I feel that concentrating on obesity is much more novel.

The review feels better now described clearly as a "scoping review" and the definitions are much clearer. The language is a little better although there are still some issues.

Page 3 line 41 – is "qualitative synthesis" the right term? It may be – but makes me think of qualitative research findings being synthesised – although I think the authors may be right about the term.

Can "cognitive and neurodevelopmental deficits be rescued"? I wonder if "rescued" is the right term? In other places, they are described as "recovered".

The authors talk about "social" development in some places and "emotional" development in other places – so it might be useful to think through these definitions.

Lines 200; "Interestingly... - this sentence is quite long and difficult to read – could it be dealt with.

Line 210 – "systematic review cum meta-analysis" – not sure about the term "cum"

Some of the conclusions – due to the very general nature of the paper – are quite broad e.g. "intervention programs involving a multidisciplinary team should aim to include reduction of childhood obesity and adequate socio-economic stimulations as

well as nutrition supplementation for catch-up growth among under-nourished children"

There are some good points about future research particularly relating to obesity and ways to move forward with research in this area. The research focus for stunting and underweight has been addressed before but can be addressed again in this review if felt helpful and the focus on the use of a multidisciplinary team in point 3 is helpful – however I would be aware that many sites may not have paediatrician, nutritionist, behavioural specialist – so might need to think through how to make these recommendations more generic.

Again – I wonder if the review would benefit from being more targeted as I still worry that it is very generic and not sure how much it adds to the previous literature.

Otherwise, it is a clear review which outlines some of the issues.

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## RESPONSE TO REVIEWERS

Kuala Lumpur, December 12, 2020

To:

**Prof. Christine Edwards**

Editor in Chief

Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review"

Thank you for the acceptable-in-principle of our manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review" in Nutrition Research Reviews. We really appreciate the further inputs given by the reviewers and have revised the manuscript to the best of our capabilities as per below explanation. We also have submitted to third-party services specialising in language editing and/or translation for final language check.

We hope that the revised manuscript is satisfactory and that it can be published soon. We look forward to having your favourable response.

Yours sincerely,



**Prof Dr Muhammad Yazid Jalaludin**

Corresponding authors

Reviewer: 1

Comments to the Author:

The manuscript is much improved. There are still minor issues with English language. The only significant concern is that the conclusions do not directly align with the results. In the abstract and overall conclusion, it states that 'intervention programs should involve multidisciplinary teams' - I don't see this evidence in the results section.

Response to reviewers:

We have changed the statement on "involve multidisciplinary teams" in the abstract and conclusion to "multidimensional aspects" in order to better reflect the findings of the review. The manuscript has been sent to third party specializing in language editing.

The abstract also states that programs should 'provide adequate socio-economic stimulation' - apart from not knowing what this means, there also is not evidence presented in the paper to support this conclusion.

Response to reviewers:

We have changed the statement on "provide adequate socio-economic stimulation" in the abstract and conclusion into "improvement of socio-economic condition" as there are several evidences in the text, for example on line 140-143 as follows: "This is similar to the results among Bangladeshi children which reported cognitive impairment associated with poverty, birth condition ..." and on Table 3 – "Non-employment between pregnancy and the child's first 12 months of life" which could support the statement on the influence of socio-economic factors.

Similarly, it states programmes should reduce childhood obesity as measures to improve cognition and neurodevelopment. Again, the evidence for reduction in childhood obesity improving outcomes is not presented. The fact that overweight and obesity are associated with worse outcomes does not mean that reducing overweight and obesity will reverse that - there may be numerous confounders.

Response to reviewers:

We have changed the following statements to further clarify the intention.

- In the abstract into: "In conclusion, as underweight, stunting and overweight/obesity have impact on cognitive neurodevelopment, intervention programs should involve multidimensional aspects to supply adequate intakes for catch-up growth before the age of 8 years for those who are underweight or stunted, improve socio-economic condition, and to reduce childhood obesity"
- In the conclusion into: "Given the Global Nutrition Targets for 2025 [35], intervention programs involving a multidimensional aspects to include not only reduction of childhood undernutrition, but also obesity and to improve socio-economic conditions".

Abstract - the sentence beginning "The rescue period coincides with..." is not needed in the abstract and can be deleted.

Response to reviewer:

This statement has been deleted from the abstract.

Introduction, first page, define severe stunting and overweight here. Define overweight and obesity at the bottom of page 3.

Response to reviewer:

These definitions have been added on line 78 of page 3.

Reviewer: 2

Comments to the Author

This paper is much better and clearer than it was. There are still some grammatical issues that need to be addressed and a fluent English speaker or a copy-editor might want to check these.

Response to reviewer:

The manuscript has been sent to third party specializing in language editing.

I am still not sure that a review which has such a large scope is as meaningful as one which decided to take one issue or another – but the authors do say that both undernutrition and overnutrition are issues globally and both may have an impact on cognition... just seems that you lose the detail with doing both of these. As the authors say; “the negative impact of severe underweight or stunting is documented and well reported” The research on obesity and information as to what is out there and what might help move the research forward may be the most interesting e.g. what are the confounders/issues that might need to be addressed to do better research? I think at this stage though, having gone through the review once, it would be up to the editors if they wanted to limit the scope. I feel that concentrating on obesity is much more novel.

Response to reviewer:

Based on the retrieved literature, the number of research on the impact of underweight on cognitive development still continues to increase even in this last 10 years. Indeed, although the number of research on overweight/obesity and cognitive neurodevelopment seems quite limited, having both extreme conditions could provide more complete situation to the readers. Therefore, we still see the merit of discussing both conditions in one manuscript.

The review feels better now described clearly as a “scoping review” and the definitions are much clearer. The language is a little better although there are still some issues.

Response to reviewer:

The manuscript has been sent to third party specializing in language editing.

Page 3 line 41 – is “qualitative synthesis” the right term? It may be – but makes me think of qualitative research findings being synthesised – although I think the authors may be right about the term.

Response to reviewer:

The statement has been changed into : “Data extraction tables incorporated important information from eligible full-texts to allow the extraction of significant information for the review”.

Can “cognitive and neurodevelopmental deficits be rescued”? I wonder if “rescued” is the right term? In other places, they are described as “recovered”.

Response to reviewer:

The term ‘rescue’ in the manuscript has been changed into : “ recovered” whenever appropriate.

The authors talk about “social” development in some places and “emotional” development in other places – so it might be useful to think through these definitions.

Response to reviewer:

We have changed the term “social development ” into “ social skills development” in the text to further distinguish with “emotional development”. Specifically on line 143, we have changed the text into “Evidence for the impact of underweight and stunting on emotional skills development” as the following information focus more on the ability to express certain emotions of the affected children.

Lines 200; “Interestingly... - this sentence is quite long and difficult to read – could it be dealt with.

Response to reviewer:

We have split the statements which is now line 195 to make it more concise into : “This is in contrast with a multiple micronutrient supplementations (vitamin B12 and folic acid) intervention trial with and without responsive stimulation for around 20 months among 1486 mother-child pairs in Pakistan. In this study, children who were exposed to the combined intervention, regardless of their nutrition status, had significantly higher developmental scores (cognitive, language, and social-emotional scales) at 12 months than the control group [21]”.

Line 210 – “systematic review cum meta-analysis” – not sure about the term “cum”

Response to reviewer:

We have changed “cum” into “and” in now line 205.



Some of the conclusions – due to the very general nature of the paper – are quite broad e.g. “intervention programs involving a multidisciplinary team should aim to include reduction of childhood obesity and adequate socio-economic stimulations as well as nutrition supplementation for catch-up growth among under-nourished children”

There are some good points about future research particularly relating to obesity and ways to move forward with research in this area. The research focus for stunting and underweight has been addressed before but can be addressed again in this review if felt helpful and the focus on the use of a multidisciplinary team in point 3 is helpful – however I would be aware that many sites may not have paediatrician, nutritionist, behavioural specialist – so might need to think through how to make these recommendations more generic.

Response to reviewer:

We have changed the statement on “involve multidisciplinary teams” in the abstract and conclusion to “multidimensional aspects” in order to better reflect the findings of the review.

Again – I wonder if the review would benefit from being more targeted as I still worry that it is very generic and not sure how much it adds to the previous literature. Otherwise, it is a clear review which outlines some of the issues.

Response to reviewer:

Based on the retrieved literature, the number of research on the impact of underweight on cognitive development still continues to increase even in this last 10 years. Indeed, although the number of research on overweight/obesity and cognitive neurodevelopment seems quite limited, having both extreme conditions could provide more complete situation to the readers. Therefore, we still see the merit of discussing both conditions in one manuscript.

<b>4</b>	<b>Third revision (ID NRR-20 0.32.R3)</b> was submitted to Journal	<b>18 Dec 2020</b>
	Decision: Acceptable in principle (due date 12-May-2021)	

## Cover Letter: NRR-20-032.R3



Kuala Lumpur, December 18, 2020

To:  
 Prof. Christine Edwards  
 Editor in Chief  
 Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review"

Thank you for the acceptable-in-principle of our manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review" in Nutrition Research Reviews. We really appreciate the further inputs given by the reviewers and have revised the manuscript to the best of our capabilities as per below explanation. The revisions are written to italics for ease of reference.

We have submitted the manuscript to a third-party service that specialises in language editing for final language check with attached certificate. We hope that the revised manuscript is satisfactory and that it can be published soon. In addition, would it be possible to still opt for Open Access for this manuscript?

We look forward to having your favourable response.

Close

<ul style="list-style-type: none"> <li>● Acceptable as received (31-May-2021)</li> <li>● In Production</li> </ul> <p><input checked="" type="checkbox"/> <a href="#">Contact Journal</a></p>	<p>032.R5</p> <p>neurodevelopmental and cognitive consequences: A Scoping review</p> <p>Submitting Author: Muhardi, Leilani</p> <p><a href="#">Cover Letter</a></p>
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<p>EA: Sage, Alison</p> <ul style="list-style-type: none"> <li>● Acceptable in principle (12-May-2021)</li> <li>● a revision has been submitted</li> </ul> <p><input checked="" type="checkbox"/> <a href="#">Contact Journal</a></p>	<p>NRR-20-032.R4</p> <p>Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review</p> <p><a href="#">View Submission</a></p> <p>Submitting Author: Muhardi, Leilani</p> <p><a href="#">Cover Letter</a></p>	<p>31-Mar-2021</p> <p>31-Mar-2021</p>
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<p>EA: Sage, Alison</p>	<p>NRR-20-032.R3</p> <p>Malnutrition in early life and its neurodevelopmental and cognitive</p>	<p>18-Dec-2020</p> <p>18-Dec-</p>
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# NUTRITION RESEARCH REVIEWS



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## **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review**

Journal:	<i>Nutrition Research Reviews</i>
Manuscript ID	NRR-20-032.R3
Manuscript Type:	Review
Date Submitted by the Author:	18-Dec-2020
Complete List of Authors:	Suryawan, Ahmad; Airlangga University, Department of Child Health JALALUDIN, MUHAMMAD ; University of Malaya, Department of Pediatrics Sanusi, Rasaki; University of Ibadan, College of Medicine TAN, MING HUI ; Singapore Institute of Technology, Dietetics and Nutrition Programme, Health and Social Sciences cluster Muhardi, Leilani; FrieslandCampina AMEA, Medical Affairs Geurts, Jan; Koninklijke FrieslandCampina NV Innovation Centre Wageningen Koon, Poh ; Universiti Kebangsaan Malaysia, Department: Nutritional Sciences Programme, Centre for Community Health Studies, Faculty of Health Sciences
Keywords:	underweight, stunting, obesity, cognition, neurodevelopment

**SCHOLARONE™**  
Manuscripts

1 **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A**  
2 **scoping review**

3  
4 *Running title: Malnutrition and cognitive neurodevelopmental consequences*

5  
6 A. Suryawan A<sup>1</sup>, M.Y. Jalaludin<sup>2</sup>, B.K. Poh<sup>3</sup>, R. Sanusi<sup>4</sup>, V.M.H. Tan<sup>5</sup>, J.M.Geurts<sup>6</sup>, L. Muhardi<sup>7</sup>

7  
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14 4. Department of Human Nutrition & Dietetics, University of Ibadan, Nigeria.

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19  
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30  
31 241 words in the Abstract, 3596 words in the Main Text (excluding tables, figures and references), 4  
32 Tables, 2 Figures, 41 References

33

34 **Abstract**

35           The negative impact of stunting and severe underweight on the cognitive neurodevelopment of  
36 children is documented and well-reported; however, the effect of overweight/obesity is still unclear. The  
37 2018 Global Nutrition Report reported that stunting and overweight affect 189 million children  
38 worldwide.

39           This scoping review aims to document the impact of mild/moderate and severe underweight,  
40 stunting, and overweight/obesity on neurodevelopmental and cognitive aspects across life stages among  
41 children aged 0-60 months. *Twenty-six articles were analysed to allow the extraction of significant*  
42 *information from literature retrieved from PubMed and Cochrane databases published from 1 January*  
43 *2009 to 31 October 2019.*

44           Growth in length is associated with cognitive neurodevelopment in normo-nourished and stunted  
45 children aged under 24 months. It seems that among stunted children, cognitive and neurodevelopmental  
46 deficits can still potentially be recovered before 8 years of age, particularly in those whose nutrition  
47 status have improved. The impact of overweight/obesity on cognitive neurodevelopment appears to be  
48 limited and is mainly related to attention, gross motor skills and executive control. Parental education  
49 level, birth weight/length, breastfeeding duration, and sanitation level are some identifiable factors that  
50 modify the impact of under- and overnutrition on cognitive and neurodevelopment.

51           *In conclusion, as underweight, stunting and overweight/obesity have impacts on cognitive*  
52 *neurodevelopment, intervention programmes should involve a multidimensional approach that consists*  
53 *of supplying adequate intakes for catch-up growth before the age of 8 years for those who are*  
54 *underweight or stunted, improving socioeconomic conditions, and reducing childhood*  
55 *overweight/obesity.*

56

57 **Keywords (max 5):** underweight, stunting, obesity, cognition, neurodevelopment

58

## 59 INTRODUCTION

60 Malnutrition (wasting or low weight-for-height, stunting or low height-for-age, and underweight  
61 or low weight-for-age), micronutrient deficiencies and overweight/obesity are public health problems  
62 that can affect children aged less than 60 months. However, while the number of stunted children  
63 worldwide has decreased recently, the number of overweight children has increased, and the total  
64 number of affected children is approximately 189 million (1).

65 Malnutrition leads to economic, social, and health issues for families, at the community and  
66 national level (2). *More importantly, severe undernutrition in this case was defined as severe stunting*  
67 *(below HAZ (height-for-age Z score) minus three standard deviations ( $-3 SD$ ))(3) and severe*  
68 *underweight (below WAZ (weight-for-age Z score) minus three standard deviations ( $-3 SD$ ))(3) impair*  
69 *children's development in the short (delayed cognitive, behavioural and motor development), medium*  
70 *(lower IQ and school/academic achievement) and long term (human capital), mostly in low and middle-*  
71 *income countries (4-7). Still, it is currently unclear whether overnutrition impacts neurodevelopment*  
72 *and cognition or, vice versa, whether neurodevelopmental deficits impact overnutrition or both.*

73 Despite the reduction in stunting over the last decade (1), there still exists a need to better  
74 understand if there are opportunities to mitigate the negative, long-term impact of stunting on human  
75 capital development. It is also currently unclear whether interventions can be targeted at specific aspects  
76 of neurodevelopment and cognition, taking into consideration the timing of malnutrition with the timing  
77 of cognitive neurodevelopment in early childhood. More information is also needed to understand the  
78 aspects of neurodevelopment and cognition that are affected among overweight/obese children to design  
79 specific interventions.

80 *This scoping review was therefore designed to extract from the published literature, the impact*  
81 *of undernutrition (stunting defined as height for age z-score (HAZ)  $< -2$ ), underweight defined as weight*  
82 *for age z-score (WAZ)  $< -2$ ) and overnutrition (overweight defined as  $2 SD > WAZ < 3 SD$  and obesity*  
83 *as  $WAZ \geq 3 SD$ ) (3) in children aged 0-60 months compared to normo-nourished children (defined as*

84 *not stunted, wasted, underweight, or overweight/obese) on cognitive neurodevelopmental aspects*  
85 *(cognition, behavioural, motor and emotional development) in early, mid and later life.*

86

## 87 **METHODS**

88 This review followed the consistent approach of a scoping review to compile findings from  
89 studies with different designs and methodologies to answer the stated critical research questions (8). The  
90 research questions are as follows: (1) Which developmental consequences are affected by over- and  
91 undernutrition during the first 60 months of life? (2) What other factors can modify these outcomes? (3)  
92 Which factors can mitigate the impact of over- and undernutrition on neurodevelopment and cognition?  
93 (4) Is the effect on cognitive neurodevelopment partly or fully reversible? and (5) What are the  
94 implications for intervention strategies?

95 Literature published from 1 January 2009 to 31 October 2019 in the PubMed and Cochrane  
96 databases was retrieved using formulated search terms. The title and abstract of each article retrieved  
97 were screened based on the inclusion criteria by all authors. A simple grading of controlling study biases  
98 using *JADAD* criteria for randomized controlled (RCT) studies, Newcastle Ottawa Scale for cohort  
99 studies, and National Heart, Lung and Blood Institute (NHLBI) criteria for observational cross-sectional  
100 studies were then conducted by five authors (AS, MYJ, PBK, LM and JG) to select studies for further  
101 qualitative analyses (Tables 1 and 2). References of relevant narrative reviews (cross-references) were  
102 also examined to search for further studies that met the inclusion criteria. JG and LM then independently  
103 extracted data from the identified full-text articles. Data extraction tables incorporated important  
104 information from eligible full texts to allow the extraction of significant information for the review.

105



## 106 **RESULTS AND DISCUSSION**

### 107 *Descriptive summary of included studies*

108 From the 91 articles originally identified through the search strategy, 26 full-text articles were  
109 selected after a review of cross-references in eligible narrative reviews. The full text was used for  
110 information extraction and grading for quality assessment (Figure 1).

111 Information was categorised based on the type of study and nutritional status of the children  
112 (Table 1 and Table 2) as well as by factors influencing the impact of nutritional status on cognitive  
113 neurodevelopment (Table 3). Information was extracted from 14 observational studies (undernutrition  
114 (n=8 articles), normo-nutrition (n=5 articles) and overnutrition (n=1 article), 4 intervention trials  
115 (undernutrition (n=2 articles) and normo-nutrition (n=2 articles)), 4 systematic reviews (undernutrition  
116 (n=1 article), normo-nutrition (n=2 articles) and overnutrition (n=2 articles)) and 4 meta-analyses (all  
117 on undernutrition). All publications on under- and normo-nourished children were conducted in low- to  
118 middle-income countries, while all articles about over-nourished children reported data from high-  
119 income countries. No intervention study was retrieved on overweight/obese children. Approximately  
120 85% (n=22) of the retrieved literature had good quality in controlling bias.

121 To the best of our knowledge, this review complements previous meta-analyses and systematic  
122 reviews (5-7) and includes a wider spectrum of suboptimal nutritional status (ranging from  
123 mild/moderate to severe underweight and stunting to overweight/obesity as markers of overnutrition)  
124 during the first 60 months of life on various neurodevelopment aspects (cognition, motor development,  
125 temperament, socioeconomic status, and academic achievement) that manifest from infancy and school  
126 age to adulthood (Figure 2). This review also covers observational longitudinal cohorts and  
127 interventional studies with nutrition- and non-nutrition-related interventions on the outcomes of interest.

128

129

130

131 **The importance of monitoring weight, length and head circumference during the first 24 months**  
132 **of age**

133 From the reviewed studies, length-for-age z-scores (LAZ) and height-for-age z-scores (HAZ)  
134 (anthropometric measures of stunting in children) were associated with various elements of cognitive  
135 functioning, such as attention span, time to proper walking, mathematics and language abilities in early  
136 life, and income and choice of partner/age at marriage in later life (Table 1). It was reported that healthy  
137 infants in the highest quartile of neonatal weight-, length-, and head circumference-gain during the first  
138 4 weeks of life had higher IQ scores at 6 years of age than those in the lowest quartile (9).

139 From a longitudinal study in the Philippines, all HAZ categories at 6 months (defined as  
140 mild/moderate/severe stunting ( $-2 \leq \text{HAZ} < -1.01$ ), at risk for stunting ( $-1 \leq \text{HAZ} < 0$ ) or normal height  
141 ( $\text{HAZ} \geq 0$ )) were positively associated with cognitive function at 11 years of age. In addition, changes  
142 in HAZ from 6 to 24 months and changes in HAZ from 24 months to 11 years were also positively  
143 associated with cognitive ability at 11 years in the same study (10). These outcomes are similar to the  
144 results among children in Bangladesh. In this study, cognitive impairment was associated with poverty,  
145 birth condition and postnatal growth that started at 7 months of age and worsened up to 64 months when  
146 it became even more substantial (11). While one study reported that stunting in the second year of life  
147 is more harmful than stunting before 12 months of age (12), HAZ at 4-6 years of age among healthy  
148 Malaysian children was also reported to be significantly related to cognitive function (13).

149 *Evidence for the impact of underweight and stunting on the development of emotional skills is*  
150 *largely variable across the identified studies.* Two meta-analyses that described data from lower- and  
151 middle-income countries showed the limited influence of undernutrition on a child's attachment,  
152 emotionality, social competence and temperament (5, 7). However, in a study among Bangladeshi  
153 children aged 6-24 months, it was reported that severely underweight children (weight-for-age z-score,  
154  $\text{WAZ} < -2$ ) were less sociable, less attentive, more fearful and had more negative emotional traits than  
155 normo-nourished children (14). There is evidence, therefore, that underweight and stunting impact social  
156 skill development. Low HAZ and WAZ correlated strongly with children having less schooling or

157 needing a longer time to complete schooling (15), and in later life, with lower income and living in a  
158 less conducive environment, such as having a higher number of pregnancies and having the first child  
159 at a younger age (16).

160

161 ***Improvements in linear growth and potential window of opportunity for neurodevelopment and***  
162 ***cognitive abilities recovery***

163 This review further strengthens the importance of the first 1000 days of life as a window of  
164 opportunity for rescuing neurocognitive deficits. It was reported that HAZ velocity between 6 and 24  
165 months among undernourished children is positively associated with cognitive function (10) and that  
166 every 1-unit increase in HAZ below the age of 24 months is associated with a higher increment in motor,  
167 communication and cognitive ability scores at 26 to 80 months of age compared to a 1 unit increase in  
168 HAZ after 24 months of age (5, 15).

169 Data from the Young Lives cohort in Ethiopia, India, Peru, Cambodia, and Vietnam indicated  
170 that children who were in the recovered group (stunted at 12 months of age but not stunted at 8 years of  
171 age) had better academic achievement (maths scores, receptive vocabulary scores, and reading  
172 comprehension scores) than those who stayed persistently stunted (15). However, their academic  
173 achievement was still lower than those who had never been stunted. This finding is consistent with the  
174 finding from a cohort in Malawi that reported those who had recovered from stunting had better  
175 academic achievements at 11 years of age than those who were persistently stunted from age 4 to 8 years  
176 (17). Based on the above, it seems likely that the period in which neurocognitive deficits can recover  
177 following appropriate interventions goes beyond the age of 2 years, up until 8 years of age, which is in  
178 line with prefrontal cortex development and ongoing synaptogenesis at that age (4). Interestingly,  
179 another study reported that children who were stunted at 24 months of age and experienced catch-up  
180 growth often did worse on cognitive tests at 4-5 years of age than children who were never stunted and  
181 almost as poorly as children who had remained stunted (18). This finding appears to contradict  
182 previously stated findings from the Young Lives and Malawi cohorts. It is important to note, however,

183 that the exact definition of ‘catch-up’ plays a critical role in this observation. Recently, five definitions  
184 were formulated for ‘catch-up growth’, ranging from lenient to strict (I: increase in HAZ, II: recovery  
185 from stunting (HAZ at 5 years >-2), III: increase in height-for-age difference, IV: recovery from stunting  
186 and increase in height-for-age difference, and V: recovery from stunting with a stricter cut-off point,  
187 where HAZ falls within ‘normal’ range (HAZ at 5 years >-1) (19). The observation reported above is  
188 based on definitions I-IV of ‘catch-up’. Thus, the term ‘catch-up’ should be carefully defined when  
189 determining the optimal goal for catch-up growth to recover neurodevelopment and, consequently,  
190 cognitive ability in later life.

191

### 192 ***The importance of interventions in improving cognitive outcomes among undernourished children***

193 Seven publications assessed the effectiveness of intervention studies in improving cognitive  
194 outcomes among undernourished children. The publications covered 3 randomized controlled trials, 2  
195 systematic reviews and 2 meta-analyses. The overall quality of these studies was judged as good when  
196 considering the risk for bias (Table 2).

197 Stunted children with high levels of plasma homocysteine and those who were younger than 24  
198 months at the end of the follow-up period showed the largest improvement in gross motor function and  
199 problem-solving skills after being supplemented with vitamin B12 on a daily basis (20). *In contrast, the*  
200 *effect of the vitamin/nutrition intervention on recovering or maintaining normal neurodevelopment and*  
201 *cognitive deficits in normo-nourished children remained inconclusive (6, 20, 21). No benefits in growth*  
202 *or cognitive performance were reported among 422 healthy children aged 12 to 24 months receiving*  
203 *daily multi-micronutrient supplementation (iron and zinc) (21). This finding is in contrast with an*  
204 *intervention trial in which multiple micronutrients were supplemented (vitamin B12 and folic acid), with*  
205 *and without responsive stimulation, for approximately 20 months among 1486 mother-child pairs in*  
206 *Pakistan. In this study, children who were exposed to the combined intervention had, regardless of their*  
207 *nutrition status, significantly higher developmental scores (cognitive, language, and social-emotional*  
208 *scales) at 12 months than the control group (22). Another group of children who received responsive*

209 stimulation had significantly higher development scores on the cognitive, language, and motor scales at  
210 12 and 24 months of age and on the social emotional scale at 12 months of age than the control group.  
211 In comparison, the treatment effect on cognition, language and motor development at 24 months was  
212 moderate-to-large for responsive simulation and was low to moderate for the combined group (22).

213 *A recent systematic review and meta-analysis* that assessed the impact of nutrition with or  
214 without stimulation interventions concluded that parent-led responsive learning, more than nutrition  
215 supplementation, appeared to have a better influence on the neurodevelopment of children aged 0-60  
216 months (6). This systematic review, which was based on 75 retrieved studies from various databases,  
217 reported that the pooled effect of these supplementations is one-fourth smaller than the pooled effect  
218 size of responsive care and learning opportunities on cognitive, language, and motor scales. The review  
219 also suggested that postnatal multiple nutrient supplementation can improve linear growth and, to a  
220 smaller extent, cognitive development and socio-temperament, while interventions promoting  
221 responsive care and learning opportunities affect only cognitive development but not linear growth (6).

### 222

### 223 ***The impact of overweight/obesity on neurodevelopment and cognition***

224 Only one cross-sectional study and two systematic reviews that were retrieved described the  
225 impact of overweight/obesity on cognitive neurodevelopmental aspects (23-25) (Table 1). All studies  
226 seemed to point towards a more limited impact of overweight/obesity on aspects of neurodevelopment  
227 and cognition in the studied affluent populations in contrast with those describing the impact of  
228 undernutrition. All retrieved literature demonstrated that attention, executive control (inhibitory control,  
229 working memory, reward sensitivity, and impulsivity) and gross motor skills were the most affected  
230 areas.

231 A study among overweight Italian children showed poorer gross motor skills in overweight  
232 children than their normal-weight peers (23), while other systematic reviews reported poorer executive  
233 control and more difficulty with inhibition in overweight children than in healthy weight children (24,  
234 25). There is a suggestion of directionality in the association between obesity and executive function.

235 Children with lower executive function are speculated to have lower self-regulation of energy/caloric  
236 intake and decreased participation in physical activity, which leads to or potentiates overweight or  
237 obesity. It was also reported that low executive function stimulates excess adiposity, leading to  
238 exacerbating decrements in executive function in childhood (26). On the other hand, various studies  
239 have shown that obesity/early life adiposity reduces executive function via several biological  
240 mechanisms. Proinflammatory cytokines produced by adipose tissue can stimulate inflammatory  
241 pathways in all age categories, leading to cognitive development deficits, and dysregulation of appetite-  
242 regulating hormones could further harm cognitive skills (25). The limited affected cognitive  
243 neurodevelopmental areas reported in these affluent populations may be more diverse and pronounced  
244 in less-affluent societies. In conclusion, poor gross motor skills, which are correlated with less physical  
245 activity (24) and reduced attention span (24, 25), should be taken into consideration when designing  
246 intervention programs for these overweight/obese children.

247

#### 248 ***Factors influencing the impact of suboptimal growth on neurodevelopment and cognition***

249 From the literature, the influencing factors identified were further classified into maternal and  
250 paternal factors, the child's characteristics and health conditions, and socioeconomic factors (Table 3).  
251 Several pregnancy-related maternal parameters, such as maternal weight gain and smoking, have been  
252 consistently reported to increase the impact of suboptimal growth on cognitive neurodevelopment in  
253 addition to infant condition at birth, such as low birth weight and short length at birth, suggesting the  
254 importance of prenatal nutrition and maternal health for later life (11, 14, 18, 27, 28).

255 The influence of sex on suboptimal growth and cognitive neurodevelopment appeared  
256 conflicting in the literature; normo-nourished and undernourished girls had slightly higher intelligence  
257 scores (9), social maturity (18), and manageability (14) than boys of the same nutritional status, while  
258 the opposite findings were reported in normo-nourished children (13).

259 Particularly among undernourished children, it appeared that parents with a low level of  
260 nutritional knowledge, those who perceived less responsibility in the parenting task, or those who were

261 less restrictive towards access to unhealthy foods had children who experienced suboptimal growth with  
262 resultant impaired cognitive development (5, 13).

263 Diet quality was demonstrated to be a positive predictor of improved cognitive outcomes in these  
264 children (5, 13). For instance, food fortified with calcium, iron, zinc, vitamins B2, and proteins was  
265 associated with improved cognitive outcomes because of the probable role of these nutrients in early  
266 brain development (6, 22). In contrast, a lack of dietary protein may delay or inhibit brain and cognitive  
267 development (5, 29). On that note, recent evidence proposed supplementation of animal protein, in  
268 particular cow's milk, as an essential component in a child's diet to prevent undernutrition and to  
269 improve cognition (30-32).

270 The influence of the Home Observation for Measurement of the Environment (HOME)  
271 parameter as a proxy indicator for socioeconomic factors was reported in several studies among  
272 undernourished children to be correlated with the impact of undernutrition and overweight/obesity on  
273 neurodevelopment and cognition (5, 9, 22, 27, 28, 33, 34). This parameter was developed to measure  
274 responsiveness and stimulation of the home environment, which consisted of several questions,  
275 including questions about home ownership and the possession of books and toys. Among overweight  
276 children, socioeconomic status was the only influencing factor reported in the papers in this review.  
277 Those in lower socioeconomic situations had lower motor skills than their counterparts with higher  
278 socioeconomic status (23).

279 This review has several limitations. First, chronic illnesses and hospital malnutrition were  
280 excluded, although they could have a similar impact on overall developmental aspects. A second  
281 limitation is that the statistical significance of pooled effects of all studies combined was not calculated,  
282 as this review is of scoping nature and not a systematic review. Furthermore, the search strategy may  
283 have missed some relevant papers because of the search scope that limited peer-reviewed research papers  
284 to those published in the past decade only. To overcome this issue, reviewing reports outside the peer-  
285 reviewed literature (i.e., grey literature) should be done in the future.

286 One of the strengths of this scoping review is that it expeditiously provides comprehensive and  
287 updated scientific evidence for healthcare professionals and policymakers. The synthesized evidence  
288 may allow key stakeholders to plan and to execute necessary intervention programs for preventing and  
289 managing suboptimal growth, with a focus on achieving optimal cognitive potential in young children.  
290 In addition, this scoping review was conducted using specific methodological approaches that would  
291 allow more accuracy in literature screening with less bias. A cross-referencing of eligible studies from  
292 retrieved narrative reviews enhanced the completeness of the evidence and enabled the retrieval of  
293 information on not only the populations that experience undernutrition and overweight/obesity but also  
294 the normal population that identified children with faltering growth. It also enabled the retrieval of  
295 studies from various geographical areas (low- to high-income studies) as well as studies on various  
296 developmental deficits. Emphasis has been hitherto placed on the impact of malnutrition in children on  
297 morbidity and mortality; in contrast, this review points to the quality of life that may be affected by  
298 suboptimal nutrition on neurodevelopment and cognition. From a public health perspective, prevention  
299 of childhood malnutrition must be addressed not only by economic empowerment but also through health  
300 promotion and education as well as policy.

301

302 ***Consideration for future research and actions:***

303 1) More studies should be conducted on the impact of nutritional/behavioural interventions in  
304 overweight/obese children on neurodevelopment and cognition, especially in low-income countries, as  
305 all the currently retrieved literature came from high-income countries. Overweight/obesity in childhood  
306 is on the rise and can coexist with undernutrition within the same population, for example, as seen in  
307 India and Indonesia. Approximately 46.6 and 36.6 million children under the age of five are stunted in  
308 India and Indonesia, respectively, and more than 1 million children in the same age group are overweight  
309 in these two countries. This amounts to almost a total 1.85 million Indian and Indonesian children who  
310 are at risk of suboptimal neurodevelopment and cognitive function (2). An increase in childhood obesity



311 prevalence may have adverse long-term consequences on human capital in these countries, in addition  
312 to the negative consequences of undernutrition.

313 2) Intervention studies for both undernutrition and overweight/obesity must assess the association  
314 between these nutritional statuses and cognitive neurodevelopment, as most interventions usually focus  
315 only on providing nutrients related to brain development and not for optimal growth and vice versa as  
316 also suggested by Prado et al. (6). For example, several recently published studies and systematic reviews  
317 assessed the impact of animal-based food supplementation or milk interventions on growth among  
318 stunted children or only cognitive neurodevelopment but not on both aspects simultaneously (30, 31).

319 3) Any program or intervention for growth monitoring in community or hospital settings should engage  
320 nutritionists, general practitioners, paediatricians, and behavioural specialists in a collaborative  
321 multidisciplinary team. These groups of healthcare providers have the dual responsibility of considering  
322 both ends of the malnutrition spectrum when planning and implementing multi-disciplinary intervention  
323 programs (35). Actions should be taken to tackle both undernutrition and overweight/obesity  
324 concurrently – not just one or the other – to ensure successful and comprehensive outcomes in terms of  
325 childhood growth and cognitive neurodevelopment.

326

## 327 CONCLUSION

328 Under- and overnutrition during the first 60 months of postnatal life affect the cognitive  
329 neurodevelopmental trajectories of children later in life. Weight and length/height need to be monitored  
330 even beyond 24 months of life to enable early recognition of growth retardation/deviations and to allow  
331 appropriate and timely interventions to address their negative neurodevelopmental and cognitive  
332 impacts. Given the Global Nutrition Targets for 2025 (36), intervention programs should leverage a  
333 *multidimensional approach* that not only addresses childhood undernutrition but also overweight/obesity  
334 and improves socioeconomic conditions. Nutritional interventions for catch-up growth among  
335 undernourished children can potentially recover neurocognitive development up to the age of 8 years,  
336 particularly in those whose nutrition status have improved. These specific, targeted and simultaneous

337 interventions may be key to safeguarding future human capital, especially in countries with a high  
338 prevalence of stunting, overweight/obesity or both.

For Peer Review

340 **DECLARATIONS**

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350 **Author contributions**

351 All authors were involved in setting the concept, objective and selection criteria for the review. All  
352 authors were also involved in the selection of eligible articles based on titles and abstracts. A simple  
353 grading of controlling study biases was then conducted by five authors (AS, MYJ, PBK, LM and JG).  
354 Afterwards, LM and JG selected eligible articles based on full texts. All authors provided agreement on  
355 the final included articles. All authors participated in data extraction, synthesis and interpretation. All  
356 authors provided inputs and agreed on the final version of the manuscript.

357

358 **Competing interests**

359 Verena Tan was an employee of FrieslandCampina at the time of the manuscript's development. Leilani  
360 Muhandi and Jan Geurts were employees of FrieslandCampina at the time of the manuscript's  
361 development, submission and revision.

362

363 **Consent for publication**

364 Not applicable.

365

366 **Ethics approval and consent to participate**

367 Not applicable.

368

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## Nutrition Research Reviews - NRR-20-032.R3: Update

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Wed, Mar 10, 2021 at 7:10 AM

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Dear Authors,

Please find the decision later from the journal below.

Would it be possible to share your suggestions for each below point perhaps by Mar 17?

I will compile them and make suggested revisions by Mar 22.

The due date for revision is May 9, however, we can perhaps aim to re-submit by Mar 26?

Looking forward to hearing from you soon.

Kind regards,

Leilani

From:

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To:

[yazidj@ummc.edu.my](mailto:yazidj@ummc.edu.my)

CC:

Subject:

Nutrition Research Reviews NRR-20-032.R3

Body:

09-Mar-2021

**\*\*A copy of this decision email has also been sent to the reviewers\*\***

**\*\*Please ensure that all co-authors are made aware of the content of this email\*\***

Dear Prof. JALALUDIN,

Your manuscript "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review" has been evaluated and, while considered positively by the reviewers, some minor revisions are needed before a final decision can be made. The comments of the reviewer(s) who looked at your manuscript are included at the foot of this letter (if applicable). Please take these into account when preparing a revised version of the manuscript. Use the following link to create a revision now:

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If English language editing has been requested in the below comments, we list a number of third-party services specialising in language editing and/or translation. Use of any of these services is voluntary, and at your own expense.

<https://www.cambridge.org/core/services/authors/language-services>

Sincerely,

Prof. Christine Edwards

Editor-in-Chief, Nutrition Research Reviews

[christine.edwards@glasgow.ac.uk](mailto:christine.edwards@glasgow.ac.uk)

Editor

Comments to the Author:

In the Introduction please include a rationale for including both underweight and overweight within the same review.

As your research questions are interlinked for under- and overweight, please ensure your Results and Discussion section brings these two together.

Reviewer: 1

Comments to the Author

The comments have been addressed appropriately.

Reviewer: 2

Comments to the Author

I am still not entirely sure that doing a review of both stunting and obesity justifies either topic sufficiently and that this should be published like this but will leave this up to the editors.

Conclusion sentence is very long – particularly as the authors are trying to provide a conclusion for work conducted on children with stunting as well as those for overweight/obesity and the conclusions are different and separate. I would aim to separate this sentence. Also, what is “adequate intakes”? And what do the authors mean by “improving socio-economic conditions” – this is so generic that it does not mean much – e.g. does this mean “improved social welfare, improved housing, improving job security”? Some of this is pointed out in table 3.

“In conclusion, as underweight, stunting and overweight/obesity have impacts on cognitive neurodevelopment, intervention programmes should involve a multidimensional approach that consists of supplying adequate intakes for catch-up growth before the age of 8 years for those who are underweight or stunted, improving socioeconomic conditions, and reducing childhood overweight/obesity.

Line 72 – don’t start with “Still,…”

Line 139 “From a longitudinal study in the Philippines, all HAZ categories at 6 months (defined as mild/moderate/severe stunting ( $-2 \leq \text{HAZ} < -1.01$ ), at risk for stunting ( $-1 \leq \text{HAZ} < 0$ ) or normal height ( $\text{HAZ} \geq 0$ )) were positively associated…” What do the authors mean by “positively associated with”? Do they mean that if the child has a  $\text{HAZ} < -2$  they were more likely to have poor cognitive development at the age of 6? Could this be clearer in the way it is written?

Similarly the team describe; “HAZ at 4-6 years of age among healthy

Malaysian children was also reported to be significantly related to cognitive function”. Do they mean “HAZ of 0 and above” or an “HAZ  $> 1-2$  SD above the mean”. Can the authors again be clearer?

The authors mention a study from Bangladesh; “However, in a study among Bangladeshi children aged 6-24 months, it was reported that severely underweight children (weight-for-age z-score,  $\text{WAZ} < -2$ ) were less sociable, less attentive, more fearful and had more negative emotional traits than normo-nourished children”. Could they critically appraise this study a little better? Were the outcomes well considered? Were the results believable? Not clear from reading this review. Could there be a little more comment?

The authors describe the HOME environment as being a useful proxy indicator for socioeconomic status (273) and that this may have influenced outcomes for some children in the studies retrieved. The authors describe how the reviews they mention discuss how; “This parameter was developed to measure responsiveness and stimulation of the home environment, which consisted of several questions, including questions about home ownership and the possession of books and toys”. Could the authors be clearer as to how the HOME tool assesses socioeconomic status in the way they (or other authors) feel is relevant? Is it only in terms of home ownership and possession of books and toys? Could they discuss this or mention this as a limitation?

This sentence (line 320-321) ; “Any program or intervention for growth monitoring in community or hospital settings should engage nutritionists, general practitioners, paediatricians, and behavioural specialists in a collaborative multidisciplinary team” depends very much on the setting that the programme is in and may be very variable in LMIC settings – the authors need to be more aware of this and consider how to make this more relevant to other settings.

Date Sent:

09-Mar-2021

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## RESPONSE TO REVIEWERS

Kuala Lumpur, March 30, 2021

To:

**Prof. Christine Edwards**  
Editor in Chief  
Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review"

Thank you for the further evaluation of our manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review" in Nutrition Research Reviews after the approval-in-principle status. We have further revised the manuscript to address the further concerns with the revised statements are written in blue below, and in italics in the manuscript for ease of reference.

We hope that this version of revised manuscript is satisfactory and that it can be accepted for publication soon. In addition, would it be possible to still opt for Open Access for this manuscript?

We look forward to having your favourable response.

Yours sincerely,



**Prof Dr Muhammad Yazid Jalaludin**  
Corresponding authors

Editor

Comments to the Author:

In the Introduction please include a rationale for including both underweight and overweight within the same review.

As your research questions are interlinked for under- and overweight, please ensure your Results and Discussion section brings these two together.

Response to Editor:

We have added the following statements in introduction:

- the first paragraph – “It is therefore important to discuss both spectrums of the malnutrition together”
- the last paragraph- “This combined approach hopefully will allow for a holistic view of the situation commonly found in many countries across the world.”

to further underline the importance of discussing under-and over-nutrition in the one review.

We also have ensured that the Results and Discussion section brings these two together such as on:

- lines 125-127; lines 347-357

To the best of our knowledge, this review complements previous meta-analyses and systematic reviews (5-7) and includes a wider spectrum of suboptimal nutritional status (ranging from mild/moderate to severe underweight and stunting to overweight/obesity as markers of overnutrition).

- Lines 319-324

Overweight/obesity in childhood is on the rise and can coexist with undernutrition within the same population, for example, as seen in India and Indonesia. Approximately 46.6 and 36.6 million children under the age of five are stunted in India and Indonesia, respectively, and more than 1 million children in the same age group are overweight in these two countries. This amounts to almost a total 1.85 million Indian and Indonesian children who are at risk of suboptimal neurodevelopment and cognitive function (2).

Reviewer: 1

Comments to the Author

The comments have been addressed appropriately.

Response to reviewer #1

We appreciate that the first revision is well-received.

Reviewer: 2

Comments to the Author

I am still not entirely sure that doing a review of both stunting and obesity justifies either topic sufficiently and that this should be published like this but will leave this up to the editors.

Page 2

Conclusion sentence is very long – particularly as the authors are trying to provide a conclusion for work conducted on children with stunting as well as those for overweight/obesity and the conclusions are different and separate. I would aim to separate this sentence.

Also, what is “adequate intakes”? And what do the authors mean by “improving socio-economic conditions” – this is so generic that it does not mean much – e.g. does this mean “improved social welfare, improved housing, improving job security”?? Some of this is pointed out in table 3.

Response to reviewer #2:

The sentences in the conclusion section in the abstract has been revised and made more concise. The revised statements are as follows: “Multidimensional approaches, such as supplying adequate nutrient intakes for catch-up growth among underweight or stunted children, providing adequate socio-economic stimulations including parental job security, social welfare and sanitation levels, while reducing childhood overweight/obesity, are important measures that can improve neurodevelopment and cognition.”

Line 72 – don’t start with “Still,…”

Response to reviewer #2:

Revision has been made to remove the word “Still, …”

Line 139 “From a longitudinal study in the Philippines, all HAZ categories at 6 months (defined as mild/moderate/severe stunting ( $-2 \leq \text{HAZ} < -1.01$ ), at risk for stunting ( $-1 \leq \text{HAZ} < 0$ ) or normal height ( $\text{HAZ} \geq 0$ )) were positively associated…” What do the authors mean by “positively associated with”? Do they mean that if the child has a  $\text{HAZ} < -2$  they were more likely to have poor cognitive development at the age of 6? Could this be clearer in the way it is written?

Response to reviewer #2:

Thank you for the comments. We have revised the statement into “From a longitudinal study in the Philippines, regardless of HAZ categories at 6 months (defined as moderate/severe stunting ( $\text{HAZ} < -2$ ), mild stunting ( $-2 < \text{HAZ} < -1$ ), at risk of stunting ( $-1 < \text{HAZ} < 0$ ) or normal height ( $\text{HAZ} \geq 0$ ), more gain (or less loss) in HAZ after the age of 6 months were positively associated with cognitive function at 11 years of age.” (lines 148-151)

Similarly the team describe; “HAZ at 4-6 years of age among healthy Malaysian children was also reported to be significantly related to cognitive function”. Do they mean “HAZ of 0 and above” or an “HAZ  $> 1-2$  SD above the mean”. Can the authors again be clearer?

Response to reviewer #2:

To provide more clarity, we would like to propose to split the statement into: “The impact on timing of stunting is still unclear. One study reported that stunting in

the second year of life is more harmful than stunting before 12 months of age (12). Another study reported that higher HAZ at 4-6 years of age among healthy Malaysian children contributed significantly to higher cognitive function after controlling for socio-demographic background, parent's nutrition knowledge and dinner consumption (DR2 = 0.009, DF = 18.605,  $p < 0.001$ ).” (lines 156-160)

We also have reached out to the authors who further clarified that:

1. They analyzed continuous variables, therefore they obtain the result as above i.e the higher the HAZ the higher the cognitive scores. That means at any value of HAZ, the higher the HAZ, the better the cognitive function.
2. They did not analyze categorical variables, i.e. stunted vs non stunted; however, the author has kindly re-done the analysis as per below information. It clearly shows that stunted children have significantly lower cognitive scores. However, this result is not available in the actual paper.

**Stunting and Cognitive Performance in Preschoolers aged 4-6 years in Peninsular Malaysia:**

**Data from the NutriStudy (Mohd Nasir *et al.*, 2012)**

**Table 1.** Mean difference in the cognitive scores between stunted ( $n= 162$ ) and non-stunted ( $n=1771$ ) children ( $N=1933$ )

Height-for-age (HAZ) status	<i>n</i> (%)	Cognitive scores Mean $\pm$ SD	MD	<i>t</i>	<i>p</i>
Stunted (HAZ < -2SD)	162 (8.4)	100.28 $\pm$ 13.13	-3.47	-2.94	0.003*
Not stunted	1771 (91.6)	103.75 $\pm$ 14.51			

\*Significant at  $p < 0.01$

The authors mention a study from Bangladesh; “However, in a study among Bangladeshi children aged 6-24 months, it was reported that severely underweight children (weight-for-age z-score, WAZ < -2) were less sociable, less attentive, more fearful and had more negative emotional traits than normo-nourished children”. Could they critically appraise this study a little better? Were the outcomes well considered? Were the results believable? Not clear from reading this review. Could there be a little more comment?

**Response to reviewer #2:**

We have further revised the statement to incorporate more information about the study as follows: “However, in a study among Bangladeshi children aged 6-24 months comparing undernourished ( $n=212$ ) and better-nourished ( $n=108$ ), it was reported that severely underweight children (weight-for-age z-score, WAZ < -2) were less sociable, less attentive, more fearful and had more negative emotional traits than normo-nourished children. The effect size of these temperaments which were assessed using validated interviewer-administered questionnaire to parents were small to moderate.” (lines 164-170)

The authors describe the HOME environment as being a useful proxy indicator for socioeconomic status (273) and that this may have influenced outcomes for some children in the studies retrieved. The authors describe how the reviews they mention discuss how; "This parameter was developed to measure responsiveness and stimulation of the home environment, which consisted of several questions, including questions about home ownership and the possession of books and toys". Could the authors be clearer as to how the HOME tool assesses socioeconomic status in the way they (or other authors) feel is relevant? Is it only in terms of home ownership and possession of books and toys? Could they discuss this or mention this as a limitation?

Response to reviewer #2:

Thank you for the comments. We have added this as part of the limitation as follows: "Second, the limitations of the HOME instrument as an indicator of socioeconomic status must be adjusted to various sociocultural conditions in each group or country." (lines 301-303)

This sentence (line 320-321) ; "Any program or intervention for growth monitoring in community or hospital settings should engage nutritionists, general practitioners, paediatricians, and behavioural specialists in a collaborative multidisciplinary team" depends very much on the setting that the programme is in and may be very variable in LMIC settings – the authors need to be more aware of this and consider how to make this more relevant to other settings.

Response to reviewer #2:

The statement has been revised to accommodate the suggestion and provide further clarification to as follow: "Optimally, any program or intervention for growth monitoring in community or hospital settings should engage a multidisciplinary team of health care professionals. Depending on the local conditions, such a team could consist of nutritionists, general practitioners, paediatricians, and/or behavioural specialists" (lines 344-347)

<b>5</b>	<b>Fourth revision (ID NRR-20 0.32.R4)</b> was submitted to Journal	<b>31 March 2021</b>
	Decision: Acceptable as received (due date 31-May-2021)	

## Cover Letter: NRR-20-032.R4



Kuala Lumpur, March 31, 2021

To:  
Prof. Christine Edwards  
Editor in Chief  
Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review"

Thank you for the further evaluation of our manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review" in Nutrition Research Reviews after the acceptable-in-principle status. We have further revised the manuscript to address the further concerns with the revised statements are written in blue below, and in italics in the manuscript for ease of reference.

We hope that this version of the revised manuscript is satisfactory and that it can be accepted for publication soon. In addition, would it be possible to still opt for Open Access for this manuscript?

We look forward to having your favourable response.

Close

- 032.R5 neurodevelopmental and cognitive consequences: A Scoping review
- Acceptable as received (31-May-2021)
- In Production

Contact Journal

Submitting Author: Muhardi, Leilani

[Cover Letter](#)

EA: Sage, Alison    NRR-20-032.R4    Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review    31-Mar-2021    31-Mar-2021

- Acceptable in principle (12-May-2021)
- a revision has been submitted

Contact Journal

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Submitting Author: Muhardi, Leilani

[Cover Letter](#)

EA: Sage, Alison    NRR-20-032.R3    Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review    18-Dec-2020    18-Dec-2020



# NUTRITION RESEARCH REVIEWS



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## Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review

Journal:	<i>Nutrition Research Reviews</i>
Manuscript ID	NRR-20-032.R4
Manuscript Type:	Review
Date Submitted by the Author:	31-Mar-2021
Complete List of Authors:	Suryawan, Ahmad; Airlangga University, Department of Child Health JALALUDIN, MUHAMMAD ; University of Malaya, Department of Pediatrics Poh, Bee; Universiti Kebangsaan Malaysia, Department: Nutritional Sciences Programme, Centre for Community Health Studies, Faculty of Health Sciences Sanusi, Rasaki; University of Ibadan, College of Medicine TAN, MING HUI ; Singapore Institute of Technology, Dietetics and Nutrition Programme, Health and Social Sciences cluster Geurts, Jan; Koninklijke FrieslandCampina NV Innovation Centre Wageningen Muhardi, Leilani; FrieslandCampina AMEA, Medical Affairs
Keywords:	underweight, stunting, obesity, cognition, neurodevelopment

SCHOLARONE™  
Manuscripts



1 **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A**  
2 **scoping review**

3  
4 *Running title: Malnutrition and cognitive neurodevelopmental consequences*

5  
6 A. Suryawan<sup>1</sup>, M.Y. Jalaludin<sup>2</sup>, B.K. Poh<sup>3</sup>, R. Sanusi<sup>4</sup>, V.M.H. Tan<sup>5</sup>, J.M. Geurts<sup>6</sup>, L. Muhandi<sup>7</sup>

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30  
31 247 words in the Abstract, 3827 words in the Main Text (excluding tables, figures and references), 4  
32 Tables, 2 Figures, 42 References

33

34 **Abstract**

35 The negative impact of stunting and severe underweight on cognitive neurodevelopment of  
36 children is well-documented; however, the effect of overweight/obesity is still unclear. The 2018 Global  
37 Nutrition Report reported that stunting and overweight concurrently affect 189 million children  
38 worldwide.

39 *As existing reviews separately discuss undernutrition from overnutrition, this scoping review*  
40 *aims to document the impact of mild/moderate and severe underweight, stunting, and overweight/obesity*  
41 *among children aged 0-60 months on their cognitive neurodevelopmental trajectories. Twenty-six*  
42 *articles were analysed to extract significant information from literature retrieved from PubMed and*  
43 *Cochrane databases published from 1 January 2009 to 31 October 2019.*

44 Length gain is associated with cognitive neurodevelopment in normo-nourished and stunted  
45 children aged under 24 months. Among stunted children, it seems that cognitive and neurodevelopmental  
46 deficits can potentially be recovered before 8 years old, particularly in those whose nutritional status  
47 have improved. The impact of overweight/obesity on cognitive neurodevelopment appears to be limited  
48 to attention, gross motor skills and executive control. Parental education level, birth weight/length,  
49 breastfeeding duration, and sanitation level are some identifiable factors that modify the impact of under-  
50 and overnutrition on cognitive and neurodevelopment.

51 In conclusion, underweight, stunting and overweight/obesity have significant impact on  
52 cognitive neurodevelopment. Thus, intervention programmes should address these issues  
53 simultaneously. *Multidimensional approaches, such as supplying adequate nutrient intakes for catch-*  
54 *up growth among underweight or stunted children, providing adequate socio-economic stimulations*  
55 *including parental job security, social welfare and sanitation levels, while reducing childhood*  
56 *overweight/obesity, are important measures that can improve neurodevelopment and cognition.*

57  
58 **Keywords (max 5):** underweight, stunting, obesity, cognition, neurodevelopment

59

## 60 INTRODUCTION

61 Malnutrition (wasting or low weight-for-height, stunting or low height-for-age, and underweight  
62 or low weight-for-age), micronutrient deficiencies and overweight/obesity are public health problems  
63 that can affect children aged less than 60 months. However, while the number of stunted children  
64 worldwide has decreased recently, the number of overweight children has increased, and the total  
65 number of children affected by stunting and overweight is approximately 189 million (1). **It is therefore**  
66 **important to discuss both ends of the malnutrition spectrum together.**

67 Malnutrition leads to economic, social, and health issues for families, at the community and  
68 national level (2). More importantly, severe undernutrition – defined as severe stunting (below HAZ  
69 (height-for-age Z score) minus three standard deviations ( $-3\text{ SD}$ ))(3) and severe underweight (below  
70 WAZ (weight-for-age Z score) minus three standard deviations ( $-3\text{ SD}$ ))(3) – impair children's  
71 development in the short (delayed cognitive, behavioural and motor development), medium (lower IQ  
72 and school/academic achievement) and long term (human capital), mostly in low and middle-income  
73 countries (4-7). It is currently unclear whether overnutrition impacts neurodevelopment and cognition  
74 or, vice versa, whether neurodevelopmental deficits impact overnutrition, or both.

75 Despite the reduction in stunting over the last decade (1), there still exists a need to better  
76 understand if there are opportunities to mitigate the negative, long-term impact of stunting on human  
77 capital development. It is also currently unclear whether interventions can be targeted at specific aspects  
78 of neurodevelopment and cognition, taking into consideration the timing of malnutrition with the timing  
79 of cognitive neurodevelopment in early childhood. More information is also needed to understand the  
80 aspects of neurodevelopment and cognition that are affected among overweight/obese children in order  
81 to design specific interventions.

82 **As most existing reviews discuss under-nutrition from overnutrition separately,** this scoping  
83 review was therefore designed to extract from the published literature, **to study the impact of both the**  
84 **conditions of** undernutrition (stunting defined as height for age z-score (HAZ)  $< -2$ ), underweight  
85 defined as weight for age z-score (WAZ)  $< -2$ ) and overnutrition (overweight defined as  $2\text{ SD} > \text{WAZ} <$

86 3 SD and obesity as  $WAZ \geq 3$  SD) (3) as compared to normo-nourished (defined as not stunted, wasted,  
87 underweight, or overweight/obese) children aged 0-60 months on cognitive neurodevelopmental aspects  
88 (cognition, behavioural, motor and emotional development) in early, mid and later life. **This combined  
89 approach will conceivably allow for a more holistic view of the situation commonly found in many  
90 countries across the world.**

91

## 92 **METHODS**

93 This review followed the consistent approach of a scoping review to compile findings from  
94 studies with different designs and methodologies to answer the stated critical research questions (8). The  
95 research questions are as follows: (i) Which developmental consequences are affected by over- and  
96 undernutrition during the first 60 months of life? (ii) What other factors can modify these outcomes?  
97 (iii) Which factors can mitigate the impact of over- and undernutrition on neurodevelopment and  
98 cognition? (iv) Is the effect on cognitive neurodevelopment partly or fully reversible? and (v) What are  
99 the implications for intervention strategies?

100 Literature published from 1 January 2009 to 31 October 2019 in the PubMed and Cochrane  
101 databases was retrieved using formulated search terms. The title and abstract of each article retrieved  
102 were screened based on the inclusion criteria by all authors. A simple grading of controlling study biases  
103 using JADAD criteria for randomized controlled (RCT) studies, Newcastle Ottawa Scale for cohort  
104 studies, and National Heart, Lung and Blood Institute (NHLBI) criteria for observational cross-sectional  
105 studies were then conducted by five authors (AS, MYJ, PBK, LM and JG) to select studies for further  
106 qualitative analyses (Tables 1 and 2). References of relevant narrative reviews (cross-references) were  
107 also examined to search for further studies that met the inclusion criteria. JG and LM then independently  
108 extracted data from the identified full-text articles. Data extraction tables incorporated important  
109 information from eligible full texts to allow the extraction of significant information for the review.

110

## 111 **RESULTS AND DISCUSSION**

### 112 **Descriptive summary of included studies**

113 From the 91 articles originally identified through the search strategy, 26 full-text articles were  
114 selected after a review of cross-references in eligible narrative reviews. The full text was used for  
115 information extraction and grading for quality assessment (Figure 1).

116 Information was categorised based on the type of study and nutritional status of the children  
117 (Table 1 and Table 2) as well as by factors influencing the impact of nutritional status on cognitive  
118 neurodevelopment (Table 3). Information was extracted from 14 observational studies (undernutrition  
119 (n=8 articles), normo-nutrition (n=5 articles) and overnutrition (n=1 article), 4 intervention trials  
120 (undernutrition (n=2 articles) and normo-nutrition (n=2 articles)), 4 systematic reviews (undernutrition  
121 (n=1 article), normo-nutrition (n=2 articles) and overnutrition (n=2 articles)) and 4 meta-analyses (all  
122 on undernutrition). All publications on under- and normo-nourished children were conducted in low- to  
123 middle-income countries, while all articles about over-nourished children reported data from high-  
124 income countries. No intervention study was retrieved on overweight/obese children. Approximately  
125 85% (n=22) of the retrieved literature had good quality in controlling bias.

126 To the best of our knowledge, this review complements previous meta-analyses and systematic  
127 reviews (5-7) and includes a wider spectrum of suboptimal nutritional status (ranging from  
128 mild/moderate to severe underweight and stunting to overweight/obesity as markers of overnutrition)  
129 during the first 60 months of life on various neurodevelopment aspects (cognition, motor development,  
130 temperament, socioeconomic status, and academic achievement) that manifest from infancy and school  
131 age to adulthood (Figure 2). This review also covers observational longitudinal cohorts and  
132 interventional studies with nutrition- and non-nutrition-related interventions on the outcomes of interest.

133

134

135

136 **The importance of monitoring weight, length and head circumference during the first 24 months**  
137 **of age**

138 From the reviewed studies, length-for-age z-scores (LAZ) and height-for-age z-scores (HAZ)  
139 (anthropometric measures of stunting in children) were associated with various elements of cognitive  
140 functioning, such as attention span, time to proper walking, mathematics and language abilities in early  
141 life, and income and choice of partner/age at marriage in later life (Table 1). It was reported that healthy  
142 infants in the highest quartile of neonatal weight-, length-, and head circumference-gain during the first  
143 4 weeks of life had higher IQ scores at 6 years of age than those in the lowest quartile (9).

144 From a longitudinal study in the Philippines, **regardless of HAZ categories at 6 months (defined**  
145 **as moderate/severe stunting ( $HAZ < -2$ ), mild stunting ( $-2 \leq HAZ < -1$ ), at risk of stunting ( $-1 < HAZ <$**   
146 **0) or normal height ( $HAZ \geq 0$ )), more gain (or less loss) in HAZ after the age of 6 months** were positively  
147 associated with cognitive function at 11 years of age. In addition, changes in HAZ from 6 to 24 months  
148 and changes in HAZ from 24 months to 11 years were also positively associated with cognitive ability  
149 at 11 years in the same study (10). These outcomes are similar to the results among children in  
150 Bangladesh. In this study, cognitive impairment was associated with poverty, birth condition and  
151 postnatal growth that started at 7 months of age and worsened up to 64 months when it became even  
152 more substantial (11). **The impact of the timing of stunting is still unclear. One study reported that**  
153 **stunting in the second year of life is more harmful than stunting before 12 months of age (12). Another**  
154 **study reported that higher HAZ at 4-6 years of age among healthy Malaysian children significantly**  
155 **contributed to higher cognitive function after controlling for socio-demographic background, parent's**  
156 **nutrition knowledge and dinner consumption ( $DR2 = 0.009$ ,  $DF = 18.605$ ,  $p < 0.001$ ) (13).**

157 Evidence for the impact of underweight and stunting on the development of emotional skills is  
158 largely variable across the identified studies. Two meta-analyses that described data from lower- and  
159 middle-income countries showed the limited influence of undernutrition on a child's attachment,  
160 emotionality, social competence and temperament (5, 7). **However, in a study among Bangladeshi**  
161 **children aged 6-24 months comparing undernourished ( $n=212$ ) and better-nourished ( $n=108$ ), it was**

162 reported that severely underweight children (weight-for-age z-score, WAZ < -2) were less sociable, less  
163 attentive, more fearful and had more negative emotional traits than normo-nourished children. The effect  
164 size of these temperaments which were assessed using validated interviewer-administered questionnaire  
165 to parents were small to moderate (14). There is evidence, therefore, that underweight and stunting  
166 impact social skill development. Low HAZ and WAZ correlated strongly with children having less  
167 schooling or needing a longer time to complete schooling (15), and in later life, with lower income and  
168 living in a less conducive environment, such as having a higher number of pregnancies and having the  
169 first child at a younger age (16).

170

### 171 **Improvements in linear growth and potential window of opportunity for neurodevelopment and** 172 **cognitive abilities recovery**

173 This review further strengthens the importance of the first 1000 days of life as a window of  
174 opportunity for rescuing neurocognitive deficits. It was reported that HAZ velocity between 6 and 24  
175 months among undernourished children is positively associated with cognitive function (10) and that  
176 every 1-unit increase in HAZ below the age of 24 months is associated with a higher increment in motor,  
177 communication and cognitive ability scores at 26 to 80 months of age compared to a 1 unit increase in  
178 HAZ after 24 months of age (5, 15).

179 Data from the Young Lives cohort in Ethiopia, India, Peru, Cambodia, and Vietnam indicated  
180 that children who were in the recovered group (stunted at 12 months of age but not stunted at 8 years of  
181 age) had better academic achievement (maths scores, receptive vocabulary scores, and reading  
182 comprehension scores) than those who stayed persistently stunted (15). However, their academic  
183 achievement was still lower than those who had never been stunted. This finding is consistent with the  
184 finding from another cohort in Malawi, which reported that those who had recovered from stunting had  
185 better academic achievements at 11 years of age than those who were persistently stunted from age 4 to  
186 8 years (17). Based on the above, it appears likely that the period in which neurocognitive deficits can  
187 recover following appropriate interventions goes beyond the age of 2 years, up until 8 years of age,

188 which is in line with prefrontal cortex development and ongoing synaptogenesis at that age (4).  
189 Interestingly, another study reported that children who were stunted at 24 months of age and experienced  
190 catch-up growth often did worse on cognitive tests at 4-5 years of age than children who were never  
191 stunted and almost as poorly as children who had remained stunted (18). This finding appears to  
192 contradict previously stated findings from the Young Lives and Malawi cohorts. It is important to note,  
193 however, that the exact definition of 'catch-up' plays a critical role in this observation. Recently, five  
194 definitions were formulated for 'catch-up growth', ranging from lenient to strict (I: increase in HAZ, II:  
195 recovery from stunting (HAZ at 5 years  $>-2$ ), III: increase in height-for-age difference, IV: recovery  
196 from stunting and increase in height-for-age difference, and V: recovery from stunting with a stricter  
197 cut-off point, where HAZ falls within 'normal' range (HAZ at 5 years  $>-1$ ) (19). The observation  
198 reported above is based on definitions I-IV of 'catch-up'. Thus, the term 'catch-up' should be carefully  
199 defined when determining the optimal goal for catch-up growth to recover neurodevelopment and,  
200 consequently, cognitive ability in later life.

201

### 202 **The importance of interventions in improving cognitive outcomes among undernourished children**

203 Seven publications assessed the effectiveness of intervention studies in improving cognitive  
204 outcomes among undernourished children. The publications covered 3 randomized controlled trials, 2  
205 systematic reviews and 2 meta-analyses. The overall quality of these studies was judged as good when  
206 considering the risk for bias (Table 2).

207 Stunted children with high levels of plasma homocysteine and those who were younger than 24  
208 months at the end of the follow-up period showed the largest improvement in gross motor function and  
209 problem-solving skills after being supplemented with vitamin B12 on a daily basis (20). In contrast, the  
210 effect of the vitamin/nutrition intervention on recovering or maintaining normal neurodevelopment and  
211 cognitive deficits in normo-nourished children remained inconclusive (6, 20, 21). No benefits in growth  
212 or cognitive performance were reported among 422 healthy children aged 12 to 24 months receiving  
213 daily multi-micronutrient supplementation (iron and zinc) (21). This finding is in contrast with an



214 intervention trial in which multiple micronutrients were supplemented (vitamins B12, A, C, folic acid  
215 and iron ), with and without responsive stimulation, for approximately 20 months among 1489 mother-  
216 child pairs in Pakistan. In this study, children who were exposed to the enhanced nutrition intervention  
217 had, regardless of their nutrition status, significantly higher developmental scores (cognitive, language,  
218 and social-emotional scales) at 12 months than the control group (22). Another group of children who  
219 received responsive stimulation had significantly higher developmental scores on the cognitive,  
220 language, and motor scales at 12 and 24 months of age and on the social emotional scale at 12 months  
221 of age than the control group. In comparison, the treatment effect on cognition, language and motor  
222 development at 24 months was moderate-to-large for responsive simulation and was low to moderate  
223 for the enhanced nutrition group (22). This study also found that linear growth in children exposed to  
224 enhanced nutrition were significantly better at 6 and 18 months compared to those not exposed to  
225 enhanced nutrition (22).

226 A recent systematic review and meta-analysis that assessed the impact of nutrition with or  
227 without stimulation interventions concluded that parent-led responsive learning, more than nutrition  
228 supplementation, appeared to have a better influence on the neurodevelopment of children aged 0-60  
229 months (6). This systematic review, which was based on 75 retrieved studies from various databases,  
230 reported that the pooled effect of these supplementations is one-fourth smaller than the pooled effect  
231 size of responsive care and learning opportunities on cognitive, language, and motor scales. The review  
232 also suggested that postnatal multiple nutrient supplementation can improve linear growth in children  
233 and, to a smaller extent, cognitive development and socio-temperament, while interventions promoting  
234 responsive care and learning opportunities affect only cognitive development but not linear growth (6).

235

### 236 **The impact of overweight/obesity on neurodevelopment and cognition**

237 Only one cross-sectional study and two systematic reviews that were retrieved described the  
238 impact of overweight/obesity on cognitive neurodevelopmental aspects (23-25) (Table 1). All studies  
239 seemed to point towards a more limited impact of overweight/obesity on aspects of neurodevelopment

240 and cognition in the studied affluent populations in contrast with those describing the impact of  
241 undernutrition. All retrieved literature demonstrated that attention, executive control (inhibitory control,  
242 working memory, reward sensitivity, and impulsivity) and gross motor skills were the most affected  
243 areas.

244 A study among overweight Italian children showed poorer gross motor skills in overweight  
245 children than their normal-weight peers (23), while other systematic reviews reported poorer executive  
246 control and more difficulty with inhibition in overweight children than in healthy weight children (24,  
247 25). There is a suggestion of directionality in the association between obesity and executive function.  
248 Children with lower executive function are speculated to have lower self-regulation of energy intake and  
249 decreased participation in physical activity, which leads to or potentiates overweight or obesity. It was  
250 also reported that low executive function stimulates excess adiposity, leading to exacerbating decrements  
251 in executive function in childhood (26). On the other hand, various studies have shown that child obesity  
252 or early life adiposity reduces executive function via several biological mechanisms. Proinflammatory  
253 cytokines produced by adipose tissue can stimulate inflammatory pathways in all age categories, leading  
254 to cognitive development deficits, and dysregulation of appetite-regulating hormones could further harm  
255 cognitive skills (25). Although there is limited affected cognitive neurodevelopmental areas reported in  
256 these affluent populations, the effect may be more diverse and pronounced in less-affluent societies. In  
257 conclusion, poor gross motor skills, which are correlated with less physical activity (24) and reduced  
258 attention span (24, 25), should be taken into consideration when designing intervention programs for  
259 these overweight/obese children.

260

### 261 **Factors influencing the impact of suboptimal growth on neurodevelopment and cognition**

262 From the literature, the influencing factors identified were further classified into maternal and  
263 paternal factors, child characteristics and health conditions, and socioeconomic factors (Table 3). Several  
264 pregnancy-related maternal parameters, such as maternal weight gain and smoking, have been  
265 consistently reported to increase the impact of suboptimal growth on cognitive neurodevelopment in

266 addition to infant condition at birth, such as low birth weight and short length at birth, suggesting the  
267 importance of prenatal nutrition and maternal health for later life (11, 14, 18, 27, 28).

268 The influence of sex on suboptimal growth and cognitive neurodevelopment appeared  
269 conflicting in the literature; normo-nourished and undernourished girls had slightly higher intelligence  
270 scores (9), social maturity (18), and manageability (14) than boys with the same nutritional status, while  
271 the opposite findings were reported in normo-nourished children (13).

272 Particularly among undernourished children, it appeared that parents with a low level of  
273 nutritional knowledge, those who perceived less responsibility in the parenting task, or those who were  
274 less restrictive towards access to unhealthy foods had children who experienced suboptimal growth with  
275 resultant impaired cognitive development (5, 13).

276 Diet quality was demonstrated to be a positive predictor of improved cognitive outcomes in these  
277 children (5, 13). For instance, food fortified with calcium, iron, zinc, vitamins B2, and proteins was  
278 associated with improved cognitive outcomes because of the probable role of these nutrients in early  
279 brain development (6, 22). In contrast, a lack of dietary protein may delay or inhibit brain and cognitive  
280 development (5, 29). On that note, recent evidence proposed supplementation of animal protein, in  
281 particular cow's milk, as an essential component of a child's diet to prevent undernutrition and to  
282 improve cognition (30-32).

283 The influence of the Home Observation for Measurement of the Environment (HOME)  
284 parameter as a proxy indicator for socioeconomic factors was reported in several studies among  
285 undernourished children to be correlated with the impact of undernutrition and overweight/obesity on  
286 neurodevelopment and cognition (5, 9, 22, 27, 28, 33, 34). This parameter was developed to measure  
287 responsiveness and stimulation in the home environment, which consisted of several questions,  
288 including questions about home ownership and the possession of books and toys. Among overweight  
289 children, socioeconomic status was the only influencing factor reported in the papers in this review.  
290 Those in lower socioeconomic situations had lower motor skills than their counterparts with higher  
291 socioeconomic status (23).

292 This review has several limitations. First, chronic illnesses and hospital malnutrition were  
293 excluded, although they could have a similar impact on overall developmental aspects. A second  
294 limitation is that the HOME instrument as an indicator of socioeconomic status must be adjusted to  
295 various sociocultural conditions in each group or country. In addition, the statistical significance of  
296 pooled effects of all studies combined was not calculated, as this review is of scoping nature and not a  
297 systematic review. Furthermore, the search strategy may have missed some relevant papers because of  
298 the search scope that limited peer-reviewed research papers to those published in the past decade only.  
299 To overcome this issue, reviewing reports outside the peer-reviewed literature (i.e., grey literature)  
300 should be done in the future.

301 One of the strengths of this scoping review is that it expeditiously provides comprehensive and  
302 updated scientific evidence for healthcare professionals and policymakers. The synthesized evidence  
303 may allow key stakeholders to plan and to execute necessary intervention programs for preventing and  
304 managing suboptimal growth, with a focus on achieving optimal cognitive potential in young children.  
305 In addition, this scoping review was conducted using specific methodological approaches that would  
306 allow more accuracy in literature screening with less bias. A cross-referencing of eligible studies from  
307 retrieved narrative reviews enhanced the completeness of the evidence and enabled the retrieval of  
308 information on not only the populations that experience undernutrition and overweight/obesity but also  
309 the general population that identified children with faltering growth. It also enabled the retrieval of  
310 studies from various geographical areas (low- to high-income studies) as well as studies on various  
311 developmental deficits. Emphasis had been hitherto placed on the impact of malnutrition in children on  
312 morbidity and mortality; in contrast, this review points to the quality of life that may be affected by  
313 suboptimal nutrition on neurodevelopment and cognition. From a public health perspective, prevention  
314 of childhood malnutrition must be addressed not only by economic empowerment but also through health  
315 promotion and education as well as policy.

316

317

318 **Consideration for future research and actions:**

319 1) More studies should be conducted on the impact of nutritional/behavioural interventions in  
320 overweight/obese children on neurodevelopment and cognition, especially in low-income countries, as  
321 all the currently retrieved literature came from high-income countries. Overweight/obesity in childhood  
322 is on the rise and can coexist with undernutrition within the same population, for example, as seen in  
323 India and Indonesia. Approximately 46.6 and 36.6 million children under the age of five are stunted in  
324 India and Indonesia, respectively, and more than 1 million children in the same age group are overweight  
325 in these two countries. This amounts to almost a total 1.85 million Indian and Indonesian children who  
326 are at risk of suboptimal neurodevelopment and cognitive function (2). In addition to the negative  
327 consequences of undernutrition, an increase in childhood obesity prevalence can lead to adverse long-  
328 term consequences on human capital in these countries.

329 2) Intervention studies for both undernutrition and overweight/obesity must assess the association  
330 between these nutritional statuses and cognitive neurodevelopment, as most interventions usually focus  
331 only on providing nutrients related to brain development and not for optimal growth and vice versa as  
332 also suggested by Prado et al. (6). For example, several recently published studies and systematic reviews  
333 assessed the impact of animal-based food supplementation or milk interventions on either growth among  
334 stunted children or only cognitive neurodevelopment but not on both aspects simultaneously (30, 31).

335 3) **Optimally, any program or intervention for growth monitoring in the community or hospital settings**  
336 **should engage a multidisciplinary team of health care professionals. Depending on the local conditions,**  
337 **such a team could consist of nutritionists, general practitioners, paediatricians, and/or behavioural**  
338 **specialists (35). Multidimensional approaches that can improve neuro-cognitive development in children**  
339 **include providing adequate nutrient intakes for catch-up growth among underweight or stunted children,**  
340 **interventions to reduce childhood overweight/obesity as well as socio-economic stimulations, such as**  
341 **improving educational attainment, job security, social welfare, housing and sanitation levels of the**  
342 **population. Actions taken should tackle both undernutrition and overweight/obesity concurrently – not**

343 just one or the other – to ensure successful and comprehensive outcomes in terms of childhood growth  
344 and cognitive neurodevelopment.

345

## 346 CONCLUSION

347 Under- and over-nutrition during the first 60 months of postnatal life affect the cognitive  
348 neurodevelopmental trajectories of children later in life. Weight and length/height need to be monitored  
349 even beyond 24 months of life to enable early recognition of growth retardation/deviations and to allow  
350 appropriate and timely interventions to address their negative neurodevelopmental and cognitive  
351 impacts. Given the Global Nutrition Targets for 2025 (36), intervention programs should leverage a  
352 multidimensional approach that addresses not only childhood undernutrition but also overweight/obesity  
353 and improves socioeconomic conditions. Nutrition interventions for catch-up growth among  
354 undernourished children can potentially recover neurocognitive development up to the age of 8 years,  
355 particularly in those whose nutrition status have improved. These specific, targeted and simultaneous  
356 interventions may be key to safeguarding future human capital, especially in countries with a high  
357 prevalence of stunting, overweight/obesity or both.

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368

369 **Author contributions**

370 All authors were involved in setting the concept, objective and selection criteria for the review. All  
371 authors were also involved in the selection of eligible articles based on titles and abstracts. A simple  
372 grading of controlling study biases was then conducted by five authors (AS, MYJ, PBK, LM and JG).  
373 Afterwards, LM and JG selected eligible articles based on full texts. All authors provided agreement on  
374 the final included articles. All authors participated in data extraction, synthesis and interpretation. All  
375 authors provided inputs and agreed on the final version of the manuscript.

376

377 **Competing interests**

378 Verena Tan was an employee of FrieslandCampina at the time of the manuscript's development. Leilani  
379 Muhandi and Jan Geurts were employees of FrieslandCampina at the time of the manuscript's  
380 development, submission and revision.

381

382 **Consent for publication**

383 Not applicable.

384

385 **Ethics approval and consent to participate**

386 Not applicable.

387

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Yth. Dr. Wawan,

Terlampir sy sampaikan email dari Prof. Yazid.  
Nanti sore sy lihat lagi boleh ya dok.

Salam hormat,

Leilani

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Dear Prof. JALALUDIN,

Your revised manuscript "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review" has been evaluated and, while considered positively by the reviewers, some minor revisions are needed before a final decision can be made. The comments of the reviewer(s) who looked at your manuscript are included at the foot of this letter. Please take these into account when preparing a revised version of the manuscript. You must also provide point-by-point responses to these comments during the resubmission process on ScholarOne.

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Editor

Comments to the Author:

Abstract

Line 59 – revise to ‘undernutrition and overnutrition’ (also consider replacing the term ‘overnutrition’, see below)

Line 47 – should read ‘has improved’

Lines 54-56 – ‘providing adequate socio-economic stimulations’ This terminology isn’t familiar to me, please re-word. The examples given are very broad and there’s no clear indication of how to make this happen. There are no suggestions for reducing childhood obesity, rather it is treated as a choice, this needs to be considered in the context of a consequence of low socioeconomic status too. Consideration of the pricing of ‘healthy’ food could be added.

Introduction

Line 63 – remove ‘However,’

Line 66 – Consider revising to ‘Given the potential for both ends of the malnutrition spectrum to affect neurodevelopment, it is important to consider them together.’ Also consider adding a sentence pertaining to the double burden of malnutrition (the coexistence of undernutrition along with overweight and obesity).

Line 73 and throughout – consider replacing the term ‘overnutrition’ since obesity is often linked with food insufficiency and a lack of nutrients

Line 82 - revise to ‘undernutrition and overnutrition’

Line 83 – revise to ‘review was therefore designed to extract from the published literature, to examine the impact of both the’ This sentence is also long and difficult to follow, consider re-phrasing as 2 sentences

Results and discussion

Line 146 – revise to ‘was positively’

Line 224 – revise to ‘was significantly greater’

Line 261-291 – the Discussion is largely focussed on undernutrition, perhaps line 288 would be a good place to indicate that there are similarities between undernutrition and overweight but far more research is needed to further understand the latter. This section may also benefit from description of the importance of education since this is indicated in Line 315 but not described in the text.

Line 271 – expand to state what the findings were in ref 13 since this appears to contradict the previous refs.

Line 292 – should this be a new sub-section?

Line 293 – please expand on how the HOME tool assesses socioeconomic status and any limitations beyond the need for adjustment to various sociocultural conditions. Does this mean that the adjustments are made or should be made but aren’t?

Lines 340-342 - ‘providing adequate socio-economic stimulations’ This terminology isn’t familiar to me, please re-word. Whilst it is important to highlight the factors of job insecurity, social welfare etc. I think it needs to be acknowledged just how big a task this is to overcome.

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## **RESPONSE TO EDITORS**

Kuala Lumpur, May 26, 2021

To:

**Prof. Christine Edwards**  
Editor in Chief  
Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review"

We have further revised the manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review" to address the further concerns of the editor. The changes are written in blue below, and highlighted in blue and italics in the manuscript for ease of reference. In addition, would it be possible to still opt for Open Access for this manuscript?

We hope that this version of the manuscript is satisfactory and that it can be accepted for publication soon.

We look forward to having your favourable response.

Yours sincerely,

**Prof Dr Muhammad Yazid Jalaludin**  
Corresponding author

## Abstract

Comments to the Author:

Line 59 – revise to ‘undernutrition and overnutrition’ (also consider replacing the term ‘overnutrition’, see below)

*Response to the editor:*

Line 59 is empty in the abstract. We have changed the term under- and overnutrition in Line 51 to undernutrition and overweight/obesity.

Comments to the Author:

Line 47 – should read ‘has improved’

*Response to the editor:*

The statement in Line 47 has been revised to “...has improved”

Comments to the Author:

Lines 54-56 – ‘providing adequate socio-economic stimulations’ This terminology isn’t familiar to me, please re-word. The examples given are very broad and there’s no clear indication of how to make this happen. There are no suggestions for reducing childhood obesity, rather it is treated as a choice, this needs to be considered in the context of a consequence of low socioeconomic status too. Consideration of the pricing of ‘healthy’ food could be added.

*Response to the editor:*

The statements in Line 54-56 have been revised as follows: “Multidimensional approaches with various stakeholders should address all issues simultaneously, such as improving sanitation levels, assuring parental job security and adequate social welfare, providing access to adequate nutrients for catch-up growth among underweight or stunted children and to affordable healthy foods for those who are overweight/obese and from low socio-economic status.”

Comments to the Author:

Introduction

Line 63 – remove ‘However,’

*Response to the editor:*

The word “However” has been removed from Line 63

Comments to the Author:

Line 66 – Consider revising to ‘Given the potential for both ends of the malnutrition spectrum to affect neurodevelopment, it is important to consider them together.’ Also consider adding a sentence pertaining to the double burden of malnutrition (the coexistence of undernutrition along with overweight and obesity).

*Response to the editor:*

We have revised the statement and added one more sentence on now Line 65 to 68 as follows: “World Health Organization (WHO) in 2019 reported that undernutrition and overweight/obese coexist together in more than one-third of low- and middle-income countries (Popkin et al 2020). Given the potential for both ends of the malnutrition spectrum to affect neurodevelopment, it is important to consider them together.”

Comments to the Author:

Line 73 and throughout – consider replacing the term ‘overnutrition’ since obesity is often linked with food insufficiency and a lack of nutrients

*Response to the editor:*

We have checked the document throughout and changed the term "overnutrition" to "overweight/obesity" .

Comments to the Author:

Line 82 - revise to 'undernutrition and overnutrition'

*Response to the editor:*

The term "under-nutrition from overnutrition" has been revised to "undernutrition and overweight/obesity" in now Line 84.

Comments to the Author:

Line 83 – revise to 'review was therefore designed to extract from the published literature, to examine the impact of both the' This sentence is also long and difficult to follow, consider re-phrasing as 2 sentences

*Response to the editor:*

The sentence has been rephrased into two sentences as follows: "As most existing reviews discuss undernutrition and overweight/obesity separately, this scoping review was designed to extract information on both conditions from the published literature, to study their impact as compared to normo-nourished children aged 0-60 months on cognitive neurodevelopmental aspects (cognition, behavioural, motor and emotional development) in early, mid and later life. Undernutrition is defined as stunting (height for age z-score (HAZ) < -2) and underweight (weight for age z-score (WAZ) < -2), while overweight is defined as  $2\text{ SD} < \text{WAZ} < 3\text{ SD}$  and obesity as  $\text{WAZ} \geq 3\text{ SD}$  (3)" in now Line 84-90.

Results and discussion

Comments to the Author:

Line 146 – revise to 'was positively'

*Response to the editor:*

The statement ".. were positively" has been revised to "...was positively" in now line 147

Comments to the Author:

Line 224 – revise to 'was significantly greater'

*Response to the editor:*

The statement " were significantly better" has been revised to "...was significantly greater " in now line 225

Comments to the Author:

Line 261-291 – the Discussion is largely focussed on undernutrition, perhaps line 288 would be a good place to indicate that there are similarities between undernutrition and overweight but far more research is needed to further understand the latter. This section may also benefit from description of the importance of education since this is indicated in Line 315 but not described in the text.

*Response to the editor:*

The following statements have been revised/added to incorporate the above-mention suggestions:

1. "From the literature, there seems to be similarities of influencing factors between undernutrition and overweight on cognitive neurodevelopment but far more research is needed to further understand the latter" has been added in now Line 263-266.

2. "The influence of the Home Observation for Measurement of the Environment (HOME) parameter as a proxy indicator..." has been revised to the following: "Low socioeconomic status was reported to be correlated with the impact on neurodevelopment and cognition among undernourished and overweight/obese children in several studies [6, 10, 23, 28, 29, 34, 35]. The Home Observation for Measurement of the Environment (HOME) parameter was used as a proxy indicator of the socio-economic status. It was developed to measure responsiveness and stimulation in the home environment and parental behaviours. HOME consisted of questions, among others, on homeownership and possession of books and toys. The tool needs to be validated to accommodate sociocultural differences [29, 36] which is now in Line 287-293.
3. Addition of the term education has been added on the following statement: "Particularly among undernourished children, it appeared that parents with a low level of education and nutritional knowledge" in now line 277.

Comments to the Author:

Line 271 – expand to state what the findings were in ref 13 since this appears to contradict the previous refs.

*Response to the editor:*

The statement has been further expanded to the following : "In contrast, another study found that normo-nourished boys tended to have higher intelligence score as compared to normo-nourished girls (13)" in now Line 273-275 to further explain the contradiction.

Comments to the Author:

Line 292 – should this be a new sub-section?

*Response to the editor:*

New subsection on limitations and strengths of the review has been added in now Line 294.

Comments to the Author:

Line 293 – please expand on how the HOME tool assesses socioeconomic status and any limitations beyond the need for adjustment to various sociocultural conditions. Does this mean that the adjustments are made or should be made but aren't?

*Response to the editor:*

The statement has been revised to as follows to further provide clarity:" The Home Observation for Measurement of the Environment (HOME) parameter was used as a proxy indicator of the socio-economic status. It was developed to measure responsiveness and stimulation in the home environment and parental behaviours. HOME consisted of questions, among others, on homeownership and possession of books and toys. The tool needs to be validated to accommodate sociocultural differences (Nguyen et al 2018, Bradley et al 1988) " which is now in Line 289-293.

Comments to the Author:

Lines 340-342 - 'providing adequate socio-economic stimulations' This terminology isn't familiar to me, please re-word. Whilst it is important to highlight the factors of job insecurity, social welfare etc. I think it needs to be acknowledged just how big a task this is to overcome.

*Response to the editor:*

The statement has been revised to acknowledge how big a task the issue is to overcome and to also reflect the statements in the abstract to as follows: "Multidimensional approaches involving various relevant stakeholders need to address all issues simultaneously as the root causes are quite complex. These could include improving housing and sanitation levels, assuring parental job security and adequate social welfare, improving parental education attainment and nutritional knowledge, providing access to adequate nutrient intakes for catch-up growth among underweight or stunted children as well as to affordable healthy food for those who are overweight/obese especially those in the low socio-economic category" which is now in Line 338-343.

<b>6</b>	<b>Fifth revision (ID NRR-20 0.32.R5)</b> was submitted to Journal	<b>26 May 2021</b>
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## Cover Letter: NRR-20-032.R5



Kuala Lumpur, May 26, 2021

To:  
 Prof. Christine Edwards  
 Editor in Chief  
 Nutrition Research Reviews

Re: Manuscript titled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review"

We have further revised the manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review" to address the further concerns of the editor. The changes are written in blue below, and highlighted in blue and italics in the manuscript for ease of reference. In addition, would it be possible to still opt for Open Access for this manuscript?

We hope that this version of the manuscript is satisfactory and that it can be accepted for publication soon.

We look forward to having your favourable response.

Close

<ul style="list-style-type: none"> <li>● Acceptable as received (31-May-2021)</li> <li>● In Production</li> </ul> <p><input checked="" type="checkbox"/> <a href="#">Contact Journal</a></p>	<p>032.R5</p> <p>neurodevelopmental and cognitive consequences: A Scoping review</p> <p>Submitting Author: Muhardi, Leilani</p> <p><a href="#">Cover Letter</a></p>
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<p>EA: Sage, Alison</p> <ul style="list-style-type: none"> <li>● Acceptable in principle (12-May-2021)</li> <li>● a revision has been submitted</li> </ul> <p><input checked="" type="checkbox"/> <a href="#">Contact Journal</a></p>	<p>NRR-20-032.R4</p> <p>Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review</p> <p><a href="#">View Submission</a></p> <p>Submitting Author: Muhardi, Leilani</p> <p><a href="#">Cover Letter</a></p>	<p>31-Mar-2021</p> <p>31-Mar-2021</p>
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<p>EA: Sage, Alison</p>	<p>NRR-20-032.R3</p> <p>Malnutrition in early life and its neurodevelopmental and cognitive</p>	<p>18-Dec-2020</p> <p>18-Dec</p>
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# NUTRITION RESEARCH REVIEWS



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## **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review**

Journal:	<i>Nutrition Research Reviews</i>
Manuscript ID	NRR-20-032.R5
Manuscript Type:	Review
Date Submitted by the Author:	n/a
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Keywords:	underweight, stunting, obesity, cognition, neurodevelopment

**SCHOLARONE™**  
Manuscripts

1 **Malnutrition in early life and its neurodevelopmental and cognitive consequences: A**  
2 **scoping review**

3  
4 *Running title: Malnutrition and cognitive neurodevelopmental consequences*

5  
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30

31 249 words in the Abstract, 3891 words in the Main Text (excluding tables, figures and references), 4  
32 Tables, 2 Figures, 44 References

33

34 **Abstract**

35 The negative impact of stunting and severe underweight on cognitive neurodevelopment of children is  
36 well-documented; however, the effect of overweight/obesity is still unclear. The 2018 Global Nutrition  
37 Report reported that stunting and overweight concurrently affect 189 million children worldwide. As  
38 existing reviews separately discuss undernutrition from **overweight/obesity**, this scoping review aims to  
39 document the impact of mild/moderate and severe underweight, stunting, and overweight/obesity among  
40 children aged 0-60 months on their cognitive neurodevelopmental trajectories. Twenty-six articles were  
41 analysed to extract significant information from literature retrieved from PubMed and Cochrane  
42 databases published from 1 January 2009 to 31 October 2019. Length gain is associated with cognitive  
43 neurodevelopment in normo-nourished and stunted children aged under 24 months. Among stunted  
44 children, it seems that cognitive and neurodevelopmental deficits can potentially be recovered before 8  
45 years old, particularly in those whose nutritional status **has improved**. The impact of overweight/obesity  
46 on cognitive neurodevelopment appears to be limited to attention, gross motor skills and executive  
47 control. Parental education level, birth weight/length, breastfeeding duration, and sanitation level are  
48 some identifiable factors that modify the impact of undernutrition and overweight/obesity on cognitive  
49 and neurodevelopment. In conclusion, **underweight, stunting and overweight/obesity** have a significant  
50 impact on cognitive neurodevelopment. **Multidimensional approaches with various stakeholders should**  
51 **address all issues simultaneously, such as improving sanitation levels, assuring parental job security**  
52 **and adequate social welfare, providing access to adequate nutrients for catch-up growth among**  
53 **underweight or stunted children and to affordable healthy foods for those who are overweight/obese and**  
54 **from low socio-economic status.**

55

56 **Keywords (max 5):** underweight, stunting, obesity, cognition, neurodevelopment

57

## 58 INTRODUCTION

59 Malnutrition, including wasting or low weight-for-height, stunting or low height-for-age, and  
60 underweight or low weight-for-age, micronutrient deficiencies, and overweight/obesity, are public  
61 health problems that can affect children aged less than 60 months. While the number of stunted children  
62 worldwide has decreased in recent years, the number of overweight children has increased, and the total  
63 number of children affected by stunting and overweight is approximately 189 million [1]. *The World  
64 Health Organization (WHO) in 2019 reported that undernutrition and overweight/obesity coexist  
65 together in more than one-third of low- and middle-income countries [2]. Given the potential for both  
66 ends of the malnutrition spectrum to affect neurodevelopment, it is important to consider them together.*

67 Malnutrition leads to economic, social, and health issues for families, at the community and  
68 national level [3]. More importantly, severe undernutrition – defined as severe stunting (below HAZ  
69 (height-for-age Z score) minus three standard deviations (-3 SD)) and severe underweight (below WAZ  
70 (weight-for-age Z score) minus three standard deviations (-3 SD))[4] – impair children’s development  
71 in the short (delayed cognitive, behavioural and motor development), medium (lower IQ and  
72 school/academic achievement) and long term (human capital), mostly in low and middle-income  
73 countries [5-8]. It is currently unclear whether overweight and *obesity* impacts neurodevelopment and  
74 cognition or, vice versa, whether neurodevelopmental deficits impact overweight and obesity, or both.

75 Despite the reduction in stunting over the last decade [1], there still exists a need to better  
76 understand if there are opportunities to mitigate the negative, long-term impact of stunting on human  
77 capital development. It is also currently unclear whether interventions can be targeted at specific aspects  
78 of neurodevelopment and cognition, taking into consideration the timing of malnutrition with the timing  
79 of cognitive neurodevelopment in early childhood. More information is also needed to understand the  
80 aspects of neurodevelopment and cognition that are affected among overweight/obese children in order  
81 to design specific interventions.

82 *As most existing reviews discuss undernutrition and overweight/obesity separately, this scoping  
83 review was designed to extract information on both conditions from the published literature, to study*

84 *their impact as compared to normo-nourished children aged 0-60 months on cognitive*  
85 *neurodevelopmental aspects (cognition, behavioural, motor and emotional development) in early, mid*  
86 *and later life. Undernutrition is defined as stunting (height for age z-score (HAZ) < -2) and underweight*  
87 *(weight for age z-score (WAZ) < -2), while overweight is defined as  $2 SD > WAZ < 3 SD$  and obesity as*  
88  *$WAZ \geq 3 SD$  (3). This combined approach will conceivably allow for a more holistic view of the*  
89 *situation commonly found in many countries across the world.*

90

## 91 **METHODS**

92 This review followed the consistent approach of a scoping review to compile findings from studies with  
93 different designs and methodologies to answer the stated critical research questions [9]. The research  
94 questions are as follows: (i) Which developmental aspects are affected by *obesity/overweight* and  
95 undernutrition during the first 60 months of life? (ii) What other factors can modify these outcomes?  
96 (iii) Which factors can mitigate the impact of *obesity/overweight* and undernutrition on  
97 neurodevelopment and cognition? (iv) Is the effect on cognitive neurodevelopment partly or fully  
98 reversible? and (v) What are the implications for intervention strategies?

99 Literature published from 1 January 2009 to 31 October 2019 in the PubMed and Cochrane  
100 databases was retrieved using formulated search terms. The title and abstract of each article retrieved  
101 were screened based on the inclusion criteria by all authors. A simple grading of controlling study biases  
102 using JADAD criteria for randomized controlled (RCT) studies, Newcastle Ottawa Scale for cohort  
103 studies, and National Heart, Lung and Blood Institute (NHLBI) criteria for observational cross-sectional  
104 studies were then conducted by five authors (AS, MYJ, PBK, LM and JG) to select studies for further  
105 qualitative analyses (Tables 1 and 2). References of relevant narrative reviews (cross-references) were  
106 also examined to search for further studies that met the inclusion criteria. JG and LM then independently  
107 extracted data from the identified full-text articles. Data extraction tables incorporated important  
108 information from eligible full texts to allow the extraction of significant information for the review.

109

## 110 RESULTS AND DISCUSSION

### 111 Descriptive summary of included studies

112 From the 91 articles originally identified through the search strategy, 26 full-text articles were selected  
113 after a review of cross-references in eligible narrative reviews. The full text was used for information  
114 extraction and grading for quality assessment (Figure 1).

115 Information was categorised based on the type of study and nutritional status of the children  
116 (Table 1 and Table 2) as well as by factors influencing the impact of nutritional status on cognitive  
117 neurodevelopment (Table 3). Information was extracted from 14 observational studies (undernutrition  
118 (n=8 articles), normo-nutrition (n=5 articles) and **overweight/obesity** (n=1 article), 4 intervention trials  
119 (undernutrition (n=2 articles) and normo-nutrition (n=2 articles)), 4 systematic reviews (undernutrition  
120 (n=1 article), normo-nutrition (n=2 articles) and **overweight/obesity** (n=2 articles)) and 4 meta-analyses  
121 (all on undernutrition). All publications on under- and normo-nourished children were conducted in low-  
122 to middle-income countries, while all articles about **overweight/obese** children reported data from high-  
123 income countries. No intervention study was retrieved on overweight/obese children. Approximately  
124 85% (n=22) of the retrieved literature had good quality in controlling bias.

125 To the best of our knowledge, this review complements previous meta-analyses and systematic  
126 reviews [6-8] and includes a wider spectrum of suboptimal nutritional status (ranging from  
127 mild/moderate to severe underweight and stunting to overweight/obesity) during the first 60 months of  
128 life on various neurodevelopment aspects (cognition, motor development, temperament, socioeconomic  
129 status, and academic achievement) that manifest from infancy through school-age to adulthood (Figure  
130 2). This review also covers observational longitudinal cohorts and interventional studies with nutrition-  
131 and non-nutrition-related interventions on the outcomes of interest.

132

133

134

135 **The importance of monitoring weight, length and head circumference during the first 24 months**  
136 **of age**

137 From the reviewed studies, length-for-age z-scores (LAZ) and height-for-age z-scores (HAZ)  
138 (anthropometric measures of stunting in children) were associated with various elements of cognitive  
139 functioning, such as attention span, time to proper walking, mathematics and language abilities in early  
140 life, and income and choice of partner/age at marriage in later life (Table 1). It was reported that healthy  
141 infants in the highest quartile of neonatal weight-, length-, and head circumference-gain during the first  
142 4 weeks of life had higher IQ scores at 6 years of age than those in the lowest quartile [10].

143 From a longitudinal study in the Philippines, regardless of HAZ categories at 6 months (defined  
144 as moderate/severe stunting ( $HAZ < -2$ ), mild stunting ( $-2 \leq HAZ < -1$ ), at risk of stunting ( $-1 < HAZ <$   
145  $0$ ) or normal height ( $HAZ \geq 0$ )), more gain (or less loss) in HAZ after the age of 6 months was positively  
146 associated with cognitive function at 11 years of age. In addition, changes in HAZ from 6 to 24 months  
147 and changes in HAZ from 24 months to 11 years were also positively associated with cognitive ability  
148 at 11 years in the same study [11]. These outcomes are similar to the results among children in  
149 Bangladesh. In this study, cognitive impairment was associated with poverty, birth condition and  
150 postnatal growth that started at 7 months of age and worsened up to 64 months when it became even  
151 more substantial [12]. The impact of the timing of stunting is still unclear. One study reported that  
152 stunting in the second year of life is more harmful than stunting before 12 months of age [13]. Another  
153 study reported that higher HAZ at 4-6 years of age among healthy Malaysian children significantly  
154 contributed to higher cognitive function after controlling for socio-demographic background, parent's  
155 nutrition knowledge and dinner consumption ( $DR2 = 0.009$ ,  $DF = 18.605$ ,  $p < 0.001$ ) [14].

156 Evidence for the impact of underweight and stunting on the development of emotional skills is  
157 largely variable across the identified studies. Two meta-analyses that described data from lower- and  
158 middle-income countries showed the limited influence of undernutrition on a child's attachment,  
159 emotionality, social competence and temperament [6, 8]. However, in a study among Bangladeshi  
160 children aged 6-24 months comparing undernourished ( $n=212$ ) and better-nourished ( $n=108$ ), it was



161 reported that severely underweight children (weight-for-age z-score, WAZ < -2) were less sociable, less  
162 attentive, more fearful and had more negative emotional traits than normo-nourished children. The effect  
163 size of these temperament **differences**, which were assessed using validated interviewer-administered  
164 questionnaire to parents, were small to moderate [15]. There is evidence, therefore, that underweight and  
165 stunting impact social skill development. Low HAZ and WAZ correlated strongly with children having  
166 less schooling or needing a longer time to complete schooling [16], and in later life, with lower income  
167 and living in a less conducive environment, such as having a higher number of pregnancies and having  
168 the first child at a younger age [17].

169

### 170 **Improvements in linear growth and potential window of opportunity for neurodevelopment and** 171 **cognitive abilities recovery**

172 This review further strengthens the importance of the first 1000 days of life as a window of opportunity  
173 for rescuing neurocognitive deficits. It was reported that HAZ velocity between 6 and 24 months among  
174 undernourished children is positively associated with cognitive function [11] and that every 1-unit  
175 increase in HAZ before the age of 24 months is associated with a higher increment in motor,  
176 communication and cognitive ability scores at 26 to 80 months of age compared to a 1 unit increase in  
177 HAZ after 24 months of age [6, 16].

178 Data from the Young Lives cohort in Ethiopia, India, Peru, Cambodia, and Vietnam indicated  
179 that children who were in the recovered group (stunted at 12 months of age but not stunted at 8 years of  
180 age) had better academic achievement (maths scores, receptive vocabulary scores, and reading  
181 comprehension scores) than those who stayed persistently stunted [16]. However, their academic  
182 achievement was still lower than those who had never been stunted. This finding is consistent with the  
183 finding from another cohort in Malawi, which reported that those who had recovered from stunting had  
184 better academic achievements at 11 years of age than those who were persistently stunted from age 4 to  
185 8 years [18]. Based on the above, it appears likely that the period in which neurocognitive deficits can  
186 recover following appropriate interventions goes beyond the age of 2 years, up until 8 years of age,

187 which is in line with prefrontal cortex development and ongoing synaptogenesis at that age [5].  
188 Interestingly, another study reported that children who were stunted at 24 months of age and experienced  
189 catch-up growth often did worse on cognitive tests at 4-5 years of age than children who were never  
190 stunted and did almost as poorly as children who had remained stunted [19]. This finding appears to  
191 contradict previously stated findings from the Young Lives and Malawi cohorts. It is important to note,  
192 however, that the exact definition of 'catch-up' plays a critical role in this observation. Recently, five  
193 definitions were formulated for 'catch-up growth', ranging from lenient to strict (I: increase in HAZ, II:  
194 recovery from stunting (HAZ at 5 years  $>-2$ ), III: increase in height-for-age difference, IV: recovery  
195 from stunting and increase in height-for-age difference, and V: recovery from stunting with a stricter  
196 cut-off point, where HAZ falls within 'normal' range (HAZ at 5 years  $>-1$ ) [20]. The observation  
197 reported above is based on definitions I-IV of 'catch-up'. Thus, the term 'catch-up' should be carefully  
198 defined when determining the optimal goal for catch-up growth to recover neurodevelopment and,  
199 consequently, cognitive ability in later life.

200

### 201 **The importance of interventions in improving cognitive outcomes among undernourished children**

202 Seven publications assessed the effectiveness of intervention studies in improving cognitive outcomes  
203 among undernourished children. The publications covered 3 randomized controlled trials, 2 systematic  
204 reviews and 2 meta-analyses. The overall quality of these studies was judged as good when considering  
205 the risk for bias (Table 2).

206 Stunted children with high levels of plasma homocysteine and those who were younger than 24  
207 months at the end of the follow-up period showed the largest improvement in gross motor function and  
208 problem-solving skills after being supplemented with vitamin B12 on a daily basis [21]. In contrast, the  
209 effect of the vitamin/nutrition intervention on recovering or maintaining normal neurodevelopment and  
210 cognitive deficits in normo-nourished children remained inconclusive [7, 21, 22]. No benefits in growth  
211 or cognitive performance were reported among 422 healthy children aged 12 to 24 months receiving  
212 daily multi-micronutrient supplementation (iron and zinc) [22]. This finding is in contrast with an

213 intervention trial in which multiple micronutrients were supplemented (vitamins B12, A, C, folic acid  
214 and iron), with and without responsive stimulation, for approximately 20 months among 1489 mother-  
215 child pairs in Pakistan. In this study, children who were exposed to the enhanced nutrition intervention  
216 had, regardless of their nutrition status, significantly higher developmental scores (cognitive, language,  
217 and social-emotional scales) at 12 months than the control group [23]. Another group of children who  
218 received responsive stimulation had significantly higher developmental scores on the cognitive,  
219 language, and motor scales at 12 and 24 months of age and on the social emotional scale at 12 months  
220 of age than the control group. In comparison, the treatment effect on cognition, language and motor  
221 development at 24 months was moderate-to-large for responsive simulation and was low to moderate  
222 for the enhanced nutrition group [23]. This study also found that linear growth in children exposed to  
223 enhanced nutrition was significantly **greater** at 6 and 18 months compared to those not exposed to  
224 enhanced nutrition (22).

225 A recent systematic review and meta-analysis that assessed the impact of nutrition with or  
226 without stimulation interventions concluded that parent-led responsive learning, more than nutrition  
227 supplementation, appeared to have a **stronger** influence on the neurodevelopment of children aged 0-60  
228 months [7]. This systematic review, which was based on 75 retrieved studies from various databases,  
229 reported that the pooled effect of these supplementations is one-fourth smaller than the pooled effect  
230 size of responsive care and learning opportunities on cognitive, language, and motor scales. The review  
231 also suggested that postnatal multiple nutrient supplementation can improve linear growth in children  
232 and, to a smaller extent, cognitive development and socio-temperament, while interventions promoting  
233 responsive care and learning opportunities affect only cognitive development but not linear growth [7].

234

### 235 **The impact of overweight/obesity on neurodevelopment and cognition**

236 Only one cross-sectional study and two systematic reviews that were retrieved described the impact of  
237 overweight/obesity on cognitive neurodevelopmental aspects [24-26] (Table 1). All studies seemed to  
238 point towards a more limited impact of overweight/obesity on aspects of neurodevelopment and

239 cognition in the studied affluent populations in contrast with those describing the impact of  
240 undernutrition. All retrieved literature demonstrated that attention, executive control (inhibitory control,  
241 working memory, reward sensitivity, and impulsivity) and gross motor skills were the most affected  
242 areas.

243 A study among overweight Italian children showed poorer gross motor skills in overweight  
244 children than their normal-weight peers [24], while other systematic reviews reported poorer executive  
245 control and more difficulty with inhibition in overweight children than in healthy weight children [25,  
246 26]. There is a suggestion of directionality in the association between obesity and executive function.  
247 Children with lower executive function are speculated to have lower self-regulation of energy intake and  
248 decreased participation in physical activity, which leads to or potentiates overweight or obesity. It was  
249 also reported that low executive function stimulates excess adiposity, leading to exacerbating decrements  
250 in executive function in childhood [27]. On the other hand, various studies have shown that child obesity  
251 or early life adiposity reduces executive function via several biological mechanisms. Proinflammatory  
252 cytokines produced by adipose tissue can stimulate inflammatory pathways in all age categories, leading  
253 to cognitive development deficits, and dysregulation of appetite-regulating hormones could further harm  
254 cognitive skills [26]. Although there is limited affected cognitive neurodevelopmental areas reported in  
255 these affluent populations, the effect may be more diverse and pronounced in less-affluent societies. In  
256 conclusion, poor gross motor skills, which are correlated with less physical activity [25] and reduced  
257 attention span [25, 26], should be taken into consideration when designing intervention programs for  
258 these overweight/obese children.

259

## 260 **Factors influencing the impact of suboptimal growth on neurodevelopment and cognition**

261 *From the literature, there seems to be similarities in influencing factors between undernutrition and*  
262 *overweight/obesity on cognitive neurodevelopment but far more research is needed to further*  
263 *understand the latter.* These factors can be classified into maternal and paternal factors, child  
264 characteristics and health conditions, and socioeconomic factors (Table 3).

265 Several pregnancy-related maternal parameters, such as maternal weight gain and smoking, have  
266 been consistently reported to increase the impact of suboptimal growth on cognitive neurodevelopment  
267 in addition to infant condition at birth, such as low birth weight and short length at birth, suggesting the  
268 importance of prenatal nutrition and maternal health for later life [12, 15, 19, 28, 29].

269 The influence of sex on suboptimal growth and cognitive neurodevelopment appeared  
270 conflicting in the literature; normo-nourished and undernourished girls had slightly higher intelligence  
271 scores [10], social maturity [19], and manageability [15] than boys with the same nutritional status. *In*  
272 *contrast, another study found that normo-nourished boys tended to have higher intelligence score as*  
273 *compared to normo-nourished girls [14].*

274 Particularly among undernourished children, it appeared that parents with a low level of  
275 *education and nutritional knowledge*, those who perceived less responsibility in the parenting task, or  
276 those who were less restrictive towards access to unhealthy foods, had children who experienced  
277 suboptimal growth with resultant impaired cognitive development [6, 14].

278 Diet quality was demonstrated to be a positive predictor of improved cognitive outcomes in these  
279 children [6, 14]. For instance, food fortified with calcium, iron, zinc, vitamin B2, and protein was  
280 associated with improved cognitive outcomes because of the probable role of these nutrients in early  
281 brain development [7, 23]. In contrast, a lack of dietary protein may delay or inhibit brain and cognitive  
282 development [6, 30]. On that note, recent evidence proposed supplementation of animal protein, in  
283 particular cow's milk, as an essential component of a child's diet to prevent undernutrition and to  
284 improve cognition [31-33].

285 *Low socioeconomic status was reported to be correlated with the impact on neurodevelopment*  
286 *and cognition among undernourished and overweight/obese children in several studies [6, 10, 23, 28,*  
287 *29, 34, 35]. The Home Observation for Measurement of the Environment (HOME) parameter was used*  
288 *as a proxy indicator of the socio-economic status. It was developed to measure responsiveness and*  
289 *stimulation in the home environment and parental behaviours. HOME consisted of questions, among*

290 *others, on homeownership and possession of books and toys. The tool needs to be validated to*  
291 *accommodate sociocultural differences [29, 36].*

### 292 ***Limitations and strengths of the review***

293 First, chronic illnesses and hospital malnutrition were excluded, although they could have a similar  
294 impact on overall developmental aspects. A second limitation is that the HOME instrument as an  
295 indicator of socioeconomic status must be adjusted to various sociocultural conditions in each group or  
296 country. In addition, the statistical significance of pooled effects of all studies combined was not  
297 calculated, as this review is of scoping nature and not a systematic review. Furthermore, the search  
298 strategy may have missed some relevant papers because of the search scope that limited peer-reviewed  
299 research papers to those published in the past decade only. To overcome this issue, reviewing reports  
300 outside the peer-reviewed literature (i.e., grey literature) should be done in the future.

301 One of the strengths of this scoping review is that it expeditiously provides comprehensive and  
302 updated scientific evidence for healthcare professionals and policymakers. The synthesized evidence  
303 may allow key stakeholders to plan and to execute necessary intervention programs for preventing and  
304 managing suboptimal growth, with a focus on achieving optimal cognitive potential in young children.  
305 In addition, this scoping review was conducted using specific methodological approaches that would  
306 allow more accuracy in literature screening with less bias. A cross-referencing of eligible studies from  
307 retrieved narrative reviews enhanced the completeness of the evidence and enabled the retrieval of  
308 information on not only the populations that experience undernutrition and overweight/obesity but also  
309 the general population that identified children with faltering growth. It also enabled the retrieval of  
310 studies from various geographical areas (low- to high-income studies) as well as studies on various  
311 developmental deficits. Emphasis had been hitherto placed on the impact of malnutrition in children on  
312 morbidity and mortality; in contrast, this review points to the quality of life that may be affected by  
313 suboptimal nutrition on neurodevelopment and cognition. From a public health perspective, prevention  
314 of childhood malnutrition must be addressed not only by economic empowerment but also through health  
315 promotion and education as well as policy.

316 **Consideration for future research and actions:**

317 1) More studies should be conducted on the impact of nutritional/behavioural interventions in  
318 overweight/obese children on neurodevelopment and cognition, especially in low-income countries, as  
319 the currently retrieved literature all came from high-income countries. Overweight/obesity in childhood  
320 is on the rise and can coexist with undernutrition within the same population, for example, as seen in  
321 India and Indonesia. Approximately 46.6 and 36.6 million children under the age of five are stunted in  
322 India and Indonesia, respectively, and more than 1 million children in the same age group are overweight  
323 in these two countries. This amounts to almost a total 1.85 million Indian and Indonesian children who  
324 are at risk of suboptimal neurodevelopment and cognitive function [3]. In addition to the negative  
325 consequences of undernutrition, an increase in childhood obesity prevalence can lead to adverse long-  
326 term consequences on human capital in these countries.

327 2) Intervention studies for both undernutrition and overweight/obesity must assess the association  
328 between these nutritional statuses and cognitive neurodevelopment, as most interventions usually focus  
329 only on providing nutrients related to brain development and not for optimal growth and vice versa as  
330 also suggested by Prado et al. [7]. For example, several recently published studies and systematic reviews  
331 assessed the impact of animal-based food supplementation or milk interventions on either growth among  
332 stunted children or only cognitive neurodevelopment but not on both aspects simultaneously [31, 32].

333 3) Optimally, any program or intervention for growth monitoring in the community or hospital settings  
334 should engage a multidisciplinary team of health care professionals. Depending on the local conditions,  
335 such a team could consist of nutritionists, general practitioners, paediatricians, and/or behavioural  
336 specialists [37]. *Multidimensional approaches involving various relevant stakeholders need to address  
337 all issues simultaneously as the root causes are quite complex. These could include improving housing  
338 and sanitation levels, assuring parental job security and adequate social welfare, improving parental  
339 education attainment and nutritional knowledge, providing access to adequate nutrient intakes for  
340 catch-up growth among underweight or stunted children as well as to affordable healthy food for those  
341 who are overweight/obese especially those in the low socio-economic category.* Actions taken should

342 tackle both undernutrition and overweight/obesity concurrently – not just one or the other – to ensure  
343 successful and comprehensive outcomes in terms of childhood growth and cognitive neurodevelopment.

344

## 345 CONCLUSION

346 *Undernutrition and overweight/obesity* during the first 60 months of postnatal life affect the cognitive  
347 neurodevelopmental trajectories of children later in life. Weight and length/height need to be monitored  
348 even beyond 24 months of life to enable early recognition of growth retardation/deviations and to allow  
349 appropriate and timely interventions to address their negative neurodevelopmental and cognitive  
350 impacts. Given the Global Nutrition Targets for 2025 [38], intervention programs should leverage a  
351 multidimensional approaches that address not only childhood undernutrition but also overweight/obesity  
352 and improves socioeconomic conditions. Nutrition interventions for catch-up growth among  
353 undernourished children can potentially recover neurocognitive development up to the age of 8 years,  
354 particularly in those whose nutrition status have improved. These specific, targeted and simultaneous  
355 interventions may be key to safeguarding future human capital, especially in countries with a high  
356 prevalence of stunting, overweight/obesity or both.

357



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369 **Author contributions**

370 All authors were involved in setting the concept, objective and selection criteria for the review. All  
371 authors were also involved in the selection of eligible articles based on titles and abstracts. A simple  
372 grading of controlling study biases was then conducted by five authors (AS, MYJ, PBK, LM and JG).  
373 Afterwards, LM and JG selected eligible articles based on full texts. All authors provided agreement on  
374 the final included articles. All authors participated in data extraction, synthesis and interpretation. All  
375 authors provided inputs and agreed on the final version of the manuscript.

376

377 **Competing interests**

378 Verena Tan was an employee of FrieslandCampina at the time of the manuscript's development. Leilani  
379 Muhandi and Jan Geurts were employees of FrieslandCampina at the time of the manuscript's  
380 development, submission and revision.

381

382 **Consent for publication**

383 Not applicable.

384

385 **Ethics approval and consent to participate**

386 Not applicable.

387

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389

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For Peer Review

Table 1. Key findings from retrieved observational studies on growth and the impact on neurodevelopment and cognition

	<b>First author, year of publication</b>	<b>Country of study</b>	<b>Sample size and age at enrolment</b>	<b>Type of study (longitudinal cohort, cross-sectional, systematic review, or meta-analysis)</b>	<b>Nutritional status of the study population</b>	<b>Developmental tools and age at assessment</b>	<b>Affected cognitive and neurodevelopmental aspects by suboptimal growth</b>	<b>Study quality</b>
1.	Sudfeld CR, 2015 [6]	Low- and middle-income countries	Children aged <12 years (children aged >5-12 years were excluded from the present review)	Systematic review from longitudinal cohorts and surveys	General population	During the first 60 months of life: <ul style="list-style-type: none"> <li>• Cognitive</li> <li>• Motor</li> <li>• Socio-emotional</li> </ul>	<ul style="list-style-type: none"> <li>• General cognition</li> <li>• Odds of walking</li> <li>• Motor score</li> <li>• Social skills</li> </ul>	Good
2.	Hamadani JD, 2014 [12]	Bangladesh	2,853 singletons	Longitudinal cohort sub sample from birth to 64 months as part of a larger maternal interventional study	General population	<ul style="list-style-type: none"> <li>• Children's problem-solving ability measured using two 1-step means-end tests "Support" and "Cover" at 7 months</li> <li>• Mental development index (MDI) measured using the Bayley Scales of Infant Development Revised version at 18 months</li> <li>• Children's IQ measured using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at 64 months.</li> </ul>	IQ score	Good
3.	Camargo-Figuera FA, 2014 [10]	Brazil	4,231 singletons	Longitudinal cohort from birth to 6 years of age	General population	<ul style="list-style-type: none"> <li>• WISC-III at 72 months</li> </ul>	IQ score	Good
4.	Smithers LG, 2013 [39]	Belarus	16,692 children	Longitudinal cohort from birth to 1 year	General population	At 6.5 years:	IQ score	Good

	<b>First author, year of publication</b>	<b>Country of study</b>	<b>Sample size and age at enrolment</b>	<b>Type of study (longitudinal cohort, cross-sectional, systematic review, or meta-analysis)</b>	<b>Nutritional status of the study population</b>	<b>Developmental tools and age at assessment</b>	<b>Affected cognitive and neurodevelopmental aspects by suboptimal growth</b>	<b>Study quality</b>
				from a subsample from PROBIT Trial		<ul style="list-style-type: none"> <li>• -Cognitive ability using Wechsler Abbreviated Scales of Intelligence</li> <li>• Child behaviour using the Strengths and Difficulties Questionnaire</li> </ul>		
5.	Aubuchon-Endsley NL, 2011 [40]	Ethiopia	108 infants	Longitudinal cohort from 6 months to 9 months of age	Healthy population	<ul style="list-style-type: none"> <li>• Temperament and attention assessed using modified version of the Laboratory Temperament Assessment Battery (Lab-TAB) and MOFPTask at 6 and 9 months</li> </ul>	<ul style="list-style-type: none"> <li>• Duration and number of inattention periods</li> <li>• Mean of looking time</li> <li>• Total duration of looking</li> </ul>	Poor
6.	Mohd Nasir MT, 2012 [14]	Malaysia	1,933 pre-schoolers aged 4 to 6 years	Cross-sectional study	Healthy population	<ul style="list-style-type: none"> <li>• Raven's Coloured Progressive Matrices at 48 to 72 months</li> </ul>	Cognitive performance	Good
7	Miller AC, 2015 [8]	Low-middle income countries	58,513 children aged 36 to 59 months	Meta-analysis from 15 Multiple Indicator Cluster Surveys results (MICS-4)	Undernutrition	Early Childhood Development Index scores for children aged 36-59 months old	<ul style="list-style-type: none"> <li>• Overall development and Learning capabilities</li> <li>• Literacy skills</li> <li>• Numerical skills</li> </ul>	Good
8	Nguyen PH, 2018 [29]	Vietnam	1,458 children	Cohort study from offspring of the first phase study (a randomized controlled trial of pre-conceptional micronutrient supplementation)	General population	Bayley Scales of Infant Development-III at 12 and 24 months	<ul style="list-style-type: none"> <li>• Cognitive development</li> <li>• Language development</li> <li>• Motor development</li> </ul>	Good

	First author, year of publication	Country of study	Sample size and age at enrolment	Type of study (longitudinal cohort, cross-sectional, systematic review, or meta-analysis)	Nutritional status of the study population	Developmental tools and age at assessment	Affected cognitive and neurodevelopmental aspects by suboptimal growth	Study quality
				(PRECONCEPT study) from birth until 2 years of age				
9	Casale D, 2014 [19]	South Africa	3,273 children	Cohort study from the Birth to Twenty cohort study from 2 years to 5 years of age	Stunted	<ul style="list-style-type: none"> <li>At 48 months: social skills competence or 'daily living skills' assessed using VSMS</li> <li>At 60 months: cognitive functioning assessed using R-DPDQ</li> </ul>	<ul style="list-style-type: none"> <li>Cognitive functioning</li> <li>Social skills competence</li> <li>Fine motor skills</li> </ul>	Good
10	Crookston BT, 2013 [16]	<ul style="list-style-type: none"> <li>Ethiopia</li> <li>India</li> <li>Peru</li> <li>Vietnam</li> </ul>	8,062 infants	Cohort of multi-country studies from 1 year to 8 years of age	Stunted and healthy children	At 8 years: <ul style="list-style-type: none"> <li>Schooling average</li> <li>Mathematics test</li> <li>Reading comprehension/verbal achievement: Early Grade Reading Assessment</li> <li>Receptive vocabulary: Peabody Picture Vocabulary Test (PPVT)</li> </ul>	<ul style="list-style-type: none"> <li>Overall schooling</li> <li>Receptive vocabulary</li> <li>Mathematics score</li> </ul>	Good
11	Cheung YB, 2010 [11]	Philippines	1,516 infants	Cohort study from the "Cebu Longitudinal Health and Nutrition Survey" from 6 - 24 months old followed up at age 11 years	Stunted and Healthy children	At 11 years <ul style="list-style-type: none"> <li>Non-verbal intelligence test</li> <li>English reading comprehension test</li> <li>Mathematics test</li> </ul>	Cognitive ability	Good
12	Hoddinott J, 2013 [17]	Guatemala	1,338 adults	Retrospective cohort aged 25 to 42 years who were studied as	Healthy adults	<ul style="list-style-type: none"> <li>Age of starting and leaving school</li> <li>Highest grade attained</li> </ul>	<ul style="list-style-type: none"> <li>Overall schooling</li> <li>Reading scores</li> <li>Non-verbal cognitive scores</li> </ul>	Good

	First author, year of publication	Country of study	Sample size and age at enrolment	Type of study (longitudinal cohort, cross-sectional, systematic review, or meta-analysis)	Nutritional status of the study population	Developmental tools and age at assessment	Affected cognitive and neurodevelopmental aspects by suboptimal growth	Study quality
				24-month infants in 1969–1977		<ul style="list-style-type: none"> <li>• Inter-American Reading Series (Serie Interamericana) vocabulary (Level 3)</li> <li>• Reading comprehension (Level 2) test modules</li> <li>• Nonverbal cognitive ability: assessed using Raven's Standard Progressive Matrices test</li> </ul>	<ul style="list-style-type: none"> <li>• Characteristics of marriage partners; older age at first birth; a smaller number of pregnancies and births</li> <li>• Household per capita income</li> <li>• Adult health</li> </ul>	
13	Waber DP, 2014 [41]	Barbados	77 adults	Retrospective cohort study from an Intervention program with history of infantile malnutrition in the first year of life and healthy controls born between 1967 and 1972	Grade II-III protein energy malnutrition and healthy population	<ul style="list-style-type: none"> <li>• Adult IQ: Wechsler Abbreviated Scale of Intelligence – Vocabulary and Matrix Reasoning subtests</li> <li>• Academic Achievement: Wide Range Achievement Test-III – Reading, Spelling, and Calculation subtests</li> </ul>	IQ score	Good
14	Baker-Henningham H, 2009 [15]	Bangladesh	212 undernourished children and 108 normo-nourished controls	Cross-sectional study of children aged 6 -24 months	Underweight (weight for age z-score <-2) and normo-nourished children	<p>At 6 to 24 months:</p> <ul style="list-style-type: none"> <li>• Baseline assessment using revised version of the Bayley Scales of Infant Development</li> <li>• Temperament assessed through an interviewer-administered maternal questionnaire</li> </ul>	<ul style="list-style-type: none"> <li>• Social skills</li> <li>• Attention</li> <li>• Fear</li> <li>• Negative emotion</li> </ul>	Good



	<b>First author, year of publication</b>	<b>Country of study</b>	<b>Sample size and age at enrolment</b>	<b>Type of study (longitudinal cohort, cross-sectional, systematic review, or meta-analysis)</b>	<b>Nutritional status of the study population</b>	<b>Developmental tools and age at assessment</b>	<b>Affected cognitive and neurodevelopmental aspects by suboptimal growth</b>	<b>Study quality</b>
						consisting of 7 subscales.		
15	Sudfeld CR, 2015 [42]	Tanzania	1,036 infants aged 18 to 36 months	Cross-sectional study on existing data from a cohort of	General population	Bayley Scales of Infant Development III at 18 to 36 months: <ul style="list-style-type: none"> <li>• Cognition</li> <li>• Communication (comprising expressive and receptive communication skills)</li> <li>• Motor (comprising fine and gross motor skills)</li> </ul>	<ul style="list-style-type: none"> <li>• Cognitive development</li> <li>• Communication skills</li> <li>• Motor development</li> </ul>	Good
16	Liang J, 2014 [25]	Systematic review of 67 studies in high-income countries	Pre-school children (+ adolescents aged 18 years and under, excluded from the present review)	Systematic review from observational cross-sectional and longitudinal studies	Obese children	<ul style="list-style-type: none"> <li>• Self-regulation (laboratory tasks)</li> <li>• Motor skills (Zurich Neuromotor Assessment Test; Motor Test Battery)</li> <li>• Verbal ability (Peabody Picture Vocabulary Test)</li> <li>• Concentration (Frankfurter Test für Fünfjährige—Konzentration)</li> <li>• Intelligence (Culture Fair Test)</li> <li>• Locomotor skills, object-control skills (Test of Gross Motor Development)</li> <li>• Delay of gratification (Mischel and</li> </ul>	<ul style="list-style-type: none"> <li>• General intellectual</li> <li>• Executive control</li> <li>• Delayed gratification</li> <li>• Inhibition strategy</li> <li>• Learning and memory</li> </ul>	Poor

	<b>First author, year of publication</b>	<b>Country of study</b>	<b>Sample size and age at enrolment</b>	<b>Type of study (longitudinal cohort, cross-sectional, systematic review, or meta-analysis)</b>	<b>Nutritional status of the study population</b>	<b>Developmental tools and age at assessment</b>	<b>Affected cognitive and neurodevelopmental aspects by suboptimal growth</b>	<b>Study quality</b>
						Ebbesen's delay of gratification waiting task) • Movement skills		
17	Reinert KR, 2013 [26]	High-income countries	1- to 5-years children (+ adolescents and adults aged up to 21 years, excluded from the present review)	Systematic review of 4 observational studies	Obese children	<ul style="list-style-type: none"> <li>• Delay of Gratification Task, Self-Control Task</li> <li>• Children's Behaviour Questionnaire</li> <li>• Classroom Engagement</li> <li>• Social Behaviour Questionnaire</li> <li>• Go-No Go Task</li> <li>• Behavioural Rating Inventory of Executive Functioning (self-report)</li> <li>• Incompatibility Task of Attention Assessment Battery</li> </ul>	Inhibitory control Emotional regulation	Good
18	Morano M, 2011 [24]	Italy	Overweight children (n=38) and non-overweight children (n=42) with a mean age of 4±0.5 year	Cross-sectional study	Overweight and healthy controls	<ul style="list-style-type: none"> <li>• Test of Gross Motor Development Quotient to assess 7 locomotor skills (run, gallop, hop, leap, horizontal jump, skip and slide) and 5 object-control skills (two-hand strike, stationary bounce, catch, kick and overhand throw) at age of enrolment</li> </ul>	<ul style="list-style-type: none"> <li>• Motor competence</li> <li>• Object-control tasks</li> </ul>	Good

Table 2. Key findings from retrieved interventional studies on undernutrition and the impact on neurodevelopment and cognition

No	First author, year of publication	Country of study	Sample size and age at enrolment	Type of studies	Type of intervention	Nutritional status of the study population	Developmental tools and age at assessment	Key Findings	Affected cognitive and neurodevelopmental aspects by suboptimal growth	Study quality
1	Prado EL, 2019 [7]	Low- to high-income countries	72,275 children aged 0 to 60 months	Meta-analysis from 52 interventional studies reported in English and Spanish	<ul style="list-style-type: none"> <li>• Nutrition intervention</li> <li>• Promotion of responsive care and learning opportunities</li> <li>• Conditional cash transfer</li> </ul>	Undernutrition	Bayley Scales of Infant Development (cognitive/mental score, language score, motor score, socio-emotional score) anytime between 0 and 60 months	The effect size of promoting responsiveness on HAZ was not significant, however, its pooled effect sizes on cognitive, language and motor score were 4-5 times larger than those of nutritional supplementation.	<ul style="list-style-type: none"> <li>• Social emotional score</li> <li>• Cognitive score</li> <li>• Motor score</li> </ul>	Good
2	Kristjansson E, 2015 [30]	Low- to high-income countries	5,400 children aged 3 to 60 months	Cochrane review and meta-analysis from 32 studies	Supplementary feeding interventions, alone or with co-intervention	Undernutrition	Psychomotor Development Index Mental Development Index	Two studies showed moderate positive effects of feeding on psychomotor development	Psychomotor development	Good
3	Ip P, 2017 [43]	Low- to middle-income studies	Children aged ≤8 years	Meta-analysis from 33 intervention studies	<ul style="list-style-type: none"> <li>• Nutrition intervention</li> </ul>	Undernutrition	Cognitive development	Childhood nutritional supplementation could improve children's cognitive development (d 0.08, 95% CI 0.03–0.13) and	Cognitive development	Poor

								those with $\geq 5$ nutrients was particularly beneficial (0.15, 0.08–0.22).		
4	Yousafzai AK, 2014 [23]	Pakistan	1,486 infants aged $\leq 2.5$ months at enrolment	Community-based cluster randomized trial until the child was 24 months of age	80 clusters of children to receive the following intervention for <ul style="list-style-type: none"> <li>• Control: Routine health and nutrition services</li> <li>• Nutrition education and multiple micronutrient powders</li> <li>• Responsive stimulation (responsive stimulation)</li> <li>• Combination of both responsive stimulation and nutrition intervention.</li> </ul>	Generally healthy children	Bayley Scales of Infant and Toddler Development, Third Edition at 12 and 24 months of age	<ul style="list-style-type: none"> <li>• Children who received responsive stimulation had significantly higher development scores on the cognitive, language, and motor scales at 12 and 24 months of age, and on the social-emotional scale at 12 months of age, than control.</li> <li>• Children who received enhanced nutrition had significantly higher development scores on the cognitive, language, and social-emotional scales at 12 months of age</li> </ul>	<ul style="list-style-type: none"> <li>• Cognitive scales</li> <li>• Language scales</li> <li>• Motor scales</li> </ul>	Good

								<p>than control, but at 24 months of age only the language scores remained significantly higher.</p> <ul style="list-style-type: none"><li>• No additive benefits when responsive stimulation was combined with nutrition interventions.</li><li>• Children exposed to enhanced nutrition had significantly better HAZ at 6 and 18 months than did children not exposed to enhanced nutrition.</li><li>• Treatment effect on cognition, language and motor development at 24 months were moderate to large for responsive simulation and were low to</li></ul>		
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								moderate for the enhanced nutrition group.		
5	Rosado JL, 2011[22]	Mexico	422 children aged 1 to 24 months	Randomized, placebo-controlled longitudinal trial for 6 months	<ul style="list-style-type: none"> <li>• Oral food supplement (OFS) with higher content of carbohydrates and micronutrients, including Fe and Zn, than did the PM</li> <li>• Powdered milk (PM)</li> <li>• Placebo (PL)</li> </ul>	Healthy population	Bayley Scale of Infant Development Test for cognitive and motor functions after 6 months from enrolment	<ul style="list-style-type: none"> <li>• Daily supplementation of 12–24-month-old children with OFS has no additional benefits in growth, anaemia, morbidity or cognitive performance.</li> <li>• No significant effect of treatment was found after 6 months in the prevalence of stunting after adjusting for initial values in the OFS or PM group compared with PL.</li> </ul>	None	Good
6	Kvestad I, 2015 [21]	India	422 children aged 6 to 30 months	Randomized, double-blind, placebo-controlled trial for 6 months	Placebo group vs Intervention group (vitamin B12 only, folic acid only, and vitamin B12 and	Undernutrition	Ages and Stages Questionnaire 3rd ed. after 6 months from enrolment	<ul style="list-style-type: none"> <li>• Children who received both vitamin B12 and folic acid had 0.45 (95% CI 0.19, 0.73) and 0.28 (95%</li> </ul>	<ul style="list-style-type: none"> <li>• Gross motor</li> <li>• Problem solving skills</li> </ul>	Good

					folic acid) with (1:1:1:1 ratio)			<p>CI 0.02, 0.54) higher SD-units in the domains of gross motor and problem solving functioning, respectively.</p> <ul style="list-style-type: none"> <li>• Effect was highest in stunted children, those with high plasma homocysteine (&gt; 10 μmol/L) or in those who were younger than 24 months at end study.</li> <li>• Timing of nutritional influence is of significance for the outcome of neurodevelopment.</li> </ul>		
7	Larson LM, 2017 [44]	Low- and middle-income countries	5,400 children aged 0 to 24 months	Systematic review on interventional randomized studies	Systematic review on nutrition intervention pre- and postnatal	Undernutrition and Healthy population	<p>Assessment during the first 48 months of life:</p> <ul style="list-style-type: none"> <li>• BSID-I, -II or -III—Mental Scale</li> <li>• Griffiths Mental Developmental Scale</li> </ul>	<ul style="list-style-type: none"> <li>• Motor development, but not growth status, effect sizes were significantly associated with mental development in postnatal interventions.</li> </ul>	Motor development	Good

							<ul style="list-style-type: none"> <li>• Fagan Test of Infant Intelligence</li> </ul>	<ul style="list-style-type: none"> <li>• Nutrition interventions had small effects on mental development.</li> <li>• Baseline and endline HAZ was not a significant predictor of postnatal effect size and baseline maternal BMI was not a significant predictor of prenatal effect size.</li> </ul>		
8	Walker SP, 2010 [28]	Jamaica	normal birth weight new-borns (n=73) compared with low-birth weight, term-born new-borns (LBWT) (n=99)	Randomized control study	Psychosocial stimulation assessed with the Middle Childhood Home Observation for the Measurement of the Environment (MC-HOME)	Low birth weight and normo-birthweight	<p>At 72 months:</p> <ul style="list-style-type: none"> <li>• Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III)</li> <li>• Digit span forwards test and visual-spatial memory with the Corsi blocks test</li> <li>• Test of Everyday Attention for Children</li> <li>• Early Reading Assessment</li> <li>• Strengths and Difficulties</li> </ul>	<ul style="list-style-type: none"> <li>• Compared with normal birth weight children, LBWT had poorer selective attention and visual-spatial memory, but there were no differences in IQ, language, or behaviour.</li> <li>• LBWT who received stimulation intervention had higher IQ score and fewer</li> </ul>	<ul style="list-style-type: none"> <li>• Selective attention</li> <li>• Visual-spatial memory</li> </ul>	Poor



							Questionnaire (SDQ)	behavioural problems as compared to the control, group.		
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Table 3. Factors influencing suboptimal growth in neurodevelopment and cognition

Maternal factors	Paternal factors	Child's characteristics and health condition	Socio-economic conditions
<b>Undernourished and normo-nourished children</b>			
Schooling (<tertiary education)	Schooling (<tertiary education)	Gender (mainly boy – conflicting evidence)	Poor sanitation (not flushing the toilet during childhood)
Lower nutrition knowledge	Non-employment at child's birth	Birth weight deficit	Poor water quality
Teenage at delivery	Teenage at delivery	Birth length deficit	Wealth/household income ( $\leq 1$ monthly minimum wage)
Low BMI (18.10 kg/m <sup>2</sup> )	Height deficit	Birth head circumference deficit	No consumption of dinner
Height deficit/decreased stature	Lower nutrition knowledge	Growth trajectories (head circumference length, height and weight deficit)	Housing condition ( $\geq 3$ persons per room)
Non-employment between pregnancy and the child's first 12 months of life	Perceiving less responsibility in the feeding task	Prematurity (<37 weeks)	Low HOME environment
Perceiving less responsibility in the feeding task	Being less restrictive towards access to unhealthy foods	Exposure and duration of breastfeeding (<1 month)	Play time with a caregiver (<1 hour per day)
Being less restrictive towards access to unhealthy foods	Engagement in activities with the child (0-2 activities versus 7 activities per week)	Duration of exclusive breastfeeding (<1 month)	Having no toys or books
Presence of mental condition during the child's first year of life		No postnatal motor development interventions	Being born within less than 24 months after the first baby
Level of physical activity before and during pregnancy (inactive)		Low haemoglobin level at 9 months (<11.5 g/dL)	Number of siblings ( $\geq 3$ )
Ethnicity (mainly non-white/African)		Ethnicity (mainly non-white/African)	Non-availability of health facilities
Smoking during pregnancy			No childcare during the first year of life
Unintended pregnancy			
Having no partner			
Number of pre-natal visits (<6)			
No hospitalisation during pregnancy			
Vaginal delivery			
<b>Overweight and obese children</b>			
-	-	Low socio-economic status	-

HOME, Home Observation for Measurement of the Environment

Figure 1. PRISMA 2009 Flowchart Diagram

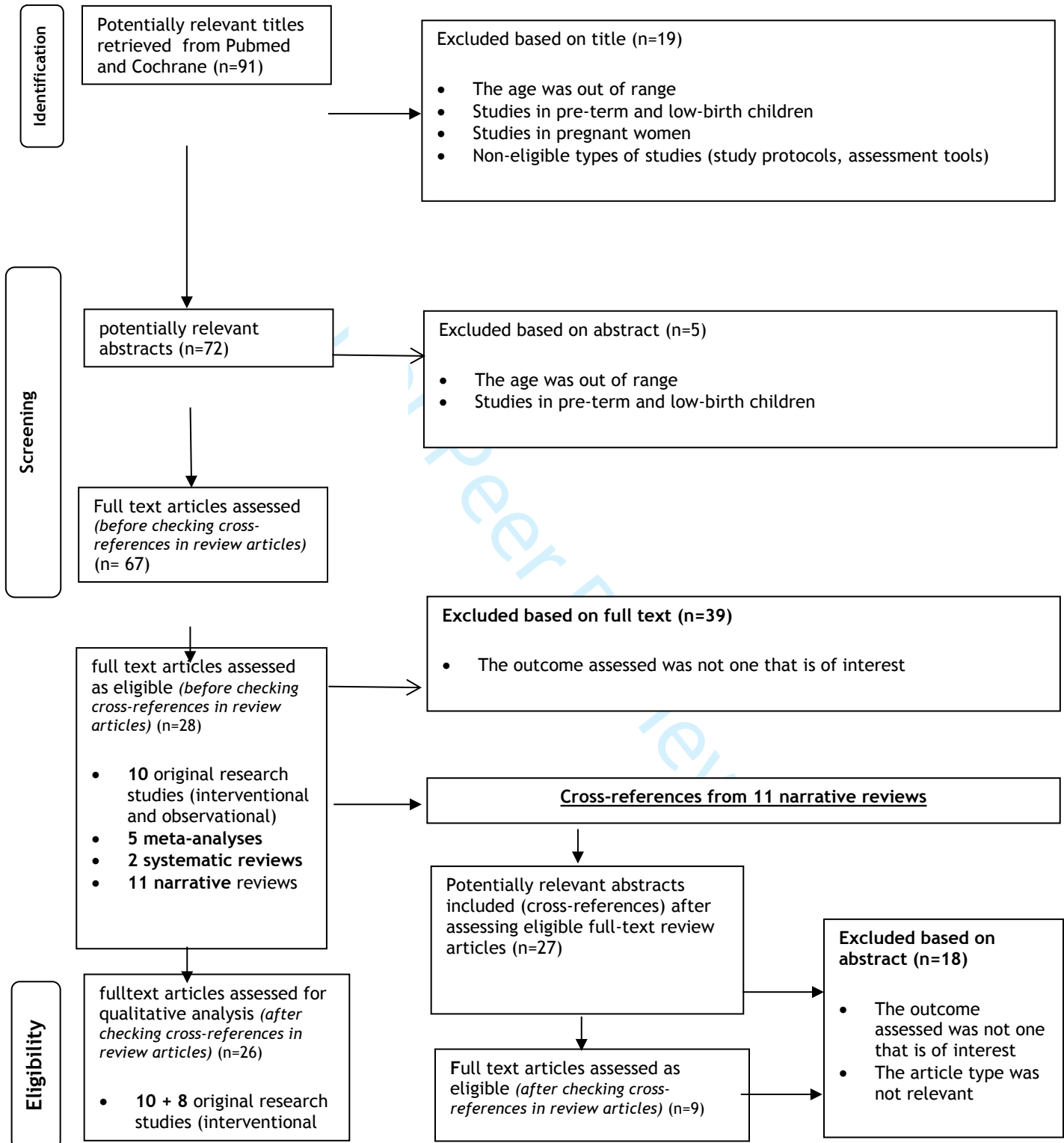
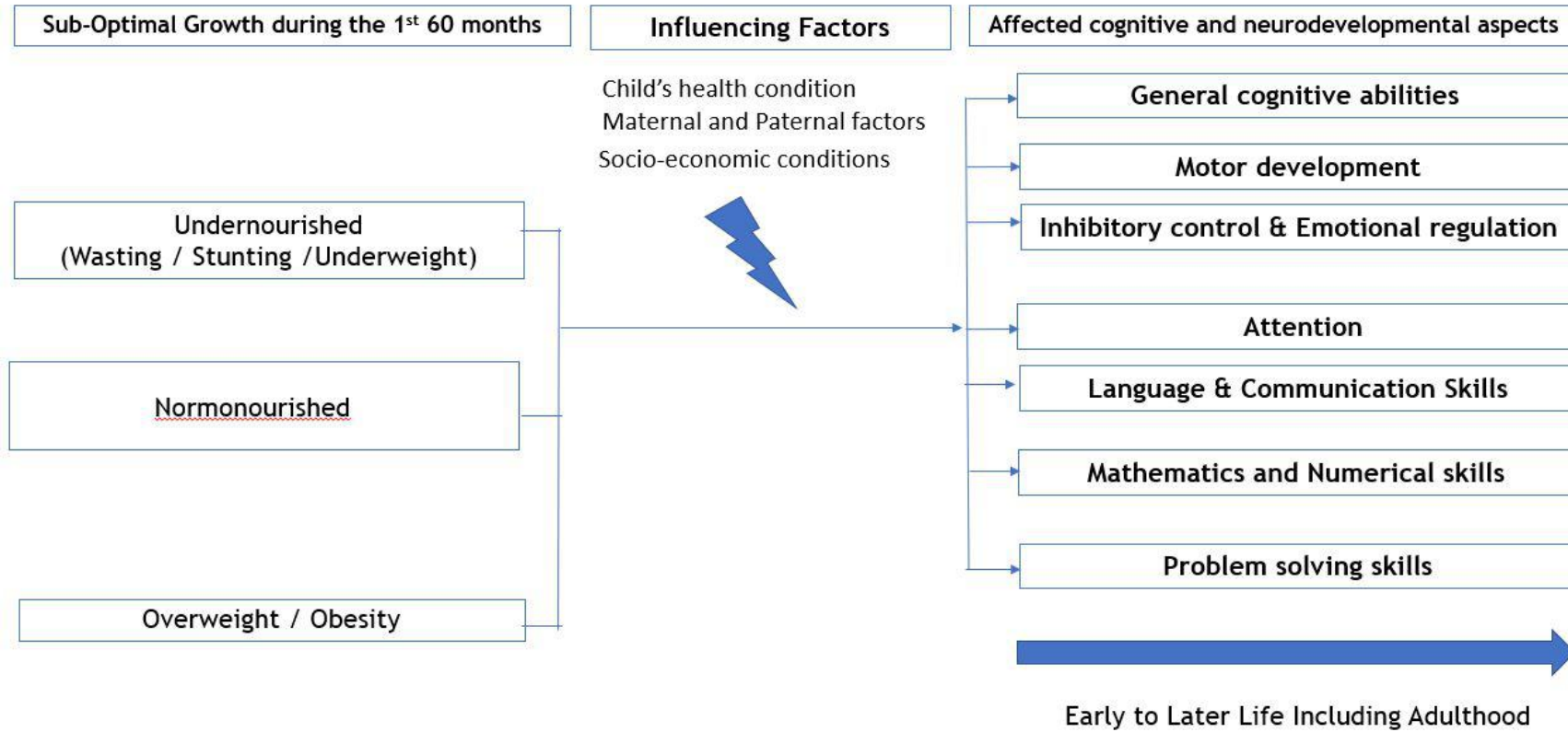


Figure 2. Impact of suboptimal growth in early childhood on developmental-related aspects



<b>7</b>	Decision: <b>Accepted for Publication</b>	<b>31 May 2021</b>
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## FW: Nutrition Research Reviews NRR-20-032.R5: Decision on Manuscript

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**Muhardi, L.M. (Leilani)** <leilani.muhardi@frieslandcampina.com>  
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Tue, Jun 1, 2021 at 7:28 AM

Yth. Dr. Wawan,

Terlampir saya sampaikan email dari Prof. Yazid.

Salam hormat,

Leilani

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**From:** Muhammad Yazid Jalaludin <yazidj@ummc.edu.my>  
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Alhamdulillah!

At last.

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Professor Dr Muhammad Yazid Jalaludin  
Deputy Dean (Undergraduate Studies)  
Faculty of Medicine  
University of Malaya

Senior Consultant Paediatrician, Consultant Paediatric Endocrinologist  
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**Muhardi, L.M. (Leilani)** <leilani.muhardi@frieslandcampina.com>

Tue, Jun 8, 2021 at 6:46 PM

To: "Geurts, J.M.W. (Jan)" <Jan.Geurts@frieslandcampina.com>, yazidj <yazidj@ummc.edu.my>, Rasaki Sanusi <sanusiadegoke2003@gmail.com>, Verena Tan Ming Hui <Verena.Tan@singaporetech.edu.sg>, Universiti Kebangsaan Malaysia <pbkoon@ukm.edu.my>, ahmad suryawan <suryawan.ahmad@gmail.com>  
Cc: "Kudla, U. (Urszula)" <Urszula.Kudla@frieslandcampina.com>

Dear Authors,

Please find the good news as shared by Prof. Yazid below. Congratulations to all!

I will share the proof read once it is available.

Kind regards,

Leilani

---

**From:** Muhammad Yazid Jalaludin <yazidj@ummc.edu.my>

**Sent:** Tuesday, June 8, 2021 7:07 PM

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Deputy Dean (Undergraduate Studies)

Faculty of Medicine

University of Malaya

Senior Consultant Paediatrician, Consultant Paediatric Endocrinologist

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A. Suryawan, M.Y. Jalaludin, B.K. Poh, R. Sanusi, V.M.H. Tan, J.M. Geurts, L. Muhandi

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doi: 10.1017/S0954422421000159, 41 pages. Published Online on 8 June 2021

**Modulation of Intestinal Stem Cell Homeostasis by Nutrients: A Novel Therapeutic Option for Intestinal Diseases**

Dan Wang, Pei Li, Jack Odle, Xi Lin, Jiangchao Zhao, Kan Xiao, Yulan Liu

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Stephanie Santos-Paulo, Samuel Costello, Samuel Forster, Simon Travis, Robert Bryant

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Dr. Ahmad Suryawan,  
Airlangga University  
Department of Child Health  
Surabaya  
Jawa Timur  
Indonesia

09 November 2021

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To whom it may concern,

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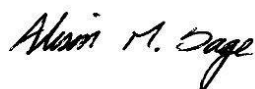
Title: **Malnutrition in early life and its neurodevelopmental and cognitive consequences: a scoping review**

Authors: **A. Suryawan, M.Y. Jalaludin, B.K. Poh, R. Sanusi, V.M.H. Tan, J.M. Geurts and L. Muhandi**

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Penny Rumbold, Nicola McCulloch, Ruth Boldon, Crystal Haskell-Ramsay, Lewis James, Emma Stevenson, Benjamin Green

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A. Suryawan, M.Y. Jalaludin, B.K. Poh, R. Sanusi, V.M.H. Tan, J.M. Geurts, L. Muhandi

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