

BUKTI KORESPONDENSI
Jurnal Internasional Bereputasi
Sebagai Syarat Khusus

Judul Artikel : Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review
 Penulis : **Ahmad Suryawan**, Muhammad Yazid Jalaludin, Poh Bee Koon, Rasaki Sanusi, Ming Hui Tan, Jan Geurts, Leilani Muhardi
 Jurnal : Nutrition Research Reviews, 2022, Volume 35(1): 136-149
 Penerbit : Cambridge University Press

1	Naskah manuskrip disubmit ke Jurnal “ Nutrition Research Review ” (ID NRR-20-032)	05 May 2020
	Keputusan: Hanya dapat diterima setelah revisi mayor (tanggal jatuh tempo 18-Agu-2020)	
2	Revisi ke-1 (ID NRR-20 0.32.R1) disubmit ke Jurnal	21 May 2020
	Keputusan: Dapat diterima secara prinsip (jatuh tempo 01-Des-2020)	
3	Revisi ke-2 (ID NRR-20 0.32.R2) disubmit ke Jurnal	18 Sept 2020
	Keputusan: Dapat diterima secara prinsip (jatuh tempo 09-Mar-2021)	
4	Revisi ke-3 (ID NRR-20 0.32.R3) disubmit ke Jurnal	18 Dec 2020
	Keputusan: Dapat diterima secara prinsip (jatuh tempo 12-May-2021)	
5	Revisi ke-4 (ID NRR-20 0.32.R4) disubmit ke Jurnal	31 March 2021
	Keputusan: <i>Acceptable as received</i> (jatuh tempo 31-May-2021)	
6	Revisi ke-5 (ID NRR-20 0.32.R5) disubmit ke Jurnal	26 May 2021
7	Keputusan: <i>Accepted for Publication</i>	31 May 2021
8	Published online	08 June 2021
9	Published on Nutrition Research Review, Volume 35 Issue 1	04 June 2022



Home

Author

Review

Author Dashboard

6 Manuscripts I Have Co-Authored

[Start New Submission](#)

[5 Most Recent E-mails](#)

Manuscripts I Have Co-Authored

STATUS	ID	TITLE	CREATED	SUBMITTED
EA: Sage, Alison <ul style="list-style-type: none"> Acceptable as received (31-May-2021) In Production 	NRR-20-032.R5	Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review Submitting Author: Muhardi, Leilani Cover Letter	26-May-2021	26-May-2021
EA: Sage, Alison <ul style="list-style-type: none"> Acceptable in principle (12-May-2021) a revision has been submitted 	NRR-20-032.R4	Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review View Submission Submitting Author: Muhardi, Leilani Cover Letter	31-Mar-2021	31-Mar-2021
EA: Sage, Alison	NRR-20-032.R3	Malnutrition in early life and its neurodevelopmental and cognitive	18-Dec-2020	18-Dec



STATUS	ID	TITLE	CREATED	SUBMITTED
<ul style="list-style-type: none"> Acceptable in principle (09-Mar-2021) a revision has been submitted ✉ Contact Journal		consequences: A Scoping review View Submission Submitting Author: Muhardi, Leilani Cover Letter		
EA: Sage, Alison <ul style="list-style-type: none"> Acceptable in principle (01-Dec-2020) a revision has been submitted ✉ Contact Journal	NRR-20-032.R2	Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review View Submission Submitting Author: Muhardi, Leilani Cover Letter	18-Sep-2020	18-Sep-2020
EA: Sage, Alison <ul style="list-style-type: none"> Acceptable only after major revisions (18-Aug-2020) a revision has been submitted ✉ Contact Journal	NRR-20-032.R1	Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review View Submission Submitting Author: Muhardi, Leilani Cover Letter	19-May-2020	21-May-2020
EA: Sage, Alison <ul style="list-style-type: none"> Accept Proposal (15-May-2020) a revision has been submitted ✉ Contact Journal	NRR-20-032	Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review View Submission Submitting Author: Muhardi, Leilani	04-May-2020	05-May-2020

© Clarivate | © ScholarOne, Inc., 2023. All Rights Reserved.

ScholarOne Manuscripts and ScholarOne are registered trademarks of ScholarOne, Inc.

ScholarOne Manuscripts Patents #7,257,767 and #7,263,655.

 [@Clarivate for Academia & Government](#) |  [System Requirements](#) |  [Privacy Statement](#) |  [Terms of Use](#)

1	Naskah manuskrip disubmit ke Jurnal “ Nutrition Research Review ” (ID NRR-20-032)	05 May 2020
	<u>Keputusan:</u> Hanya dapat diterima setelah revisi mayor (tanggal jatuh tempo 18-Agu-2020)	

NUTRITION RESEARCH REVIEWS



**CAMBRIDGE
UNIVERSITY PRESS**

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

Journal:	<i>Nutrition Research Reviews</i>
Manuscript ID	NRR-20-032
Manuscript Type:	Proposal
Date Submitted by the Author:	05-May-2020
Complete List of Authors:	<p>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, Department Health and Social Sciences Geurts, Jan; Koninklijke FrieslandCampina NV Innovation Centre Wageningen Muhardi, Leilani; FrieslandCampina AMEA, Medical Affairs</p>

SCHOLARONE™
Manuscripts



REVIEW PROPOSAL FORM

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

If yes, by whom?

Name of corresponding author:

Muhammad Yazid Jalaludin

Associate Professor

Head Department of Paediatrics

Faculty of Medicine

University of Malaya

59100 Kuala Lumpur

Tel: 03-79492065

Fax: 03-79494704

Email: yazidj@ummc.edu.my or yazidjal@um.edu.my

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.

NUTRITION RESEARCH REVIEWS (NRR)

THE NUTRITION SOCIETY

10 Cambridge Court
210 Shepherds Bush Road
London, W6 7NJ, UK
Tel: +44 (0)1223 347922

Email: nrr.edoffice@cambridge.org

Web: www.nutrition-society.org/publications/nutrition-society-journals





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.

NUTRITION RESEARCH REVIEWS (NRR)

THE NUTRITION SOCIETY

10 Cambridge Court
210 Shepherds Bush Road
London, W6 7NJ, UK

Tel: +44 (0)1223 347922

Email: nrr.edoffice@cambridge.org

Web: www.nutrition-society.org/publications/nutrition-society-journals



2	Revisi ke-1 (ID NRR-20 0.32.R1) disubmit ke Jurnal	21 May 2020
	<u>Keputusan:</u> Dapat diterima secara prinsip (jatuh tempo 01-Des-2020)	

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

- 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

[View Submission](#)

Submitting Author: Muhardi, Leilani

[Cover Letter](#)

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



NUTRITION RESEARCH REVIEWS



**CAMBRIDGE
UNIVERSITY PRESS**

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

SCHOLARONE™
Manuscripts

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

8 Suryawan A¹, Jalaludin MY², B.K. Poh³, Rasaki Sanusi⁴, V.M.H. Tan⁵, J. Geurts⁶, Muhandi L⁷.

9

10 1. Department of Child Health, Faculty of Medicine, Universitas Airlangga, Soetomo General
11 Academic Hospital, Surabaya, Indonesia

12 2. Department of Paediatrics, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur,
13 Malaysia.

14 3. Nutritional Sciences Programme and Centre for Community Health Studies, Faculty of Health
15 Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

16 4. University of Ibadan, Nigeria.

17 5. Dietetics and Nutrition Programme, Health and Social Sciences cluster, Singapore Institute of
18 Technology, Singapore

19 6. Friesland Campina, Amersfoort, The Netherlands

20 7. Friesland Campina AMEA, Singapore

21

22 **Corresponding author:**

23 Muhammad Yazid Jalaludin

24 Associate Professor

25 Department of Paediatrics

26 Faculty of Medicine

27 University of Malaya

28 59100 Kuala Lumpur

29 Tel: 03-79492065

30 Fax: 03-79494704

31 Email: yazidj@ummc.edu.my or yazidjal@um.edu.my

32

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

389 **DECLARATIONS**

390 **Acknowledgements**

391 The authors thank Content Ed Net Singapore for providing editorial and medical writing
392 assistance for the preparation of this manuscript.

393

394 **Funding**

395 FrieslandCampina supported the development of the manuscript by Content Ed
396 Singapore. None of the authors received educational grant from FrieslandCampina to
397 participate in the writing.

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

417 **References**

418

- 419 1. Global Nutrition Report: Action on equity to end malnutrition. Development Initiatives
420 2020.
- 421 2. Global Nutrition Report: Shining a light to spur action on nutrition. Development
422 Initiatives. 2018.
- 423 3. Grantham-McGregor S, Cheung YB, Cueto S, et al. Developmental potential in the first 5
424 years for children in developing countries. *Lancet*. 2007;369(9555):60-70.
- 425 4. Sudfeld CR, McCoy DC, Danaei G, et al. Linear growth and child development in low-
426 and middle-income countries: a meta-analysis. *Pediatrics*. 2015;135(5):e1266-75.
- 427 5. Prado EL, Larson LM, Cox K, et al. Do effects of early life interventions on linear growth
428 correspond to effects on neurobehavioural development? A systematic review and meta-
429 analysis. *Lancet Glob Health*. 2019;7(10):e1398-e413.
- 430 6. Miller AC, Murray MB, Thomson DR, et al. How consistent are associations between
431 stunting and child development? Evidence from a meta-analysis of associations between
432 stunting and multidimensional child development in fifteen low- and middle-income countries.
433 *Public Health Nutr*. 2016;19(8):1339-47.
- 434 7. Camargo-Figuera FA, Barros AJ, Santos IS, et al. Early life determinants of low IQ at age
435 6 in children from the 2004 Pelotas Birth Cohort: a predictive approach. *BMC Pediatr*.
436 2014;14:308.
- 437 8. Hamadani JD, Tofail F, Huda SN, et al. Cognitive deficit and poverty in the first 5 years
438 of childhood in Bangladesh. *Pediatrics*. 2014;134(4):e1001-8.
- 439 9. Mohd Nasir MT, Norimah AK, Hazizi AS, et al. Child feeding practices, food habits,
440 anthropometric indicators and cognitive performance among preschoolers in Peninsular
441 Malaysia. *Appetite*. 2012;58(2):525-30.
- 442 10. Baker-Henningham H, Hamadani JD, Huda SN, et al. Undernourished children have
443 different temperaments than better-nourished children in rural Bangladesh. *J Nutr*.
444 2009;139(9):1765-71.
- 445 11. Crookston BT, Schott W, Cueto S, et al. Postinfancy growth, schooling, and cognitive
446 achievement: Young Lives. *Am J Clin Nutr*. 2013;98(6):1555-63.
- 447 12. Hoddinott J, Behrman JR, Maluccio JA, et al. Adult consequences of growth failure in
448 early childhood. *Am J Clin Nutr*. 2013;98(5):1170-8.
- 449 13. Cheung YB, Ashorn P. Continuation of linear growth failure and its association with
450 cognitive ability are not dependent on initial length-for-age: a longitudinal study from 6
451 months to 11 years of age. *Acta Paediatr*. 2010;99(11):1719-23.
- 452 14. Sunny BS, DeStavola B, Dube A, et al. Does early linear growth failure influence later
453 school performance? A cohort study in Karonga district, northern Malawi. *PLoS One*.
454 2018;13(11):e0200380.
- 455 15. Casale D, Desmond C, Richter L. The association between stunting and psychosocial
456 development among preschool children: a study using the South African Birth to Twenty cohort
457 data. *Child Care Health Dev*. 2014;40(6):900-10.
- 458 16. Kvestad I, Taneja S, Kumar T, et al. Vitamin B12 and Folic Acid Improve Gross Motor
459 and Problem-Solving Skills in Young North Indian Children: A Randomized Placebo-Controlled
460 Trial. *PLoS One*. 2015;10(6):e0129915.

- 461 17. Rosado JL, Lopez P, Garcia OP, et al. Effectiveness of the nutritional supplement used
462 in the Mexican Oportunidades programme on growth, anaemia, morbidity and cognitive
463 development in children aged 12-24 months. *Public Health Nutr.* 2011;14(5):931-7.
- 464 18. Yousafzai AK, Rasheed MA, Rizvi A, et al. Effect of integrated responsive stimulation
465 and nutrition interventions in the Lady Health Worker programme in Pakistan on child
466 development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial.
467 *Lancet.* 2014;384(9950):1282-93.
- 468 19. Morano M, Colella D, Caroli M. Gross motor skill performance in a sample of overweight
469 and non-overweight preschool children. *Int J Pediatr Obes.* 2011;6 Suppl 2:42-6.
- 470 20. Liang J, Matheson BE, Kaye WH, et al. Neurocognitive correlates of obesity and obesity-
471 related behaviors in children and adolescents. *International journal of obesity (2005).*
472 2014;38(4):494-506.
- 473 21. Reinert KR, Po'e EK, Barkin SL. The relationship between executive function and obesity
474 in children and adolescents: a systematic literature review. *J Obes.* 2013;2013:820956.
- 475 22. Hayes JF, Eichen DM, Barch DM, et al. Executive function in childhood obesity:
476 Promising intervention strategies to optimize treatment outcomes. *Appetite.* 2018;124:10-23.
- 477 23. Walker SP, Chang SM, Younger N, et al. The effect of psychosocial stimulation on
478 cognition and behaviour at 6 years in a cohort of term, low-birthweight Jamaican children. *Dev*
479 *Med Child Neurol.* 2010;52(7):e148-54.
- 480 24. Nguyen PH, Kim SS, Sanghvi T, et al. Integrating Nutrition Interventions into an Existing
481 Maternal, Neonatal, and Child Health Program Increased Maternal Dietary Diversity,
482 Micronutrient Intake, and Exclusive Breastfeeding Practices in Bangladesh: Results of a Cluster-
483 Randomized Program Evaluation. *J Nutr.* 2017;147(12):2326-37.
- 484 25. Kristjansson E, Francis DK, Liberato S, et al. Food supplementation for improving the
485 physical and psychosocial health of socio-economically disadvantaged children aged three
486 months to five years. *Cochrane Database Syst Rev.* 2015(3):CD009924.
- 487 26. Pimpin L, Kranz S, Liu E, et al. Effects of animal protein supplementation of mothers,
488 preterm infants, and term infants on growth outcomes in childhood: a systematic review and
489 meta-analysis of randomized trials. *Am J Clin Nutr.* 2019;110(2):410-29.
- 490 27. Sjarif DR, Yuliati K, Iskandar WJ. Daily consumption of growing-up reduces stunting
491 among Indonesian toddlers. *Medical Journal Indonesia.* 2019;28:70-6.
- 492 28. Lee R, Singh L, van Liefde D, et al. Milk Powder Added to a School Meal Increases
493 Cognitive Test Scores in Ghanaian Children. *J Nutr.* 2018;148(7):1177-84.
- 494 29. Smithers LG, Golley RK, Mittinty MN, et al. Do dietary trajectories between infancy and
495 toddlerhood influence IQ in childhood and adolescence? Results from a prospective birth cohort
496 study. *PLoS One.* 2013;8(3):e58904.
- 497 30. Miller AL, Lee HJ, Lumeng JC. Obesity-associated biomarkers and executive function in
498 children. *Pediatr Res.* 2015;77(1-2):143-7.
- 499 31. Double-duty actions for nutrition. Policy Brief. World Health Organization. 2017.
- 500 32. World Health Organization. Global nutrition targets 2025. 2014.
- 501 33. Smithers LG, Lynch JW, Yang S, et al. Impact of neonatal growth on IQ and behavior at
502 early school age. *Pediatrics.* 2013;132(1):e53-60.
- 503 34. Aubuchon-Endsley NL, Grant SL, Berhanu G, et al. Hemoglobin, growth, and attention
504 of infants in southern Ethiopia. *Child Dev.* 2011;82(4):1238-51.
- 505 35. Waber DP, Bryce CP, Girard JM, et al. Impaired IQ and academic skills in adults who
506 experienced moderate to severe infantile malnutrition: a 40-year study. *Nutr Neurosci.*
507 2014;17(2):58-64.
- 508 36. Sudfeld CR, McCoy DC, Fink G, et al. Malnutrition and Its Determinants Are Associated
509 with Suboptimal Cognitive, Communication, and Motor Development in Tanzanian Children. *J*
510 *Nutr.* 2015;145(12):2705-14.
- 511 37. Ip P, Ho FKW, Rao N, et al. Impact of nutritional supplements on cognitive development
512 of children in developing countries: A meta-analysis. *Sci Rep.* 2017;7(1):10611.
- 513 38. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental
514 development of children under-two in low- and middle-income countries. *Matern Child Nutr.*
515 2017;13(1).



ahmad suryawan <suryawan.ahmad@gmail.com>

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

Muhardi, L.M. (Leilani) <leilani.muhardi@frieslandcampina.com>

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 2nd milestones. Congratulations to all of us!

I would like to propose the following as next steps:

Action Plans	PIC	Time line
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

From: Muhammad Yazid Jalaludin <yazidj@ummc.edu.my>
Sent: Tuesday, August 18, 2020 9:05 PM
To: Muhardi, L.M. (Leilani) <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

Begin forwarded message:

From: Nutrition Research Reviews <onbehalfof@manuscriptcentral.com>
Date: 18 August 2020 at 19:59:53 MYT
To: yazidj@ummc.edu.my
Subject: Nutrition Research Reviews NRR-20-032.R1: Decision on Manuscript
Reply-To: nrr.edoffice@cambridge.org

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:

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

https://mc.manuscriptcentral.com/nrr?URL_MASK=ac8ed20548e740238bd4461748623635

Alternatively, you may log into your Author Centre at <https://mc.manuscriptcentral.com/nrr>, where you will find your manuscript under "Manuscripts Awaiting Revision". Upon submission of the revised version, your manuscript number will be appended to denote a revision. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. Please use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

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>

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

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.

" PENAFIAN: E-mel ini dan apa-apa fail yang dikepilkan bersamanya ("Mesej") adalah ditujukan hanya untuk kegunaan penerima(-penerima) yang termaklum di atas dan mungkin mengandungi maklumat sulit. Anda dengan ini dimaklumkan bahawa mengambil apa jua tindakan bersandarkan kepada, membuat penilaian, mengulang hantar, menghebah, mengedar, mencetak, atau menyalin Mesej ini atau sebahagian daripadanya oleh sesiapa selain daripada penerima(-penerima) yang termaklum di atas adalah dilarang. Jika anda telah menerima Mesej ini kerana kesilapan, anda mesti menghapuskan Mesej ini dengan segera dan memaklumkan kepada penghantar Mesej ini menerusi balasan e-mel. Pendapat-pendapat, rumusan-rumusan, dan sebarang maklumat lain di dalam Mesej ini yang tidak berkait dengan urusan rasmi Pusat Perubatan Universiti Malaya adalah difahami sebagai bukan dikeluarkan atau diperakui oleh mana-mana pihak yang disebut.

DISCLAIMER: This e-mail and any files transmitted with it ("Message") is intended only for the use of the recipient(s) named above and may contain confidential information. You are hereby notified that the taking of any action in reliance upon, or any review, retransmission, dissemination, distribution, printing or copying of this Message or any part thereof by anyone other than the intended recipient(s) is strictly prohibited. If you have received this Message in error, you should delete this Message immediately and advise the sender by return e-mail. Opinions, conclusions and other information in this Message that do not relate to the official business of University Malaya Medical Centre shall be understood as neither given nor endorsed by any of the forementioned. "

Disclaimer: The information in this e-mail (including any attachments) is strictly confidential and may be legally privileged. If you are not the intended recipient of this message, please delete it including any attachments and immediately notify the sender. Any disclosure, copying, distribution or use either whole or partial of its contents is strictly prohibited except with formal approval. FrieslandCampina cannot guarantee that e-mail communications are secured and error-free and does not accept any liability for damages resulting from the use of e-mail. The general terms and conditions of [purchase](#) respectively [sale and delivery](#) of Royal FrieslandCampina N.V., are applicable to all transactions and undertakings resulting therefrom.

De informatie in deze e-mail (inclusief bijlagen) is strikt persoonlijk en vertrouwelijk en mogelijk juridisch geprivilegieerd. Indien u niet de bedoelde ontvanger van dit bericht bent verzoeken wij u het bericht inclusief bijlagen te vernietigen en ons hiervan onmiddellijk op de hoogte te stellen. Openbaarmaking, vermenigvuldiging of verspreiding van (een gedeelte van) dit bericht is, zonder formele toestemming, strikt verboden. FrieslandCampina kan niet garanderen dat e-mail communicatie veilig en foutloos is en accepteert geen enkele aansprakelijkheid voor schade voortvloeiende uit het

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 (≥ 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.

3	Revisi ke-2 (ID NRR-20 0.32.R2) disubmit ke Jurnal	18 Sept 2020
	<u>Keputusan</u> : Dapat diterima secara prinsip (jatuh tempo 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



**CAMBRIDGE
UNIVERSITY PRESS**

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

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 Suryawan A¹, Jalaludin MY², B.K. Poh³, Rasaki Sanusi⁴, V.M.H. Tan⁵, J. Geurts⁶, Muhandi L⁷.

7

8 1. Department of Child Health, Faculty of Medicine, Universitas Airlangga, Soetomo General Academic
9 Hospital, Surabaya, Indonesia

10 2. Department of Paediatrics, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur,
11 Malaysia.

12 3. Nutritional Sciences Programme and Centre for Community Health Studies (ReaCH), Faculty of
13 Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

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

15 5. Dietetics and Nutrition Programme, Health and Social Sciences cluster, Singapore Institute of
16 Technology, Singapore

17 6. Friesland Campina, Amersfoort, The Netherlands

18 7. Friesland Campina AMEA, Singapore

19

20 **Corresponding author:**

21 Muhammad Yazid Jalaludin

22 Professor

23 Department of Paediatrics

24 Faculty of Medicine

25 University of Malaya

26 59100 Kuala Lumpur

27 Tel: 03-79492065

28 Fax: 03-79494704

29 Email: yazidj@ummc.edu.my or yazidjal@um.edu.my

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

336 **DECLARATIONS**

337 **Acknowledgements**

338 The authors thank Content Ed Net Singapore for providing editorial and medical writing assistance in
339 retrieving relevant publications and the development of the 1st draft of the manuscript.

340

341 **Funding**

342 FrieslandCampina supported the retrieval of relevant publications and the development of the 1st
343 manuscript draft by Content Ed Singapore. None of the authors received educational grant from
344 FrieslandCampina to participate in the writing.

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**

360 Not applicable.

361

362 **Ethics approval and consent to participate**

363 Not applicable.

364

365 **References**

366

- 367 1. *Global Nutrition Report: Action on equity to end malnutrition. Development Initiatives*
368 2020.
- 369 2. *Global Nutrition Report: Shining a light to spur action on nutrition. Development*
370 *Initiatives*. 2018.
- 371 3. Grantham-McGregor, S., Y.B. Cheung, et al., *Developmental potential in the first 5 years*
372 *for children in developing countries*. *Lancet*, 2007. **369**(9555): p. 60-70.
- 373 4. Sudfeld, C.R., D.C. McCoy, et al., *Linear growth and child development in low- and middle-*
374 *income countries: a meta-analysis*. *Pediatrics*, 2015. **135**(5): p. e1266-75.
- 375 5. Prado, E.L., L.M. Larson, et al., *Do effects of early life interventions on linear growth*
376 *correspond to effects on neurobehavioural development? A systematic review and meta-*
377 *analysis*. *Lancet Glob Health*, 2019. **7**(10): p. e1398-e1413.
- 378 6. Miller, A.C., M.B. Murray, et al., *How consistent are associations between stunting and child*
379 *development? Evidence from a meta-analysis of associations between stunting and*
380 *multidimensional child development in fifteen low- and middle-income countries*. *Public*
381 *Health Nutr*, 2016. **19**(8): p. 1339-47.
- 382 7. Munn, Z., M.D.J. Peters, et al., *Systematic review or scoping review? Guidance for authors*
383 *when choosing between a systematic or scoping review approach*. *BMC Med Res Methodol*,
384 2018. **18**(1): p. 143.
- 385 8. Camargo-Figuera, F.A., A.J. Barros, et al., *Early life determinants of low IQ at age 6 in*
386 *children from the 2004 Pelotas Birth Cohort: a predictive approach*. *BMC Pediatr*, 2014. **14**:
387 p. 308.
- 388 9. Cheung, Y.B. and P. Ashorn, *Continuation of linear growth failure and its association with*
389 *cognitive ability are not dependent on initial length-for-age: a longitudinal study from 6*
390 *months to 11 years of age*. *Acta Paediatr*, 2010. **99**(11): p. 1719-23.
- 391 10. Hamadani, J.D., F. Tofail, et al., *Cognitive deficit and poverty in the first 5 years of*
392 *childhood in Bangladesh*. *Pediatrics*, 2014. **134**(4): p. e1001-8.
- 393 11. Mendez, M.A. and L.S. Adair, *Severity and timing of stunting in the first two years of life*
394 *affect performance on cognitive tests in late childhood*. *J Nutr*, 1999. **129**(8): p. 1555-62.
- 395 12. Mohd Nasir, M.T., A.K. Norimah, et al., *Child feeding practices, food habits,*
396 *anthropometric indicators and cognitive performance among preschoolers in Peninsular*
397 *Malaysia*. *Appetite*, 2012. **58**(2): p. 525-30.
- 398 13. Baker-Henningham, H., J.D. Hamadani, et al., *Undernourished children have different*
399 *temperaments than better-nourished children in rural Bangladesh*. *J Nutr*, 2009. **139**(9): p.
400 1765-71.
- 401 14. Crookston, B.T., W. Schott, et al., *Postinfancy growth, schooling, and cognitive*
402 *achievement: Young Lives*. *Am J Clin Nutr*, 2013. **98**(6): p. 1555-63.
- 403 15. Hoddinott, J., J.R. Behrman, et al., *Adult consequences of growth failure in early*
404 *childhood*. *Am J Clin Nutr*, 2013. **98**(5): p. 1170-8.
- 405 16. Sunny, B.S., B. DeStavola, et al., *Does early linear growth failure influence later school*
406 *performance? A cohort study in Karonga district, northern Malawi*. *PLoS One*, 2018. **13**(11):
407 p. e0200380.
- 408 17. Casale, D., C. Desmond, et al., *The association between stunting and psychosocial*
409 *development among preschool children: a study using the South African Birth to Twenty*
410 *cohort data*. *Child Care Health Dev*, 2014. **40**(6): p. 900-10.

- 411 18. Desmond, C. and D. Casale, *Catch-up growth in stunted children: Definitions and*
412 *predictors*. PLoS One, 2017. 12(12): p. e0189135.
- 413 19. Kvestad, I., S. Taneja, et al., *Vitamin B12 and Folic Acid Improve Gross Motor and Problem-*
414 *Solving Skills in Young North Indian Children: A Randomized Placebo-Controlled Trial*. PLoS
415 One, 2015. 10(6): p. e0129915.
- 416 20. Rosado, J.L., P. Lopez, et al., *Effectiveness of the nutritional supplement used in the*
417 *Mexican Oportunidades programme on growth, anaemia, morbidity and cognitive*
418 *development in children aged 12-24 months*. Public Health Nutr, 2011. 14(5): p. 931-7.
- 419 21. Yousafzai, A.K., M.A. Rasheed, et al., *Effect of integrated responsive stimulation and*
420 *nutrition interventions in the Lady Health Worker programme in Pakistan on child*
421 *development, growth, and health outcomes: a cluster-randomised factorial effectiveness*
422 *trial*. Lancet, 2014. 384(9950): p. 1282-93.
- 423 22. Morano, M., D. Colella, et al., *Gross motor skill performance in a sample of overweight and*
424 *non-overweight preschool children*. Int J Pediatr Obes, 2011. 6 Suppl 2: p. 42-6.
- 425 23. Liang, J., B.E. Matheson, et al., *Neurocognitive correlates of obesity and obesity-related*
426 *behaviors in children and adolescents*. Int J Obes (Lond), 2014. 38(4): p. 494-506.
- 427 24. Reinert, K.R., E.K. Po'e, et al., *The relationship between executive function and obesity in*
428 *children and adolescents: a systematic literature review*. J Obes, 2013. 2013: p. 820956.
- 429 25. Hayes, J.F., D.M. Eichen, et al., *Executive function in childhood obesity: Promising*
430 *intervention strategies to optimize treatment outcomes*. Appetite, 2018. 124: p. 10-23.
- 431 26. Walker, S.P., S.M. Chang, et al., *The effect of psychosocial stimulation on cognition and*
432 *behaviour at 6 years in a cohort of term, low-birthweight Jamaican children*. Dev Med Child
433 Neurol, 2010. 52(7): p. e148-54.
- 434 27. Nguyen, P.H., S.S. Kim, et al., *Integrating Nutrition Interventions into an Existing Maternal,*
435 *Neonatal, and Child Health Program Increased Maternal Dietary Diversity, Micronutrient*
436 *Intake, and Exclusive Breastfeeding Practices in Bangladesh: Results of a Cluster-*
437 *Randomized Program Evaluation*. J Nutr, 2017. 147(12): p. 2326-2337.
- 438 28. Kristjansson, E., D.K. Francis, et al., *Food supplementation for improving the physical and*
439 *psychosocial health of socio-economically disadvantaged children aged three months to five*
440 *years*. Cochrane Database Syst Rev, 2015(3): p. CD009924.
- 441 29. Pimpin, L., S. Kranz, et al., *Effects of animal protein supplementation of mothers, preterm*
442 *infants, and term infants on growth outcomes in childhood: a systematic review and meta-*
443 *analysis of randomized trials*. Am J Clin Nutr, 2019. 110(2): p. 410-429.
- 444 30. Sjarif, D.R., K. Yuliati, et al., *Daily consumption of growing-up reduces stunting among*
445 *Indonesian toddlers*. Medical Journal Indonesia, 2019. 28: p. 70-76.
- 446 31. Lee, R., L. Singh, et al., *Milk Powder Added to a School Meal Increases Cognitive Test*
447 *Scores in Ghanaian Children*. J Nutr, 2018. 148(7): p. 1177-1184.
- 448 32. Smithers, L.G., R.K. Golley, et al., *Do dietary trajectories between infancy and toddlerhood*
449 *influence IQ in childhood and adolescence? Results from a prospective birth cohort study*.
450 PLoS One, 2013. 8(3): p. e58904.
- 451 33. Miller, A.L., H.J. Lee, et al., *Obesity-associated biomarkers and executive function in*
452 *children*. Pediatr Res, 2015. 77(1-2): p. 143-7.
- 453 34. *Double-duty actions for nutrition*. Policy Brief. World Health Organization. 2017.
- 454 35. *World Health Organization. Global nutrition targets 2025*. 2014.
- 455 36. Smithers, L.G., J.W. Lynch, et al., *Impact of neonatal growth on IQ and behavior at early*
456 *school age*. Pediatrics, 2013. 132(1): p. e53-60.
- 457 37. Aubuchon-Endsley, N.L., S.L. Grant, et al., *Hemoglobin, growth, and attention of infants in*
458 *southern Ethiopia*. Child Dev, 2011. 82(4): p. 1238-51.
- 459 38. Waber, D.P., C.P. Bryce, et al., *Impaired IQ and academic skills in adults who experienced*
460 *moderate to severe infantile malnutrition: a 40-year study*. Nutr Neurosci, 2014. 17(2): p.
461 58-64.
- 462 39. Sudfeld, C.R., D.C. McCoy, et al., *Malnutrition and Its Determinants Are Associated with*
463 *Suboptimal Cognitive, Communication, and Motor Development in Tanzanian Children*. J
464 Nutr, 2015. 145(12): p. 2705-14.
- 465 40. Ip, P., F.K.W. Ho, et al., *Impact of nutritional supplements on cognitive development of*
466 *children in developing countries: A meta-analysis*. Sci Rep, 2017. 7(1): p. 10611.

- 467 41. Larson, L.M. and A.K. Yousafzai, *A meta-analysis of nutrition interventions on mental*
468 *development of children under-two in low- and middle-income countries*. *Matern Child*
469 *Nutr*, 2017. **13**(1).

For Peer Review



ahmad suryawan <suryawan.ahmad@gmail.com>

FW: Nutrition Research Reviews NRR-20-032.R2- Acceptable in Principle

Muhardi, L.M. (Leilani) <leilani.muhardi@frieslandcampina.com>

Wed, Dec 2, 2020 at 11:04 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>

Cc: yazidj <yazidj@ummc.edu.my>, "Kudla, U. (Urszula)" <Urszula.Kudla@frieslandcampina.com>

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
create a revision	EA: Sage, Alison	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"> Acceptable in principle (01-Dec-2020) Due on: 31-Jan-2021 		View Submission		
	view decision letter				

From: Muhammad Yazid Jalaludin <yazidj@ummc.edu.my>
Sent: Tuesday, December 1, 2020 11:30 PM
To: Muhardi, L.M. (Leilani) <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>
Date: 1 December 2020 at 23:18:16 MYT
To: yazidj@ummc.edu.my
Subject: Nutrition Research Reviews NRR-20-032.R2
Reply-To: 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. ***

https://mc.manuscriptcentral.com/nrr?URL_MASK=a0c87752080b43c1ad8419c2f65ad878

You may also log in with your user ID and password at <https://mc.manuscriptcentral.com/nrr> and access your Author Centre, where you will find your manuscript in the folder "Manuscripts With Decisions" on your author dashboard; click "create revision" and then follow the steps on the screen.

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

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.

" PENAFIAN: E-mel ini dan apa-apa fail yang dikepilkan bersamanya ("Mesej") adalah ditujukan hanya untuk kegunaan penerima(-penerima) yang termaklum di atas dan mungkin mengandungi maklumat sulit. Anda dengan ini dimaklumkan bahawa mengambil apa jua tindakan berdasarkan kepada, membuat penilaian, mengulang hantar, menghebah, mengedar, mencetak, atau menyalin Mesej ini atau sebahagian daripadanya oleh sesiapa selain daripada penerima(-penerima) yang termaklum di atas adalah dilarang. Jika anda telah menerima Mesej ini kerana kesilapan, anda mesti menghapuskan Mesej ini dengan segera dan memaklumkan kepada penghantar Mesej ini menerusi balasan e-mel. Pendapat-pendapat, rumusan-rumusan, dan sebarang maklumat lain di dalam Mesej ini yang tidak berkait dengan urusan rasmi Pusat Perubatan Universiti Malaya adalah difahami sebagai bukan dikeluarkan atau dipraktik oleh mana-mana pihak yang disebut.

DISCLAIMER: This e-mail and any files transmitted with it ("Message") is intended only for the use of the recipient(s) named above and may contain confidential information. You are hereby notified that the taking of any action in reliance upon, or any review, retransmission, dissemination, distribution, printing or copying of this Message or any part thereof by anyone other than the intended recipient(s) is strictly prohibited. If you have received this Message in error, you should delete this Message immediately and advise the sender by return e-mail. Opinions, conclusions and other information in this Message that do not relate to the official business of University Malaya Medical Centre shall be understood as neither given nor endorsed by any of the forementioned. "

Disclaimer: The information in this e-mail (including any attachments) is strictly confidential and may be legally privileged. If you are not the intended recipient of this message, please delete it including any attachments and immediately notify the sender. Any disclosure, copying, distribution or use either whole or partial of its contents is strictly prohibited except with formal approval. FrieslandCampina cannot guarantee that e-mail communications are secured and error-free and does not accept any liability for damages resulting from the use of e-mail. The general terms and conditions of [purchase](#) respectively [sale and delivery](#) of Royal FrieslandCampina N.V., are applicable to all transactions and undertakings resulting therefrom.

De informatie in deze e-mail (inclusief bijlagen) is strikt persoonlijk en vertrouwelijk en mogelijk juridisch geprivilegieerd. Indien u niet de bedoelde ontvanger van dit bericht bent verzoeken wij u het bericht inclusief bijlagen te vernietigen en ons hiervan onmiddellijk op de hoogte te stellen. Openbaarmaking, vermenigvuldiging of verspreiding van (een gedeelte van) dit bericht is, zonder formele toestemming, strikt verboden. FrieslandCampina kan niet garanderen dat e-mail communicatie veilig en foutloos is en accepteert geen enkele aansprakelijkheid voor schade voortvloeiende uit het gebruik hiervan. Op alle transacties en daaruit voortvloeiende verbintenissen zijn de algemene [inkoopvoorwaarden](#) respectievelijk [verkoopvoorwaarden](#) van Koninklijke FrieslandCampina N.V. van toepassing.

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.

4	Revisi ke-3 (ID NRR-20 0.32.R3) disubmit ke Jurnal	18 Dec 2020
	<u>Keputusan</u> : Dapat diterima secara prinsip (jatuh tempo 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

	032.R5	neurodevelopmental and cognitive consequences: A Scoping review		
<ul style="list-style-type: none"> Acceptable as received (31-May-2021) In Production 			Submitting Author: Muhardi, Leilani	
<input checked="" type="checkbox"/> Contact Journal		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
<ul style="list-style-type: none"> Acceptable in principle (12-May-2021) a revision has been submitted 		View Submission	Submitting Author: Muhardi, Leilani	
<input checked="" type="checkbox"/> Contact Journal		Cover Letter		

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



NUTRITION RESEARCH REVIEWS



**CAMBRIDGE
UNIVERSITY PRESS**

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 A¹, M.Y. Jalaludin², B.K. Poh³, R. Sanusi⁴, V.M.H. Tan⁵, J.M.Geurts⁶, L. Muhardi⁷

7
8 1. Department of Child Health, Faculty of Medicine, Universitas Airlangga, Soetomo General Academic
9 Hospital, Surabaya, Indonesia

10 2. Department of Paediatrics, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur,
11 Malaysia.

12 3. Nutritional Sciences Programme and Centre for Community Health Studies (ReaCH), Faculty of
13 Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

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

15 5. Dietetics and Nutrition Programme, Health and Social Sciences cluster, Singapore Institute of
16 Technology, Singapore

17 6. FrieslandCampina, Amersfoort, The Netherlands

18 7. FrieslandCampina AMEA, Singapore

19
20 **Corresponding author:**

21 Muhammad Yazid Jalaludin

22 Professor

23 Department of Paediatrics

24 Faculty of Medicine

25 University of Malaya

26 59100 Kuala Lumpur

27 Tel: 03-79492065

28 Fax: 03-79494704

29 Email: yazidj@ummc.edu.my or yazidjal@um.edu.my

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**

341 **Acknowledgements**

342 The authors thank Content Ed Net Singapore for providing editorial and medical writing assistance in
343 retrieving relevant publications and the development of the 1st draft of the manuscript.

344

345 **Funding**

346 FrieslandCampina supported the retrieval of relevant publications and the development of the early first
347 manuscript drafts by Content Ed Singapore. None of the authors received an educational grant from
348 FrieslandCampina to participate in the writing.

349

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

369 **References**

370

- 371 1. Global Nutrition Report: Action on equity to end malnutrition. Development Initiatives 2020.
- 372 2. Global Nutrition Report: Shining a light to spur action on nutrition. Development Initiatives. 2018.
- 373 3. de Onis M OA, Borghi E, Siyam A, Pinol A. WHO Child Growth Standards. World Health Organization;
- 374 2006.
- 375 4. Grantham-McGregor S, Cheung YB, Cueto S, et al. Developmental potential in the first 5 years for
- 376 children in developing countries. *Lancet*. 2007;369(9555):60-70.
- 377 5. Sudfeld CR, McCoy DC, Danaei G, et al. Linear growth and child development in low- and middle-
- 378 income countries: a meta-analysis. *Pediatrics*. 2015;135(5):e1266-75.
- 379 6. Prado EL, Larson LM, Cox K, et al. Do effects of early life interventions on linear growth correspond to
- 380 effects on neurobehavioural development? A systematic review and meta-analysis. *Lancet Glob Health*.
- 381 2019;7(10):e1398-e413.
- 382 7. Miller AC, Murray MB, Thomson DR, et al. How consistent are associations between stunting and child
- 383 development? Evidence from a meta-analysis of associations between stunting and multidimensional child
- 384 development in fifteen low- and middle-income countries. *Public Health Nutr*. 2016;19(8):1339-47.
- 385 8. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when
- 386 choosing between a systematic or scoping review approach. *BMC medical research methodology*.
- 387 2018;18(1):143.
- 388 9. Camargo-Figuera FA, Barros AJ, Santos IS, et al. Early life determinants of low IQ at age 6 in children
- 389 from the 2004 Pelotas Birth Cohort: a predictive approach. *BMC Pediatr*. 2014;14:308.
- 390 10. Cheung YB, Ashorn P. Continuation of linear growth failure and its association with cognitive ability are
- 391 not dependent on initial length-for-age: a longitudinal study from 6 months to 11 years of age. *Acta Paediatr*.
- 392 2010;99(11):1719-23.
- 393 11. Hamadani JD, Tofail F, Huda SN, et al. Cognitive deficit and poverty in the first 5 years of childhood in
- 394 Bangladesh. *Pediatrics*. 2014;134(4):e1001-8.
- 395 12. Mendez MA, Adair LS. Severity and timing of stunting in the first two years of life affect performance
- 396 on cognitive tests in late childhood. *J Nutr*. 1999;129(8):1555-62.
- 397 13. Mohd Nasir MT, Norimah AK, Hazizi AS, et al. Child feeding practices, food habits, anthropometric
- 398 indicators and cognitive performance among preschoolers in Peninsular Malaysia. *Appetite*. 2012;58(2):525-30.
- 399 14. Baker-Henningham H, Hamadani JD, Huda SN, et al. Undernourished children have different
- 400 temperaments than better-nourished children in rural Bangladesh. *J Nutr*. 2009;139(9):1765-71.
- 401 15. Crookston BT, Schott W, Cueto S, et al. Postinfancy growth, schooling, and cognitive achievement:
- 402 *Young Lives*. *Am J Clin Nutr*. 2013;98(6):1555-63.
- 403 16. Hoddinott J, Behrman JR, Maluccio JA, et al. Adult consequences of growth failure in early childhood.
- 404 *Am J Clin Nutr*. 2013;98(5):1170-8.
- 405 17. Sunny BS, DeStavola B, Dube A, et al. Does early linear growth failure influence later school
- 406 performance? A cohort study in Karonga district, northern Malawi. *PLoS One*. 2018;13(11):e0200380.
- 407 18. Casale D, Desmond C, Richter L. The association between stunting and psychosocial development among
- 408 preschool children: a study using the South African Birth to Twenty cohort data. *Child Care Health Dev*.
- 409 2014;40(6):900-10.
- 410 19. Desmond C, Casale D. Catch-up growth in stunted children: Definitions and predictors. *PLoS One*.
- 411 2017;12(12):e0189135.
- 412 20. Kvestad I, Taneja S, Kumar T, et al. Vitamin B12 and Folic Acid Improve Gross Motor and Problem-
- 413 Solving Skills in Young North Indian Children: A Randomized Placebo-Controlled Trial. *PLoS One*.
- 414 2015;10(6):e0129915.

- 415 21. Rosado JL, Lopez P, Garcia OP, et al. Effectiveness of the nutritional supplement used in the Mexican
416 Oportunidades programme on growth, anaemia, morbidity and cognitive development in children aged 12-24
417 months. *Public Health Nutr.* 2011;14(5):931-7.
- 418 22. Yousafzai AK, Rasheed MA, Rizvi A, et al. Effect of integrated responsive stimulation and nutrition
419 interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health
420 outcomes: a cluster-randomised factorial effectiveness trial. *Lancet.* 2014;384(9950):1282-93.
- 421 23. Morano M, Colella D, Caroli M. Gross motor skill performance in a sample of overweight and non-
422 overweight preschool children. *Int J Pediatr Obes.* 2011;6 Suppl 2:42-6.
- 423 24. Liang J, Matheson BE, Kaye WH, et al. Neurocognitive correlates of obesity and obesity-related
424 behaviors in children and adolescents. *International journal of obesity (2005).* 2014;38(4):494-506.
- 425 25. Reinert KR, Po'e EK, Barkin SL. The relationship between executive function and obesity in children and
426 adolescents: a systematic literature review. *J Obes.* 2013;2013:820956.
- 427 26. Hayes JF, Eichen DM, Barch DM, et al. Executive function in childhood obesity: Promising intervention
428 strategies to optimize treatment outcomes. *Appetite.* 2018;124:10-23.
- 429 27. Walker SP, Chang SM, Younger N, et al. The effect of psychosocial stimulation on cognition and
430 behaviour at 6 years in a cohort of term, low-birthweight Jamaican children. *Dev Med Child Neurol.*
431 2010;52(7):e148-54.
- 432 28. Nguyen PH, Kim SS, Sanghvi T, et al. Integrating Nutrition Interventions into an Existing Maternal,
433 Neonatal, and Child Health Program Increased Maternal Dietary Diversity, Micronutrient Intake, and Exclusive
434 Breastfeeding Practices in Bangladesh: Results of a Cluster-Randomized Program Evaluation. *J Nutr.*
435 2017;147(12):2326-37.
- 436 29. Kristjansson E, Francis DK, Liberato S, et al. Food supplementation for improving the physical and
437 psychosocial health of socio-economically disadvantaged children aged three months to five years. *Cochrane*
438 *Database Syst Rev.* 2015(3):CD009924.
- 439 30. Pimpin L, Kranz S, Liu E, et al. Effects of animal protein supplementation of mothers, preterm infants,
440 and term infants on growth outcomes in childhood: a systematic review and meta-analysis of randomized trials.
441 *Am J Clin Nutr.* 2019;110(2):410-29.
- 442 31. Sjarif DR, Yuliati K, Iskandar WJ. Daily consumption of growing-up reduces stunting among Indonesian
443 toddlers. *Medical Journal Indonesia.* 2019;28:70-6.
- 444 32. Lee R, Singh L, van Liefde D, et al. Milk Powder Added to a School Meal Increases Cognitive Test
445 Scores in Ghanaian Children. *J Nutr.* 2018;148(7):1177-84.
- 446 33. Smithers LG, Golley RK, Mittinty MN, et al. Do dietary trajectories between infancy and toddlerhood
447 influence IQ in childhood and adolescence? Results from a prospective birth cohort study. *PLoS One.*
448 2013;8(3):e58904.
- 449 34. Miller AL, Lee HJ, Lumeng JC. Obesity-associated biomarkers and executive function in children. *Pediatr*
450 *Res.* 2015;77(1-2):143-7.
- 451 35. Double-duty actions for nutrition. Policy Brief. World Health Organization. 2017.
- 452 36. World Health Organization. Global nutrition targets 2025. 2014.
- 453 37. Smithers LG, Lynch JW, Yang S, et al. Impact of neonatal growth on IQ and behavior at early school
454 age. *Pediatrics.* 2013;132(1):e53-60.
- 455 38. Aubuchon-Endsley NL, Grant SL, Berhanu G, et al. Hemoglobin, growth, and attention of infants in
456 southern Ethiopia. *Child Dev.* 2011;82(4):1238-51.
- 457 39. Waber DP, Bryce CP, Girard JM, et al. Impaired IQ and academic skills in adults who experienced
458 moderate to severe infantile malnutrition: a 40-year study. *Nutr Neurosci.* 2014;17(2):58-64.
- 459 40. Sudfeld CR, McCoy DC, Fink G, et al. Malnutrition and Its Determinants Are Associated with Suboptimal
460 Cognitive, Communication, and Motor Development in Tanzanian Children. *J Nutr.* 2015;145(12):2705-14.
- 461 41. Ip P, Ho FKW, Rao N, et al. Impact of nutritional supplements on cognitive development of children in
462 developing countries: A meta-analysis. *Sci Rep.* 2017;7(1):10611.
- 463 42. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children
464 under-two in low- and middle-income countries. *Matern Child Nutr.* 2017;13(1).



ahmad suryawan <suryawan.ahmad@gmail.com>

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

Muhardi, L.M. (Leilani) <leilani.muhardi@frieslandcampina.com>

Wed, Mar 10, 2021 at 7:10 AM

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

Cc: "Kudla, U. (Urszula)" <Urszula.Kudla@frieslandcampina.com>, yazidj <yazidj@ummc.edu.my>

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:

nrr.edoffice@cambridge.org

To:

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:

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

https://mc.manuscriptcentral.com/nrr?URL_MASK=0408fe57c65447b086bc49eaf97b7fe1

You may also log in with your user ID and password at <https://mc.manuscriptcentral.com/nrr> and access your Author Centre, where you will find your manuscript in the folder "Manuscripts With Decisions" on your author dashboard; click "create revision" and then follow the steps on the screen.

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

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

Disclaimer: The information in this e-mail (including any attachments) is strictly confidential and may be legally privileged. If you are not the intended recipient of this message, please delete it including any attachments and immediately notify the sender. Any disclosure, copying, distribution or use either whole or partial of its contents is strictly prohibited except with formal approval. FrieslandCampina cannot guarantee that e-mail communications are secured and error-free and does not accept any liability for damages resulting from the use of e-mail. The general terms and conditions of [purchase](#) respectively [sale and delivery](#) of Royal FrieslandCampina N.V., are applicable to all transactions and undertakings resulting therefrom.

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)

5	Revisi ke-4 (ID NRR-20 0.32.R4) disubmit ke Jurnal	31 March 2021
	<u>Keputusan:</u> <i>Acceptable as received</i> (jatuh tempo 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

<ul style="list-style-type: none"> ● Acceptable as received (31-May-2021) ● In Production <p><input checked="" type="checkbox"/> Contact Journal</p>	<p>032.R5</p> <p>neurodevelopmental and cognitive consequences: A Scoping review</p> <p>Submitting Author: Muhardi, Leilani</p> <p>Cover Letter</p>
--	---

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

<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>
-------------------------	---	----------------------------------



NUTRITION RESEARCH REVIEWS



CAMBRIDGE
UNIVERSITY PRESS

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. Suryawan¹, M.Y. Jalaludin², B.K. Poh³, R. Sanusi⁴, V.M.H. Tan⁵, J.M. Geurts⁶, L. Muhandi⁷

7

8 1. Department of Child Health, Faculty of Medicine, Universitas Airlangga, Soetomo General Academic
9 Hospital, Surabaya, Indonesia

10 2. Department of Paediatrics, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur,
11 Malaysia.

12 3. Nutritional Sciences Programme and Centre for Community Health Studies (ReaCH), Faculty of
13 Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

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

15 5. Dietetics and Nutrition Programme, Health and Social Sciences cluster, Singapore Institute of
16 Technology, Singapore

17 6. FrieslandCampina, Amersfoort, The Netherlands

18 7. FrieslandCampina AMEA, Singapore

19

20 **Corresponding author:**

21 Muhammad Yazid Jalaludin

22 Professor

23 Department of Paediatrics

24 Faculty of Medicine

25 University of Malaya

26 59100 Kuala Lumpur

27 Tel: 03-79492065

28 Fax: 03-79494704

29 Email: yazidj@ummc.edu.my or yazidjal@um.edu.my

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 SD))(3) and severe underweight (below
70 WAZ (weight-for-age Z score) minus three standard deviations (-3 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 $2\text{ SD}>WAZ<$

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.

359 **DECLARATIONS**

360 **Acknowledgements**

361 The authors thank Content Ed Net Singapore for providing editorial and medical writing assistance in
362 retrieving relevant publications and the development of the first drafts of the manuscript.

363

364 **Funding**

365 FrieslandCampina supported the retrieval of relevant publications and the development of the early first
366 manuscript drafts by Content Ed Singapore. None of the authors received an educational grant from
367 FrieslandCampina to participate in the writing.

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

388 **References**

389

- 390 1. Global Nutrition Report: Action on equity to end malnutrition. Development Initiatives 2020.
- 391 2. Global Nutrition Report: Shining a light to spur action on nutrition. Development Initiatives. 2018.
- 392 3. de Onis M OA, Borghi E, Siyam A, Pinol A. WHO Child Growth Standards. World Health Organization;
393 2006.
- 394 4. Grantham-McGregor S, Cheung YB, Cueto S, et al. Developmental potential in the first 5 years for
395 children in developing countries. *Lancet*. 2007;369(9555):60-70.
- 396 5. Sudfeld CR, McCoy DC, Danaei G, et al. Linear growth and child development in low- and middle-
397 income countries: a meta-analysis. *Pediatrics*. 2015;135(5):e1266-75.
- 398 6. Prado EL, Larson LM, Cox K, et al. Do effects of early life interventions on linear growth correspond to
399 effects on neurobehavioural development? A systematic review and meta-analysis. *Lancet Glob Health*.
400 2019;7(10):e1398-e413.
- 401 7. Miller AC, Murray MB, Thomson DR, et al. How consistent are associations between stunting and child
402 development? Evidence from a meta-analysis of associations between stunting and multidimensional child
403 development in fifteen low- and middle-income countries. *Public Health Nutr*. 2016;19(8):1339-47.
- 404 8. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when
405 choosing between a systematic or scoping review approach. *BMC medical research methodology*.
406 2018;18(1):143.
- 407 9. Camargo-Figuera FA, Barros AJ, Santos IS, et al. Early life determinants of low IQ at age 6 in children
408 from the 2004 Pelotas Birth Cohort: a predictive approach. *BMC Pediatr*. 2014;14:308.
- 409 10. Cheung YB, Ashorn P. Continuation of linear growth failure and its association with cognitive ability are
410 not dependent on initial length-for-age: a longitudinal study from 6 months to 11 years of age. *Acta Paediatr*.
411 2010;99(11):1719-23.
- 412 11. Hamadani JD, Tofail F, Huda SN, et al. Cognitive deficit and poverty in the first 5 years of childhood in
413 Bangladesh. *Pediatrics*. 2014;134(4):e1001-8.
- 414 12. Mendez MA, Adair LS. Severity and timing of stunting in the first two years of life affect performance
415 on cognitive tests in late childhood. *J Nutr*. 1999;129(8):1555-62.
- 416 13. Mohd Nasir MT, Norimah AK, Hazizi AS, et al. Child feeding practices, food habits, anthropometric
417 indicators and cognitive performance among preschoolers in Peninsular Malaysia. *Appetite*. 2012;58(2):525-30.
- 418 14. Baker-Henningham H, Hamadani JD, Huda SN, et al. Undernourished children have different
419 temperaments than better-nourished children in rural Bangladesh. *J Nutr*. 2009;139(9):1765-71.
- 420 15. Crookston BT, Schott W, Cueto S, et al. Postinfancy growth, schooling, and cognitive achievement:
421 Young Lives. *Am J Clin Nutr*. 2013;98(6):1555-63.
- 422 16. Hoddinott J, Behrman JR, Maluccio JA, et al. Adult consequences of growth failure in early childhood.
423 *Am J Clin Nutr*. 2013;98(5):1170-8.
- 424 17. Sunny BS, DeStavola B, Dube A, et al. Does early linear growth failure influence later school
425 performance? A cohort study in Karonga district, northern Malawi. *PLoS One*. 2018;13(11):e0200380.
- 426 18. Casale D, Desmond C, Richter L. The association between stunting and psychosocial development among
427 preschool children: a study using the South African Birth to Twenty cohort data. *Child Care Health Dev*.
428 2014;40(6):900-10.
- 429 19. Desmond C, Casale D. Catch-up growth in stunted children: Definitions and predictors. *PLoS One*.
430 2017;12(12):e0189135.
- 431 20. Kvestad I, Taneja S, Kumar T, et al. Vitamin B12 and Folic Acid Improve Gross Motor and Problem-
432 Solving Skills in Young North Indian Children: A Randomized Placebo-Controlled Trial. *PLoS One*.
433 2015;10(6):e0129915.

- 434 21. Rosado JL, Lopez P, Garcia OP, et al. Effectiveness of the nutritional supplement used in the Mexican
435 Oportunidades programme on growth, anaemia, morbidity and cognitive development in children aged 12-24
436 months. *Public Health Nutr.* 2011;14(5):931-7.
- 437 22. Yousafzai AK, Rasheed MA, Rizvi A, et al. Effect of integrated responsive stimulation and nutrition
438 interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health
439 outcomes: a cluster-randomised factorial effectiveness trial. *Lancet.* 2014;384(9950):1282-93.
- 440 23. Morano M, Colella D, Caroli M. Gross motor skill performance in a sample of overweight and non-
441 overweight preschool children. *Int J Pediatr Obes.* 2011;6 Suppl 2:42-6.
- 442 24. Liang J, Matheson BE, Kaye WH, et al. Neurocognitive correlates of obesity and obesity-related
443 behaviors in children and adolescents. *International journal of obesity (2005).* 2014;38(4):494-506.
- 444 25. Reinert KR, Po'e EK, Barkin SL. The relationship between executive function and obesity in children and
445 adolescents: a systematic literature review. *J Obes.* 2013;2013:820956.
- 446 26. Hayes JF, Eichen DM, Barch DM, et al. Executive function in childhood obesity: Promising intervention
447 strategies to optimize treatment outcomes. *Appetite.* 2018;124:10-23.
- 448 27. Walker SP, Chang SM, Younger N, et al. The effect of psychosocial stimulation on cognition and
449 behaviour at 6 years in a cohort of term, low-birthweight Jamaican children. *Dev Med Child Neurol.*
450 2010;52(7):e148-54.
- 451 28. Nguyen PH, Kim SS, Sanghvi T, et al. Integrating Nutrition Interventions into an Existing Maternal,
452 Neonatal, and Child Health Program Increased Maternal Dietary Diversity, Micronutrient Intake, and Exclusive
453 Breastfeeding Practices in Bangladesh: Results of a Cluster-Randomized Program Evaluation. *J Nutr.*
454 2017;147(12):2326-37.
- 455 29. Kristjansson E, Francis DK, Liberato S, et al. Food supplementation for improving the physical and
456 psychosocial health of socio-economically disadvantaged children aged three months to five years. *Cochrane*
457 *Database Syst Rev.* 2015(3):CD009924.
- 458 30. Pimpin L, Kranz S, Liu E, et al. Effects of animal protein supplementation of mothers, preterm infants,
459 and term infants on growth outcomes in childhood: a systematic review and meta-analysis of randomized trials.
460 *Am J Clin Nutr.* 2019;110(2):410-29.
- 461 31. Sjarif DR, Yuliati K, Iskandar WJ. Daily consumption of growing-up [milk](#) reduces stunting among
462 Indonesian toddlers. *Medical Journal Indonesia.* 2019;28:70-6.
- 463 32. Lee R, Singh L, van Liefde D, et al. Milk Powder Added to a School Meal Increases Cognitive Test
464 Scores in Ghanaian Children. *J Nutr.* 2018;148(7):1177-84.
- 465 33. Smithers LG, Golley RK, Mittinty MN, et al. Do dietary trajectories between infancy and toddlerhood
466 influence IQ in childhood and adolescence? Results from a prospective birth cohort study. *PLoS One.*
467 2013;8(3):e58904.
- 468 34. Miller AL, Lee HJ, Lumeng JC. Obesity-associated biomarkers and executive function in children. *Pediatr*
469 *Res.* 2015;77(1-2):143-7.
- 470 35. Double-duty actions for nutrition. Policy Brief. World Health Organization. 2017.
- 471 36. World Health Organization. Global nutrition targets 2025. 2014.
- 472 37. Smithers LG, Lynch JW, Yang S, et al. Impact of neonatal growth on IQ and behavior at early school
473 age. *Pediatrics.* 2013;132(1):e53-60.
- 474 38. Aubuchon-Endsley NL, Grant SL, Berhanu G, et al. Hemoglobin, growth, and attention of infants in
475 southern Ethiopia. *Child Dev.* 2011;82(4):1238-51.
- 476 39. Waber DP, Bryce CP, Girard JM, et al. Impaired IQ and academic skills in adults who experienced
477 moderate to severe infantile malnutrition: a 40-year study. *Nutr Neurosci.* 2014;17(2):58-64.
- 478 40. Sudfeld CR, McCoy DC, Fink G, et al. Malnutrition and Its Determinants Are Associated with Suboptimal
479 Cognitive, Communication, and Motor Development in Tanzanian Children. *J Nutr.* 2015;145(12):2705-14.
- 480 41. Ip P, Ho FKW, Rao N, et al. Impact of nutritional supplements on cognitive development of children in
481 developing countries: A meta-analysis. *Sci Rep.* 2017;7(1):10611.
- 482 42. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children
483 under-two in low- and middle-income countries. *Matern Child Nutr.* 2017;13(1).

Fwd: Nutrition Research Reviews NRR-20-032.R4

Muhardi, L.M. (Leilani) <leilani.muhardi@frieslandcampina.com>
To: "suryawan.ahmad@gmail.com" <suryawan.ahmad@gmail.com>

Thu, May 13, 2021 at 7:37 AM

Yth. Dr. Wawan,

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

Salam hormat,

Leilani

From: Muhammad Yazid Jalaludin <yazidj@ummc.edu.my>
Sent: Thursday, 13 May 2021, 01:26
To: Muhardi, L.M. (Leilani)
Subject: Fwd: Nutrition Research Reviews NRR-20-032.R4

****This message is from an EXTERNAL SENDER - be CAUTIOUS. If this message appears as suspicious, do not reply, click on links or attachments and report the email.**

Hi,
Some work given to us on the Eidul Fitri.
Yazid

Sent from my iPhone

Begin forwarded message:

From: Nutrition Research Reviews <onbehalf@manuscriptcentral.com>
Date: 13 May 2021 at 01:20:32 MYT
To: yazidj@ummc.edu.my
Subject: Nutrition Research Reviews NRR-20-032.R4
Reply-To: nrr.edoffice@cambridge.org

12-May-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 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.

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. *******

https://mc.manuscriptcentral.com/nrr?URL_MASK=7fda1d706f5e4285b92e1c13709b28df

You may also log in with your user ID and password at <https://mc.manuscriptcentral.com/nrr> and access your Author Centre, where you will find your manuscript in the folder "Manuscripts With Decisions" on your author dashboard; click "create revision" and then follow the steps on the screen.

When revising your paper, please ensure that your changes are marked using, for example a different font colour, or yellow highlighting. Please do NOT use Track Changes, as the resulting file can be difficult to read.

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

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.

" PENAFIAN: E-mel ini dan apa-apa fail yang dikepilkan bersamanya ("Mesej") adalah ditujukan hanya untuk kegunaan penerima(-penerima) yang termaklum di atas dan mungkin mengandungi maklumat sulit. Anda dengan ini dimaklumkan bahawa mengambil apa jua tindakan berdasarkan kepada, membuat penilaian, mengulang hantar, menghebah, mengedar, mencetak, atau menyalin Mesej ini atau sebahagian daripadanya oleh sesiapa selain daripada penerima(-penerima) yang termaklum di atas adalah dilarang. Jika anda telah menerima Mesej ini kerana kesilapan, anda mesti menghapuskan Mesej ini dengan segera dan memaklumkan kepada penghantar Mesej ini menerusi balasan e-mel. Pendapat-pendapat, rumusan-rumusan, dan sebarang maklumat lain di dalam Mesej ini yang tidak berkait dengan urusan rasmi Pusat Perubatan Universiti Malaya adalah difahami sebagai bukan dikeluarkan atau diperakui oleh mana-mana pihak yang disebut.

DISCLAIMER: This e-mail and any files transmitted with it ("Message") is intended only for the use of the recipient(s) named above and may contain confidential information. You are hereby notified that the taking of any action in reliance upon, or any review, retransmission, dissemination, distribution, printing or copying of this Message or any part thereof by anyone other than the intended recipient(s) is strictly prohibited. If you have received this Message in error, you should delete this Message immediately and advise the sender by return e-mail. Opinions, conclusions and other information in this Message that do not relate to the official business of University Malaya Medical Centre shall be understood as neither given nor endorsed by any of the forementioned. "

Disclaimer: The information in this e-mail (including any attachments) is strictly confidential and may be legally privileged. If you are not the intended recipient of this message, please delete it including any attachments and immediately notify the sender. Any disclosure, copying, distribution or use either whole or partial of its contents is strictly prohibited except with formal approval. FrieslandCampina cannot guarantee that e-mail communications are secured and error-free and does not accept any liability for damages resulting from the use of e-mail. The general terms and conditions of [purchase](#) respectively [sale and delivery](#) of Royal FrieslandCampina N.V., are applicable to all transactions and undertakings resulting therefrom.

De informatie in deze e-mail (inclusief bijlagen) is strikt persoonlijk en vertrouwelijk en mogelijk juridisch geprivilegieerd. Indien u niet de bedoelde ontvanger van dit bericht bent verzoeken wij u het bericht inclusief bijlagen te vernietigen en ons hiervan onmiddellijk op de hoogte te stellen. Openbaarmaking, vermenigvuldiging of verspreiding van (een gedeelte van) dit bericht is, zonder formele toestemming, strikt verboden. FrieslandCampina kan niet garanderen dat e-mail communicatie veilig en foutloos is en accepteert geen enkele aansprakelijkheid voor schade voortvloeiende uit het gebruik hiervan. Op alle transacties en daaruit voortvloeiende verbintenissen zijn de algemene [inkoopvoorwaarden](#)

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.

6

Revisi ke-5 (ID NRR-20 0.32.R5) disubmit ke Jurnal

26 May 2021

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"> ● Acceptable as received (31-May-2021) ● In Production <p><input checked="" type="checkbox"/> Contact Journal</p>	<p>032.R5</p> <p>neurodevelopmental and cognitive consequences: A Scoping review</p> <p>Submitting Author: Muhardi, Leilani</p> <p>Cover Letter</p>
--	---

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

<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>
-------------------------	---	----------------------------------



NUTRITION RESEARCH REVIEWS



**CAMBRIDGE
UNIVERSITY PRESS**

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
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. Suryawan¹, M.Y. Jalaludin², B.K. Poh³, R. Sanusi⁴, V.M.H. Tan⁵, J.M. Geurts⁶, L. Muhandi⁷

7

8 1. Department of Child Health, Faculty of Medicine, Universitas Airlangga, Soetomo General Academic
9 Hospital, Surabaya, Indonesia

10 2. Department of Paediatrics, Faculty of Medicine, University of Malaya, 59100 Kuala Lumpur,
11 Malaysia.

12 3. Nutritional Sciences Programme and Centre for Community Health Studies (ReaCH), Faculty of
13 Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

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

15 5. Dietetics and Nutrition Programme, Health and Social Sciences cluster, Singapore Institute of
16 Technology, Singapore

17 6. FrieslandCampina, Amersfoort, The Netherlands

18 7. FrieslandCampina AMEA, Singapore

19

20 **Corresponding author:**

21 Muhammad Yazid Jalaludin

22 Professor

23 Department of Paediatrics

24 Faculty of Medicine

25 University of Malaya

26 59100 Kuala Lumpur

27 Tel: 03-79492065

28 Fax: 03-79494704

29 Email: yazidj@ummc.edu.my or yazidjal@um.edu.my

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

359 **DECLARATIONS**

360 **Acknowledgements**

361 The authors thank Content Ed Net Singapore for providing editorial and medical writing assistance in
362 retrieving relevant publications and the development of the first drafts of the manuscript.

363

364 **Funding**

365 FrieslandCampina supported the retrieval of relevant publications and the development of the early first
366 manuscript drafts by Content Ed Singapore. None of the authors received an educational grant from
367 FrieslandCampina to participate in the writing.

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

388 **References**

389

- 390 1. *Global Nutrition Report: Action on equity to end malnutrition. Development Initiatives*
391 2020.
- 392 2. Popkin, B.M., C. Corvalan, and L.M. Grummer-Strawn, *Dynamics of the double burden of*
393 *malnutrition and the changing nutrition reality. Lancet, 2020. 395(10217): p. 65-74.*
- 394 3. *Global Nutrition Report: Shining a light to spur action on nutrition. Development*
395 *Initiatives. 2018.*
- 396 4. de Onis M, O.A., Borghi E, Siyam A, Pinol A, *WHO Child Growth Standards. 2006, World*
397 *Health Organization.*
- 398 5. Grantham-McGregor, S., Y.B. Cheung, S. Cueto, et al., *Developmental potential in the first*
399 *5 years for children in developing countries. Lancet, 2007. 369(9555): p. 60-70.*
- 400 6. Sudfeld, C.R., D.C. McCoy, G. Danaei, et al., *Linear growth and child development in low-*
401 *and middle-income countries: a meta-analysis. Pediatrics, 2015. 135(5): p. e1266-75.*
- 402 7. Prado, E.L., L.M. Larson, K. Cox, et al., *Do effects of early life interventions on linear*
403 *growth correspond to effects on neurobehavioural development? A systematic review and*
404 *meta-analysis. Lancet Glob Health, 2019. 7(10): p. e1398-e1413.*
- 405 8. Miller, A.C., M.B. Murray, D.R. Thomson, et al., *How consistent are associations between*
406 *stunting and child development? Evidence from a meta-analysis of associations between*
407 *stunting and multidimensional child development in fifteen low- and middle-income*
408 *countries. Public Health Nutr, 2016. 19(8): p. 1339-47.*
- 409 9. Munn, Z., M.D.J. Peters, C. Stern, et al., *Systematic review or scoping review? Guidance for*
410 *authors when choosing between a systematic or scoping review approach. BMC Med Res*
411 *Methodol, 2018. 18(1): p. 143.*
- 412 10. Camargo-Figuera, F.A., A.J. Barros, I.S. Santos, et al., *Early life determinants of low IQ at*
413 *age 6 in children from the 2004 Pelotas Birth Cohort: a predictive approach. BMC Pediatr,*
414 *2014. 14: p. 308.*
- 415 11. Cheung, Y.B. and P. Ashorn, *Continuation of linear growth failure and its association with*
416 *cognitive ability are not dependent on initial length-for-age: a longitudinal study from 6*
417 *months to 11 years of age. Acta Paediatr, 2010. 99(11): p. 1719-23.*
- 418 12. Hamadani, J.D., F. Tofail, S.N. Huda, et al., *Cognitive deficit and poverty in the first 5*
419 *years of childhood in Bangladesh. Pediatrics, 2014. 134(4): p. e1001-8.*
- 420 13. Mendez, M.A. and L.S. Adair, *Severity and timing of stunting in the first two years of life*
421 *affect performance on cognitive tests in late childhood. J Nutr, 1999. 129(8): p. 1555-62.*
- 422 14. Mohd Nasir, M.T., A.K. Norimah, A.S. Hazizi, et al., *Child feeding practices, food habits,*
423 *anthropometric indicators and cognitive performance among preschoolers in Peninsular*
424 *Malaysia. Appetite, 2012. 58(2): p. 525-30.*
- 425 15. Baker-Henningham, H., J.D. Hamadani, S.N. Huda, et al., *Undernourished children have*
426 *different temperaments than better-nourished children in rural Bangladesh. J Nutr, 2009.*
427 *139(9): p. 1765-71.*
- 428 16. Crookston, B.T., W. Schott, S. Cueto, et al., *Postinfancy growth, schooling, and cognitive*
429 *achievement: Young Lives. Am J Clin Nutr, 2013. 98(6): p. 1555-63.*
- 430 17. Hoddinott, J., J.R. Behrman, J.A. Maluccio, et al., *Adult consequences of growth failure in*
431 *early childhood. Am J Clin Nutr, 2013. 98(5): p. 1170-8.*
- 432 18. Sunny, B.S., B. DeStavola, A. Dube, et al., *Does early linear growth failure influence later*
433 *school performance? A cohort study in Karonga district, northern Malawi. PLoS One, 2018.*
434 *13(11): p. e0200380.*

- 435 19. Casale, D., C. Desmond, and L. Richter, *The association between stunting and psychosocial*
 436 *development among preschool children: a study using the South African Birth to Twenty*
 437 *cohort data*. *Child Care Health Dev*, 2014. **40**(6): p. 900-10.
- 438 20. Desmond, C. and D. Casale, *Catch-up growth in stunted children: Definitions and*
 439 *predictors*. *PLoS One*, 2017. **12**(12): p. e0189135.
- 440 21. Kvestad, I., S. Taneja, T. Kumar, et al., *Vitamin B12 and Folic Acid Improve Gross Motor*
 441 *and Problem-Solving Skills in Young North Indian Children: A Randomized Placebo-*
 442 *Controlled Trial*. *PLoS One*, 2015. **10**(6): p. e0129915.
- 443 22. Rosado, J.L., P. Lopez, O.P. Garcia, et al., *Effectiveness of the nutritional supplement used*
 444 *in the Mexican Oportunidades programme on growth, anaemia, morbidity and cognitive*
 445 *development in children aged 12-24 months*. *Public Health Nutr*, 2011. **14**(5): p. 931-7.
- 446 23. Yousafzai, A.K., M.A. Rasheed, A. Rizvi, et al., *Effect of integrated responsive stimulation*
 447 *and nutrition interventions in the Lady Health Worker programme in Pakistan on child*
 448 *development, growth, and health outcomes: a cluster-randomised factorial effectiveness*
 449 *trial*. *Lancet*, 2014. **384**(9950): p. 1282-93.
- 450 24. Morano, M., D. Colella, and M. Caroli, *Gross motor skill performance in a sample of*
 451 *overweight and non-overweight preschool children*. *Int J Pediatr Obes*, 2011. **6** Suppl 2: p.
 452 42-6.
- 453 25. Liang, J., B.E. Matheson, W.H. Kaye, et al., *Neurocognitive correlates of obesity and*
 454 *obesity-related behaviors in children and adolescents*. *Int J Obes (Lond)*, 2014. **38**(4): p.
 455 494-506.
- 456 26. Reinert, K.R., E.K. Po'e, and S.L. Barkin, *The relationship between executive function and*
 457 *obesity in children and adolescents: a systematic literature review*. *J Obes*, 2013. **2013**: p.
 458 820956.
- 459 27. Hayes, J.F., D.M. Eichen, D.M. Barch, et al., *Executive function in childhood obesity:*
 460 *Promising intervention strategies to optimize treatment outcomes*. *Appetite*, 2018. **124**: p.
 461 10-23.
- 462 28. Walker, S.P., S.M. Chang, N. Younger, et al., *The effect of psychosocial stimulation on*
 463 *cognition and behaviour at 6 years in a cohort of term, low-birthweight Jamaican children*.
 464 *Dev Med Child Neurol*, 2010. **52**(7): p. e148-54.
- 465 29. Nguyen, P.H., A.M. DiGirolamo, I. Gonzalez-Casanova, et al., *Influences of early child*
 466 *nutritional status and home learning environment on child development in Vietnam*.
 467 *Maternal & child nutrition*, 2018. **14**(1): p. e12468.
- 468 30. Kristjansson, E., D.K. Francis, S. Liberato, et al., *Food supplementation for improving the*
 469 *physical and psychosocial health of socio-economically disadvantaged children aged three*
 470 *months to five years*. *Cochrane Database Syst Rev*, 2015(3): p. CD009924.
- 471 31. Pimpin, L., S. Kranz, E. Liu, et al., *Effects of animal protein supplementation of mothers,*
 472 *preterm infants, and term infants on growth outcomes in childhood: a systematic review*
 473 *and meta-analysis of randomized trials*. *Am J Clin Nutr*, 2019. **110**(2): p. 410-429.
- 474 32. Sjarif, D.R., K. Yuliati, and W.J. Iskandar, *Daily consumption of growing-up reduces stunting*
 475 *among Indonesian toddlers*. *Medical Journal Indonesia*, 2019. **28**: p. 70-76.
- 476 33. Lee, R., L. Singh, D. van Liefde, et al., *Milk Powder Added to a School Meal Increases*
 477 *Cognitive Test Scores in Ghanaian Children*. *J Nutr*, 2018. **148**(7): p. 1177-1184.
- 478 34. Smithers, L.G., R.K. Golley, M.N. Mittinty, et al., *Do dietary trajectories between infancy*
 479 *and toddlerhood influence IQ in childhood and adolescence? Results from a prospective*
 480 *birth cohort study*. *PLoS One*, 2013. **8**(3): p. e58904.
- 481 35. Miller, A.L., H.J. Lee, and J.C. Lumeng, *Obesity-associated biomarkers and executive*
 482 *function in children*. *Pediatr Res*, 2015. **77**(1-2): p. 143-7.
- 483 36. Bradley, R., *Using the HOME inventory to assess the family environment*. *Pediatr Nurs.*,
 484 1988. **14**(2): p. 97-102.
- 485 37. *Double-duty actions for nutrition. Policy Brief. World Health Organization*. 2017.
- 486 38. *World Health Organization. Global nutrition targets 2025*. 2014.
- 487 39. Smithers, L.G., J.W. Lynch, S. Yang, et al., *Impact of neonatal growth on IQ and behavior*
 488 *at early school age*. *Pediatrics*, 2013. **132**(1): p. e53-60.
- 489 40. Aubuchon-Endsley, N.L., S.L. Grant, G. Berhanu, et al., *Hemoglobin, growth, and attention*
 490 *of infants in southern Ethiopia*. *Child Dev*, 2011. **82**(4): p. 1238-51.

- 491 41. Waber, D.P., C.P. Bryce, J.M. Girard, et al., *Impaired IQ and academic skills in adults who*
492 *experienced moderate to severe infantile malnutrition: a 40-year study*. *Nutr Neurosci*,
493 2014. **17**(2): p. 58-64.
- 494 42. Sudfeld, C.R., D.C. McCoy, G. Fink, et al., *Malnutrition and Its Determinants Are Associated*
495 *with Suboptimal Cognitive, Communication, and Motor Development in Tanzanian Children*.
496 *J Nutr*, 2015. **145**(12): p. 2705-14.
- 497 43. Ip, P., F.K.W. Ho, N. Rao, et al., *Impact of nutritional supplements on cognitive*
498 *development of children in developing countries: A meta-analysis*. *Sci Rep*, 2017. **7**(1): p.
499 10611.
- 500 44. Larson, L.M. and A.K. Yousafzai, *A meta-analysis of nutrition interventions on mental*
501 *development of children under-two in low- and middle-income countries*. *Matern Child*
502 *Nutr*, 2017. **13**(1).

For Peer Review

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

	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
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"> • Cognitive • Motor • Socio-emotional 	<ul style="list-style-type: none"> • General cognition • Odds of walking • Motor score • Social skills 	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"> • Children's problem-solving ability measured using two 1-step means-end tests "Support" and "Cover" at 7 months • Mental development index (MDI) measured using the Bayley Scales of Infant Development Revised version at 18 months • Children's IQ measured using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at 64 months. 	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"> • WISC-III at 72 months 	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

	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
				from a subsample from PROBIT Trial		<ul style="list-style-type: none"> • -Cognitive ability using Wechsler Abbreviated Scales of Intelligence • Child behaviour using the Strengths and Difficulties Questionnaire 		
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"> • Temperament and attention assessed using modified version of the Laboratory Temperament Assessment Battery (Lab-TAB) and MOFPTask at 6 and 9 months 	<ul style="list-style-type: none"> • Duration and number of inattention periods • Mean of looking time • Total duration of looking 	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"> • Raven's Coloured Progressive Matrices at 48 to 72 months 	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"> • Overall development and Learning capabilities • Literacy skills • Numerical skills 	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"> • Cognitive development • Language development • Motor development 	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"> At 48 months: social skills competence or 'daily living skills' assessed using VSMS At 60 months: cognitive functioning assessed using R-DPDQ 	<ul style="list-style-type: none"> Cognitive functioning Social skills competence Fine motor skills 	Good
10	Crookston BT, 2013 [16]	<ul style="list-style-type: none"> Ethiopia India Peru Vietnam 	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"> Schooling average Mathematics test Reading comprehension/verbal achievement: Early Grade Reading Assessment Receptive vocabulary: Peabody Picture Vocabulary Test (PPVT) 	<ul style="list-style-type: none"> Overall schooling Receptive vocabulary Mathematics score 	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"> Non-verbal intelligence test English reading comprehension test Mathematics test 	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"> Age of starting and leaving school Highest grade attained 	<ul style="list-style-type: none"> Overall schooling Reading scores Non-verbal cognitive scores 	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"> • Inter-American Reading Series (Serie Interamericana) vocabulary (Level 3) • Reading comprehension (Level 2) test modules • Nonverbal cognitive ability: assessed using Raven's Standard Progressive Matrices test 	<ul style="list-style-type: none"> • Characteristics of marriage partners; older age at first birth; a smaller number of pregnancies and births • Household per capita income • Adult health 	
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"> • Adult IQ: Wechsler Abbreviated Scale of Intelligence – Vocabulary and Matrix Reasoning subtests • Academic Achievement: Wide Range Achievement Test-III – Reading, Spelling, and Calculation subtests 	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"> • Baseline assessment using revised version of the Bayley Scales of Infant Development • Temperament assessed through an interviewer-administered maternal questionnaire 	<ul style="list-style-type: none"> • Social skills • Attention • Fear • Negative emotion 	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
						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"> • Cognition • Communication (comprising expressive and receptive communication skills) • Motor (comprising fine and gross motor skills) 	<ul style="list-style-type: none"> • Cognitive development • Communication skills • Motor development 	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"> • Self-regulation (laboratory tasks) • Motor skills (Zurich Neuromotor Assessment Test; Motor Test Battery) • Verbal ability (Peabody Picture Vocabulary Test) • Concentration (Frankfurter Test für Fünfjährige—Konzentration) • Intelligence (Culture Fair Test) • Locomotor skills, object-control skills (Test of Gross Motor Development) • Delay of gratification (Mischel and 	<ul style="list-style-type: none"> • General intellectual • Executive control • Delayed gratification • Inhibition strategy • Learning and memory 	Poor

	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
						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"> • Delay of Gratification Task, Self-Control Task • Children's Behaviour Questionnaire • Classroom Engagement • Social Behaviour Questionnaire • Go-No Go Task • Behavioural Rating Inventory of Executive Functioning (self-report) • Incompatibility Task of Attention Assessment Battery 	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"> • 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 	<ul style="list-style-type: none"> • Motor competence • Object-control tasks 	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"> • Nutrition intervention • Promotion of responsive care and learning opportunities • Conditional cash transfer 	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"> • Social emotional score • Cognitive score • Motor score 	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"> • Nutrition intervention 	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 ≥ 5 nutrients was particularly beneficial (0.15, 0.08–0.22).		
4	Yousafzai AK, 2014 [23]	Pakistan	1,486 infants aged ≤ 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"> • Control: Routine health and nutrition services • Nutrition education and multiple micronutrient powders • Responsive stimulation (responsive stimulation) • Combination of both responsive stimulation and nutrition intervention. 	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"> • 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. • Children who received enhanced nutrition had significantly higher development scores on the cognitive, language, and social-emotional scales at 12 months of age 	<ul style="list-style-type: none"> • Cognitive scales • Language scales • Motor scales 	Good

								<p>than control, but at 24 months of age only the language scores remained significantly higher.</p> <ul style="list-style-type: none"> • No additive benefits when responsive stimulation was combined with nutrition interventions. • Children exposed to enhanced nutrition had significantly better HAZ at 6 and 18 months than did children not exposed to enhanced nutrition. • Treatment effect on cognition, language and motor development at 24 months were moderate to large for responsive simulation and were low to 	
--	--	--	--	--	--	--	--	--	--

For Peer Review

								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"> • Oral food supplement (OFS) with higher content of carbohydrates and micronutrients, including Fe and Zn, than did the PM • Powdered milk (PM) • Placebo (PL) 	Healthy population	Bayley Scale of Infant Development Test for cognitive and motor functions after 6 months from enrolment	<ul style="list-style-type: none"> • Daily supplementation of 12–24-month-old children with OFS has no additional benefits in growth, anaemia, morbidity or cognitive performance. • 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. 	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"> • Children who received both vitamin B12 and folic acid had 0.45 (95% CI 0.19, 0.73) and 0.28 (95% 	<ul style="list-style-type: none"> • Gross motor • Problem solving skills 	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"> • Effect was highest in stunted children, those with high plasma homocysteine (> 10 μmol/L) or in those who were younger than 24 months at end study. • Timing of nutritional influence is of significance for the outcome of neurodevelopment. 		
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	Assessment during the first 48 months of life: <ul style="list-style-type: none"> • BSID-I, -II or -III—Mental Scale • Griffiths Mental Developmental Scale 	<ul style="list-style-type: none"> • Motor development, but not growth status, effect sizes were significantly associated with mental development in postnatal interventions. 	Motor development	Good

							<ul style="list-style-type: none"> • Fagan Test of Infant Intelligence 	<ul style="list-style-type: none"> • Nutrition interventions had small effects on mental development. • 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. 		
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"> • Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III) • Digit span forwards test and visual-spatial memory with the Corsi blocks test • Test of Everyday Attention for Children • Early Reading Assessment • Strengths and Difficulties 	<ul style="list-style-type: none"> • 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. • LBWT who received stimulation intervention had higher IQ score and fewer 	<ul style="list-style-type: none"> • Selective attention • Visual-spatial memory 	Poor

							Questionnaire (SDQ)	behavioural problems as compared to the control, group.		
--	--	--	--	--	--	--	---------------------	---	--	--

For Peer Review

Table 3. Factors influencing suboptimal growth in neurodevelopment and cognition

Maternal factors	Paternal factors	Child's characteristics and health condition	Socio-economic conditions
Undernourished and normo-nourished children			
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 (≤ 1 monthly minimum wage)
Low BMI (18.10 kg/m ²)	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 (≥ 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 (≥ 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			
Overweight and obese children			
-	-	Low socio-economic status	-

HOME, Home Observation for Measurement of the Environment

Figure 1. PRISMA 2009 Flowchart Diagram

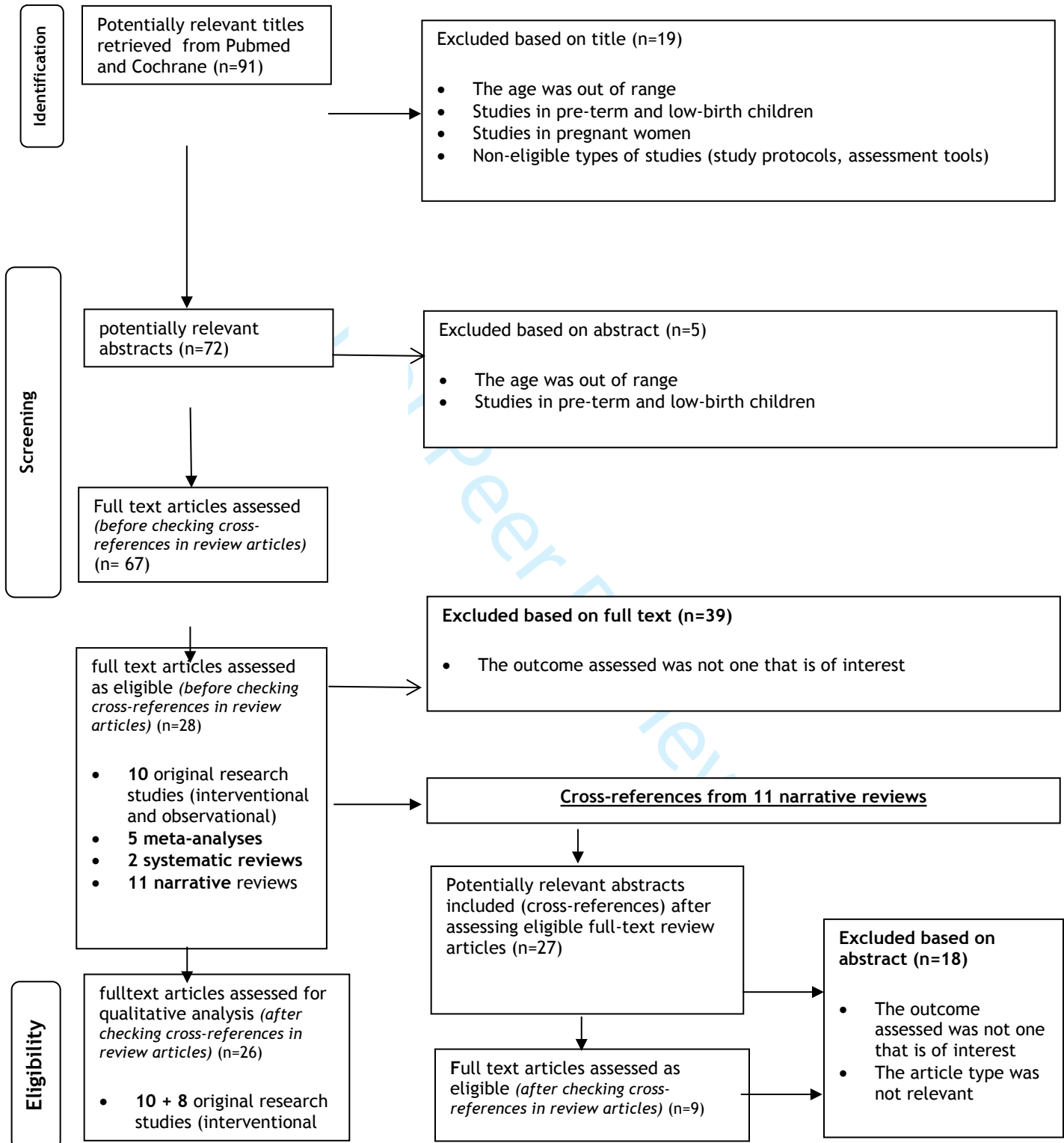
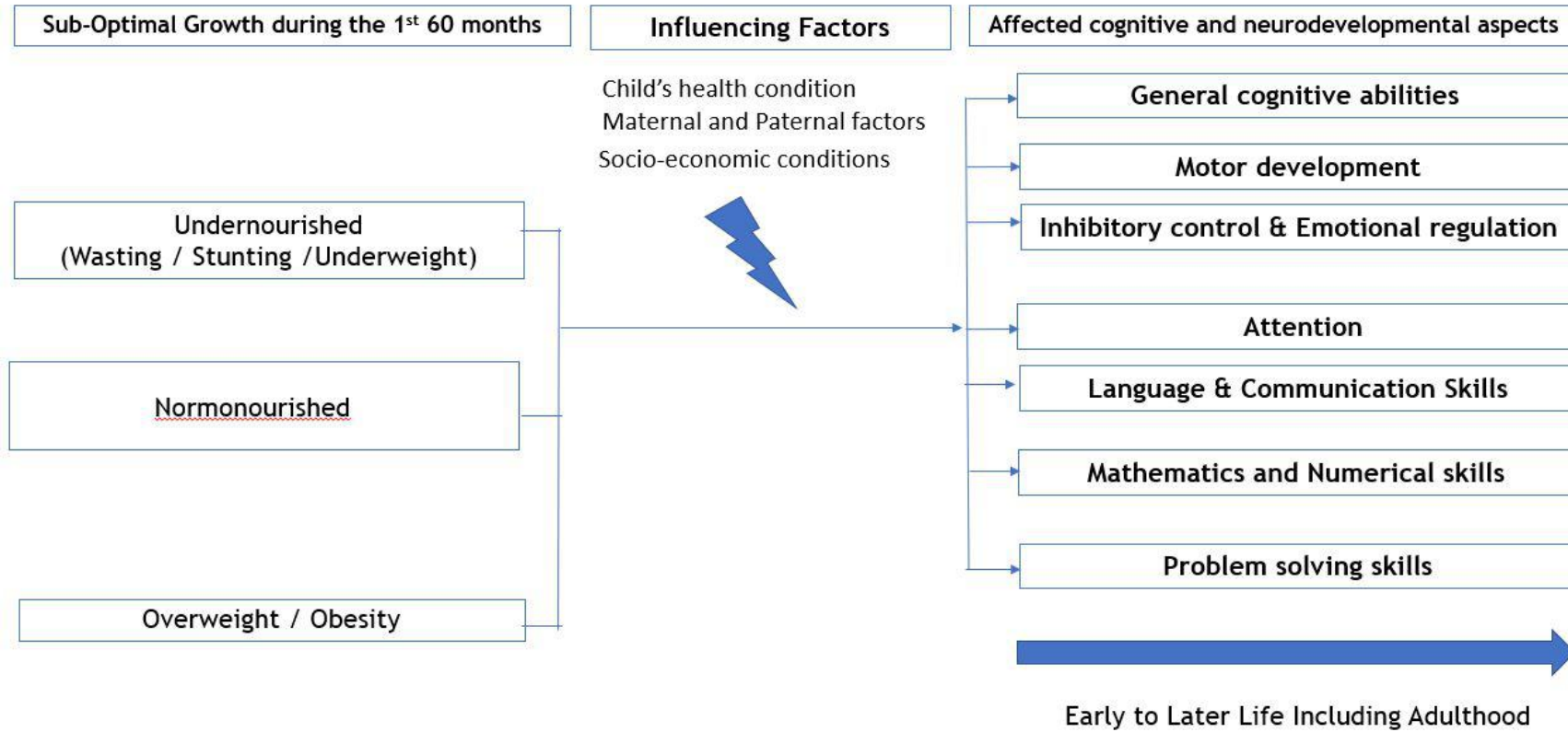


Figure 2. Impact of suboptimal growth in early childhood on developmental-related aspects



7	Keputusan: <i>Accepted for Publication</i>	31 May 2021
----------	---	--------------------



ahmad suryawan <suryawan.ahmad@gmail.com>

FW: Nutrition Research Reviews NRR-20-032.R5: Decision on Manuscript

Muhardi, L.M. (Leilani) <leilani.muhardi@frieslandcampina.com>
To: ahmad suryawan <suryawan.ahmad@gmail.com>

Tue, Jun 1, 2021 at 7:28 AM

Yth. Dr. Wawan,

Terlampir saya sampaikan email dari Prof. Yazid.

Salam hormat,

Leilani

From: Muhammad Yazid Jalaludin <yazidj@ummc.edu.my>
Sent: Monday, May 31, 2021 11:32 PM
To: Muhardi, L.M. (Leilani) <leilani.muhardi@frieslandcampina.com>
Subject: Fwd: Nutrition Research Reviews NRR-20-032.R5: Decision on Manuscript

****This message is from an EXTERNAL SENDER - be CAUTIOUS. If this message appears as suspicious, do not reply, click on links or attachments and report the email.**

Dear Dr Leilani,

Alhamdulillah!

At last.

Congratulations to all of us, after ONE year!

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

Senior Consultant Paediatrician, Consultant Paediatric Endocrinologist
Department of Paediatrics
University Malaya Medical Centre
59100 Kuala Lumpur
Tel: 03-79492065
Fax: 03-79494704

----- Forwarded message -----

From: **Nutrition Research Reviews** <onbehalf@manuscriptcentral.com>

Date: Mon, May 31, 2021 at 10:59 PM
Subject: Nutrition Research Reviews NRR-20-032.R5: Decision on Manuscript
To: <yazidj@ummc.edu.my>

31-May-2021

Dear Prof. JALALUDIN,

Thank you for submitting the final version of your manuscript entitled "Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review", which is acceptable for publication in Nutrition Research Reviews in its current form.

Your accepted manuscript will be published online in its current format (before copy-editing or typesetting), within approximately a week of final acceptance provided we have received all final files and a completed license to publish form. At this point, the article will have a DOI and be considered published and citable. You will subsequently receive a proof of your typeset, edited article, which will eventually replace the accepted manuscript online and be considered the final version of record.

If you have not yet done so, please complete and return the journal's publication agreement form (please note: you must return ALL pages of the form, even if there is nothing written on them) as soon as possible.

<https://www.cambridge.org/core/journals/nutrition-research-reviews/information/author-publishing-agreement>

PLEASE NOTE:

Nutrition Research Reviews offers authors the option to publish their article through an Open Access model upon payment of an Article Processing Charge (APC). For information about APCs, or general information on open access and the green open access options offered by The Nutrition Society, please see <https://www.cambridge.org/core/journals/nutrition-research-reviews/information/instructions-contributors#openaccess>

If you wish to publish your paper through Cambridge Open, please send an e-mail stating this choice to nrr.edoffice@cambridge.org and complete and return the alternative Open Access form which can be accessed by clicking the link below:

<https://www.cambridge.org/core/journals/nutrition-research-reviews/information/author-publishing-agreement>

Once you have returned the Open Access form, you will be contacted by CCC-Rightslink who are acting on our behalf to collect the Article Processing Charges (APCs). Please follow their instructions in order to avoid any delay in the publication of your article. Please note that your manuscript will not enter the Production workflow until we have received the signed publication agreement form or Open Access form. Once we have received this, your manuscript will enter the Production process and you will receive the proofs in due course.

The Nutrition Society welcomes new members world wide at all stages of their career, and offers a variety of member benefits. If you would like to become a member of the Nutrition Society, please visit our website here: <https://www.nutritionociety.org/become-member>

If you or your institution are planning to issue a press release for this article, please inform the Editorial Office at nrr.edoffice@cambridge.org. We also promote articles via Twitter, so if you'd like us to retweet your promotional post tag us directly at @NutritionSoc and @CUP_med_health. For more information on how you can promote your work via social media, please visit our social media guide here: <http://ow.ly/bhZY30avSus>

Sincerely,
Prof Christine Edwards
Editor-in-Chief, Nutrition Research Reviews
christine.edwards@glasgow.ac.uk

" PENAFLIAN: E-mel ini dan apa-apa fail yang dikepilkan bersamanya ("Mesej") adalah ditujukan hanya untuk kegunaan penerima(-penerima) yang termaklum di atas dan mungkin mengandungi maklumat sulit. Anda dengan ini dimaklumkan bahawa mengambil apa jua tindakan berdasarkan kepada, membuat penilaian, mengulang hantar, menghebah, mengedar, mencetak, atau menyalin Mesej ini atau sebahagian daripadanya oleh sesiapa selain daripada penerima(-penerima) yang termaklum di atas adalah dilarang. Jika anda telah menerima Mesej ini kerana kesilapan, anda mesti menghapuskan Mesej ini dengan segera dan memaklumkan kepada penghantar Mesej ini menerusi balasan e-mel. Pendapat-pendapat, rumusan-rumusan, dan sebarang maklumat lain di dalam Mesej ini yang tidak berkait dengan urusan rasmi Pusat Perubatan Universiti Malaya adalah difahami sebagai bukan dikeluarkan atau diperakui oleh mana-mana pihak yang disebut.

DISCLAIMER: This e-mail and any files transmitted with it ("Message") is intended only for the use of the recipient(s) named above and may contain confidential information. You are hereby notified that the taking of any action in reliance upon, or any review, retransmission, dissemination, distribution, printing or copying of this Message or any part thereof by anyone other than the intended recipient(s) is strictly prohibited. If you have received this Message in error, you should delete this Message immediately and advise the sender by return e-mail. Opinions, conclusions and other information in this Message that do not relate to the official business of University Malaya Medical Centre shall be understood as neither given nor endorsed by any of the forementioned. "

Disclaimer: The information in this e-mail (including any attachments) is strictly confidential and may be legally privileged. If you are not the intended recipient of this message, please delete it including any attachments and immediately notify the sender. Any disclosure, copying,

8

Published online

08 June 2021



ahmad suryawan <suryawan.ahmad@gmail.com>

FW: Congratulations, your accepted manuscript is available online in Nutrition Research Reviews!

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
To: Muhardi, L.M. (Leilani) <leilani.muhardi@frieslandcampina.com>
Subject: Fwd: Congratulations, your accepted manuscript is available online in Nutrition Research Reviews!

****This message is from an EXTERNAL SENDER - be CAUTIOUS. If this message appears as suspicious, do not reply, click on links or attachments and report the email.**

Congratulations to us!!!

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

Senior Consultant Paediatrician, Consultant Paediatric Endocrinologist
Department of Paediatrics
University Malaya Medical Centre
59100 Kuala Lumpur
Tel: 03-79492065
Fax: 03-79494704

----- Forwarded message -----

From: **Cambridge Core** <no-reply@cambridge.org>
Date: Tue, Jun 8, 2021 at 6:41 PM

Subject: Congratulations, your accepted manuscript is available online in Nutrition Research Reviews!
To: <yazidj@ummc.edu.my>

Dear Author,

Congratulations, your accepted manuscript, Malnutrition in early life and its neurodevelopmental and cognitive consequences: A scoping review, is now available online in Nutrition Research Reviews! You can view your article at <https://www.doi.org/10.1017/S0954422421000159>. You will receive further email confirmation when the version of record of your article is published online.

Your manuscript may be cited using its DOI, but citations should indicate that it is not the final version.

If your article has published as Open Access (OA), you can access it on the following link:

<https://www.doi.org/10.1017/S0954422421000159>

If your article has not published as OA:

For full personal access, and to register as the article's author, please use your personal author access code below:

C8704F5E27E887705D1361BA3DE6ABAA

You can also give full access to up to 10 of your colleagues and peers by sending them the code below:

87682F0FC762D7189D891AE0A67AA3D2

To use these codes, please follow the simple steps below:

1. [Log in](#) to your Cambridge Core account or [register for an account](#)
2. Once logged in, navigate to 'My account', then 'My content'
3. Enter your unique access code into the 'Redeem access code' field and click 'Activate'.
4. If you have any problems accessing your article, please contact our support team at academictechsupport@cambridge.org

Did you know you can choose to publish this article as OA?

Publishing OA allows anyone, anywhere to find, read, and benefit from your research, giving you increased visibility and global impact. To help you decide, you can find out more on our [Publishing OA information page](#).

Publishing Open Access requires payment of an article processing charge (APC), collected by our partner, CCC-Rightslink. However, to support OA publishing, we also offer a variety of waivers and discounts which means you may not have to pay an APC, including agreements negotiated by your institution. To check your eligibility, please visit our [waivers and discounts information page](#).

If you would like to publish this article as OA, please contact your Content Manager.

Sharing and promoting your article

We are committed to making sure your paper reaches a broad international audience in order to maximise its scholarly impact. We also have a variety of resources to support you in promoting your work and help get your article read and cited as widely as possible.



If you would like to receive email alerts to hear about new articles published in your favourite journals please log in to, or register with, [Cambridge Core](#) to create your preferences.

Once again, we'd like to thank you for publishing with Cambridge University Press, and wish your article every success.

Kind Regards
Cambridge University Press

" PENAFLIAN: E-mel ini dan apa-apa fail yang dikepilkan bersamanya ("Mesej") adalah ditujukan hanya untuk kegunaan penerima(-penerima) yang termaklum di atas dan mungkin mengandungi maklumat sulit. Anda dengan ini dimaklumkan bahawa mengambil apa jua tindakan berdasarkan kepada, membuat penilaian, mengulang hantar, menghebah, mengedar, mencetak, atau menyalin Mesej ini atau sebahagian daripadanya oleh sesiapa selain daripada penerima(-penerima) yang termaklum di atas adalah dilarang. Jika anda telah menerima Mesej ini kerana kesilapan, anda mesti menghapuskan Mesej ini dengan segera dan memaklumkan kepada penghantar Mesej ini menerusi balasan e-mel. Pendapat-pendapat, rumusan-rumusan, dan sebarang maklumat lain di dalam Mesej ini yang tidak berkait dengan urusan rasmi Pusat Perubatan Universiti Malaya adalah difahami sebagai bukan dikeluarkan atau diperakui oleh mana-mana pihak yang disebut.

DISCLAIMER: This e-mail and any files transmitted with it ("Message") is intended only for the use of the recipient(s) named above and may contain confidential information. You are hereby notified that the taking of any action in reliance upon, or any review, retransmission, dissemination, distribution, printing or copying of this Message or any part thereof by anyone other than the intended recipient(s) is strictly prohibited. If you have received this Message in error, you should delete this Message immediately and advise the sender by return e-mail. Opinions, conclusions and other information in this Message that do not relate to the official business of University Malaya Medical Centre shall be understood as neither given nor endorsed by any of the forementioned. "

Disclaimer: The information in this e-mail (including any attachments) is strictly confidential and may be legally privileged. If you are not the intended recipient of this message, please delete it including any attachments and immediately notify the sender. Any disclosure, copying, distribution or use either whole or partial of its contents is strictly prohibited except with formal approval. FrieslandCampina cannot guarantee that e-mail communications are secured and error-free and does not accept any liability for damages resulting from the use of e-mail. The general terms and conditions of [purchase](#) respectively [sale and delivery](#) of Royal FrieslandCampina N.V., are applicable to all transactions and undertakings resulting therefrom.

De informatie in deze e-mail (inclusief bijlagen) is strikt persoonlijk en vertrouwelijk en mogelijk juridisch geprivilegieerd. Indien u niet de bedoelde ontvanger van dit bericht bent verzoeken wij u het bericht inclusief bijlagen te vernietigen en ons hiervan onmiddellijk op de hoogte te stellen. Openbaarmaking, vermenigvuldiging of verspreiding van (een gedeelte van) dit bericht is, zonder formele toestemming, strikt verboden. FrieslandCampina kan niet garanderen dat e-mail communicatie veilig en foutloos is en accepteert geen enkele aansprakelijkheid voor schade voortvloeiende uit het gebruik hiervan. Op alle transacties en daaruit voortvloeiende verbintenissen zijn de algemene [inkoopvoorwaarden](#) respectievelijk [verkoopvoorwaarden](#) van Koninklijke FrieslandCampina N.V. van toepassing.

Newly published article(s) for Nutrition Research Reviews available on Cambridge Core

Cambridge University Press <academic@updates.cambridge.org>

Thu, Jun 10, 2021 at 7:35 PM

Reply-To: Academic Replies <reply-fe8213777d600c7f7c-729240_HTML-1285494483-1423905-2213@updates.cambridge.org>

To: suryawan.ahmad@gmail.com

Is this email not displaying correctly? [View it in your browser](#) | [Forward to a friend](#)

Cambridge Core

Nutrition Research Reviews

Content Alert



ISSN: 0954-4224, EISSN: 1475-2700

Nutrition Research Reviews

New article(s) available

Review article

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

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

[Nutrition Research Reviews](#)

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

[Nutrition Research Reviews](#)

doi: 10.1017/S0954422421000172, 28 pages. Published Online on 8 June 2021

The gut microbiota as a therapeutic target for obesity: a scoping review

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

[Nutrition Research Reviews](#)



Tables of contents and article abstracts are free to all on Cambridge Core. If an article is published under an Open Access agreement, readers can freely access it. Access to the full text for non-OA articles is available to users whose institutions subscribe. If your institution does not currently subscribe to the journal please [recommend it to your librarian](#).

If you have any queries regarding this email or Cambridge Core, please click [here](#).

To amend your content alerts preferences please login to your [Cambridge Core account](#) and visit 'My Alerts'.

If you would like to unsubscribe from eTOC alerts from Cambridge Core please click [here](#)

<https://www.cambridge.org/core/journals/nutrition-research-reviews>

www.journals.cambridge.org

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

09 November 2021

Ref: AMS/Confirmation of online publication

To whom it may concern,

Confirmation of online publication

DOI: <https://doi.org/10.1017/S0954422421000159>

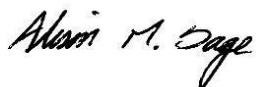
Title: **Malnutrition in early life and its neurodevelopmental and cognitive consequences: a scoping review**

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

This letter constitutes confirmation that the above paper has been accepted for publication in the Cambridge University Press journal *Nutrition Research Reviews* and **was published online on 8 June 2021**. It can be found on the NRR website at <https://www.cambridge.org/core/journals/nutrition-research-reviews> using the DOI given above.

Nutrition Research Reviews offers a comprehensive overview of nutritional science today. By distilling the latest research and linking it to established practice, the journal consistently delivers the widest range of in-depth articles in the field of nutritional science. It presents up-to-date, critical reviews of key topics in nutrition science advancing new concepts and hypotheses that encourage the exchange of fundamental ideas on nutritional well-being in both humans and animals.

Sincerely,



Mrs. Alison Sage, Peer Review Administrator

Editor-in-Chief: Prof. Christine Edwards, University of Glasgow, UK

Peer review Administrator: Mrs. Alison Sage
Email: nrr.edoffice@cambridge.org

9

**Published on Nutrition Research Review,
Tahun 2022, Volume 35, Issue 1, 136-149**

04 June 2022

New Issue of Nutrition Research Reviews available on Cambridge Core

Cambridge University Press <academic@updates.cambridge.org>

Sat, Jun 4, 2022 at 7:38 PM

Reply-To: Academic Replies <reply-fe8d1c727c64047572-729240_HTML-1285494483-1423905-35@updates.cambridge.org>

To: suryawan.ahmad@gmail.com

Is this email not displaying correctly? [View it in your browser](#) | [Forward to a friend](#) .

Cambridge Core

Nutrition Research Reviews

Content Alert



ISSN: 0954-4224, EISSN: 1475-2700

Nutrition Research Reviews

Volume 35 / Issue 1, June 2022

Published Online June 2022

Review article

[Determining the glycaemic responses of foods: conventional and emerging approaches](#)

S R Priyadarshini, J A Moses, C Anandharamakrishnan

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 1 - 27

doi: 10.1017/S0954422421000020 Published Online on 1 February 2021

[Effects of betaine on non-alcoholic liver disease](#)

Weiqiang Chen, Minjuan Xu, Minwen Xu, Yucai Wang, Qingyan Zou, Shuixiang Xie, Liefeng Wang

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 28 - 38

doi: 10.1017/S0954422421000056 Published Online on 5 April 2021

[Adolescent undernutrition in South Asia: a scoping review](#)

Sara Estecha Querol, Paramjit Gill, Romaina Iqbal, Maartje Kletter, Neslihan Ozdemir, Lena Al-Khudairy

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 39 - 49

[The potential nutrition-, physical- and health-related benefits of cow's milk for primary-school-aged children](#)

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

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 50 - 69

doi: 10.1017/S095442242100007X Published Online on 27 April 2021

[Antioxidants in smokers](#)

Emanuela Astori, Maria L. Garavaglia, Graziano Colombo, Lucia Landoni, Nicola M. Portinaro, Aldo Milzani, Isabella Dalle-Donne

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 70 - 97

doi: 10.1017/S0954422421000093 Published Online on 30 April 2021

[Sarcopenia and homocysteine: is there a possible association in the elderly? A narrative review](#)

Rachele De Giuseppe, Chiara Elena Tomasinelli, Alessandra Vincenti, Ilaria Di Napoli, Massimo Negro, Hellas Cena

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 98 - 111

doi: 10.1017/S095442242100010X Published Online on 30 April 2021

[A scoping review of chronotype and temporal patterns of eating of adults: tools used, findings, and future directions](#)

Yan Yin Phoi, Michelle Rogers, Maxine P. Bonham, Jillian Dorrian, Alison M. Coates

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 112 - 135

doi: 10.1017/S0954422421000123 Published Online on 14 May 2021

[Malnutrition in early life and its neurodevelopmental and cognitive consequences: a scoping review](#)

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

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 136 - 149

doi: 10.1017/S0954422421000159 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

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 150 - 158

doi: 10.1017/S0954422421000172 Published Online on 8 June 2021

Other

[List of Reviewers](#)

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp 159 - 160

doi: 10.1017/S0954422421000391 Published Online on 18 January 2022

e-only frontmatter

[NRR volume 35 issue 1 Front matter](#)

[Nutrition Research Reviews, Volume 35 / Issue 1](#), June 2022, pp f1 - f1

doi: 10.1017/S0954422422000051 Published Online on 3 June 2022



Tables of contents and article abstracts are free to all on Cambridge Core. If an article is published under an Open Access agreement, readers can freely access it. Access to the full text for non-OA articles is available to users whose institutions subscribe. If your institution does not currently subscribe to the journal please [recommend it to your librarian](#).

If you have any queries regarding this email or Cambridge Core, please click [here](#).

To amend your content alerts preferences please login to your [Cambridge Core account](#) and visit 'My Alerts'.

If you would like to unsubscribe from eTOC alerts from Cambridge Core please click [here](#)