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Penulis	:	**Ahmad Suryawan**, Muhammad Yazid Jalaludin, Poh Bee Koon, Rasaki Sanusi, Ming Hui Tan, Jan Geurts, Leilani Muhardi
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Malnutrition in early life and its neurodevelopmental and cognitive consequences: A narrative review

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REVIEW PROPOSAL FORM

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If yes, by whom?

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Title of proposed review:

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

Please provide the following information

A description of the content of the proposed review:

1. BACKGROUND (MAX 100 WORDS)

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

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

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

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

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

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

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

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

3. MAIN CONCLUSIONS AND IMPLICATIONS (MAX 100 WORDS)

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

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.

2	**Revisi ke-1 (ID NRR-20 0.32.R1)** disubmit ke Jurnal	**21 May 2020**
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Cover Letter: NRR-20-032.R1

May 19, 2020

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

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

Dear Prof. Edwards

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

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

Close

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

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Keywords:	double burden malnutrition, cognitive neurodevelopment, nutrition intervention, window of opportunity

Narrative Review

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

Running title: Malnutrition and cognitive developmental consequences

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

Abstract

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

INTRODUCTION

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

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

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

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

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

METHODS

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

Data collection, extraction and analysis

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

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

RESULTS AND DISCUSSION

Descriptive summary of included studies

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

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

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

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

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

Across the retrieved studies, 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 (Table 1). It was reported that healthy infants in the highest quartile of neonatal weight, length, and head circumference gain during the first 4 weeks of life had a higher IQ score at 6 years of age as compared to those in the lowest quartile (7).

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

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

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

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

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

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

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

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

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

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

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

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

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

The impact of overnutrition on neurodevelopment and cognition

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

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

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

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

Factors influencing the impact of suboptimal growth on neurodevelopment and cognition

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

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

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

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

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

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

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

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

Consideration for future research and actions:

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

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

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

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

CONCLUSIONS

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

monitored even beyond 60 months of life to enable early recognition of growth deviations and to allow appropriate and timely interventions to attenuate the negative neurodevelopmental and cognitive impacts. Given the Global Nutrition Targets for 2025 (32), intervention programs 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 potentially up to the age of 8 years given the possibility of improving cognitive achievement especially in those recovered from stunting. These specific and targeted interventions might be key to safeguard future human capital especially in countries with a high incidence of stunting and overweight.

DECLARATIONS

Acknowledgements

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

Funding

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

Authors' contribution

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

Competing interests

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

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

References

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

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

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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. ***

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

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

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.

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 ($\geqslant$ 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 Muhardi 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**
	Keputusan: 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

	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

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

Journal:	*Nutrition Research Reviews*
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

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

Running title: Malnutrition and cognitive neurodevelopmental consequences

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249 Words Abstract, 3539 words in Main Text (excluding tables, figures and references), 4 Tables, 2 Figures, 41 References

Abstract

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

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

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

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

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

INTRODUCTION

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

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

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

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

METHODS

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

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

RESULTS AND DISCUSSION

Descriptive summary of included studies

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

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

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

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

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

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

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

Evidence for the impact of underweight and stunting on social skills development is largely variable across the identified studies. 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) were less sociable, less attentive, more fearful and had more negative emotional traits as compared to normo-nourished children [13]. There is evidence therefore, that underweight and stunting have an impact on social skills development. *Low HAZ and WAZ correlated strongly with children having less schooling or needing a longer time to complete schooling [14], and in later life, with lower-income and living in less conducive environment, such as having higher number of pregnancies and having the first child at a younger age [15].*

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

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

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

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

The importance of interventions in improving cognitive outcomes among undernourished children

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

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

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

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

The impact of overweight/obesity on neurodevelopment and cognition

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

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

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

Factors influencing the impact of suboptimal growth on neurodevelopment and cognition

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

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

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

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

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

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

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

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

Consideration for future research and actions:

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

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

3) 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. They have the dual-responsibility to consider both ends of the malnutrition spectrum when planning and implementing intervention programs [34]. Actions should be taken to

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

CONCLUSION

Both under- and overnutrition during the first 60 months of post-natal life affect the developmental trajectories of children in later life. Weight and length/height need to be monitored even beyond 24 months of life to enable early recognition of growth retardation/deviations and to allow appropriate and timely interventions to address the negative neurodevelopmental and cognitive impacts. Given the Global Nutrition Targets for 2025 [35], 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. Nutrition and interventions can potentially rescue neurocognitive development up to the age of 8 years particularly in those recovering from stunting. These specific, targeted and simultaneous interventions may be key to safeguard future human capital especially in countries with high prevalence of stunting, overweight/obesity or both.

DECLARATIONS

Acknowledgements

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

Authors' contribution

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

Competing interests

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

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

References

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

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

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

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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 • Acceptable in principle (01-Dec-2020) • Due on: 31-Jan-2021 view decision letter	NRR-20-032.R2	Malnutrition in early life and its neurodevelopmental and cognitive consequences: A Scoping review View Submission	18-Sep-2020	01-Dec-2020

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:

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

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

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

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 sates 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 associate 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.

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.

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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**
	Keputusan: 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		
• 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

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

Journal:	*Nutrition Research Reviews*
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

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

Running title: Malnutrition and cognitive neurodevelopmental consequences

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

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

Abstract

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

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

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

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.

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

INTRODUCTION

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

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

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

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

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

METHODS

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

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

RESULTS AND DISCUSSION

Descriptive summary of included studies

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

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

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) during the first 60 months of life on various neurodevelopment aspects (cognition, motor development, temperament, socioeconomic status, and academic achievement) that manifest from infancy and school age to adulthood (Figure 2). This review also covers observational longitudinal cohorts and interventional studies with nutrition- and non-nutrition-related interventions on the outcomes of interest.

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

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

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

Evidence for the impact of underweight and stunting on the development of emotional skills is largely variable across the identified studies. Two meta-analyses that described data from lower- and middle-income countries showed the limited influence of undernutrition on a child's attachment, emotionality, social competence and temperament (5, 7). 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 (14). There is evidence, therefore, that underweight and stunting impact social skill development. Low HAZ and WAZ correlated strongly with children having less schooling or

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

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

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

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

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

The importance of interventions in improving cognitive outcomes among undernourished children

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

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

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

The impact of overweight/obesity on neurodevelopment and cognition

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

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

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

Factors influencing the impact of suboptimal growth on neurodevelopment and cognition

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

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

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

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

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

The influence of the Home Observation for Measurement of the Environment (HOME) parameter as a proxy indicator for socioeconomic factors was reported in several studies among undernourished children to be correlated with the impact of undernutrition and overweight/obesity on neurodevelopment and cognition (5, 9, 22, 27, 28, 33, 34). 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. Among overweight children, socioeconomic status was the only influencing factor reported in the papers in this review. Those in lower socioeconomic situations had lower motor skills than their counterparts with higher socioeconomic status (23).

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

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

Consideration for future research and actions:

1) More studies should be conducted on the impact of nutritional/behavioural interventions in overweight/obese children on neurodevelopment and cognition, especially in low-income countries, as all the currently retrieved literature came from high-income countries. 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). An increase in childhood obesity

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

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

3) 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. These groups of healthcare providers have the dual responsibility of considering both ends of the malnutrition spectrum when planning and implementing multi-disciplinary intervention programs (35). Actions should be taken to tackle both undernutrition and overweight/obesity concurrently – not just one or the other – to ensure successful and comprehensive outcomes in terms of childhood growth and cognitive neurodevelopment.

CONCLUSION

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

DECLARATIONS

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Author contributions

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

Competing interests

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

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

References

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

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

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

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

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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 ☐ HAZ < -1.01), at risk for stunting (-1 ☐ HAZ < 0) or normal height HAZ ≥ 0)) were positively associated…." What do the authors mean by "positively associated with"? Do they mean that if the child has a 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, 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

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 £ HAZ < -1.01), at risk for stunting (-1 £ HAZ < 0) or normal height HAZ ≥ 0)) were positively associated…." What do the authors mean by "positively associated with"? Do they mean that if the child has a 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 (HAZ < -2), mild stunting (-2 <HAZ < -1), at risk of stunting (-1< HAZ < 0) or normal height (HAZ ≥ 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	*n* (%)	Cognitive scores Mean ± *SD*	*MD*	*t*	*p*
Stunted (HAZ < -2SD)	162 (8.4)	100.28 ± 13.13	-3.47	-2.94	0.003*
Not stunted	1771 (91.6)	103.75 ± 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 socio-economic 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>: *Acceptable as received* (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

	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

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

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Manuscript ID	NRR-20-032.R4
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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

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

Running title: Malnutrition and cognitive neurodevelopmental consequences

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

Abstract

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

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

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

In conclusion, underweight, stunting and overweight/obesity have significant impact on cognitive neurodevelopment. Thus, intervention programmes should address these issues simultaneously. *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.*

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

INTRODUCTION

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

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

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

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

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

METHODS

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

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

RESULTS AND DISCUSSION

Descriptive summary of included studies

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

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

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) during the first 60 months of life on various neurodevelopment aspects (cognition, motor development, temperament, socioeconomic status, and academic achievement) that manifest from infancy and school age to adulthood (Figure 2). This review also covers observational longitudinal cohorts and interventional studies with nutrition- and non-nutrition-related interventions on the outcomes of interest.

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

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

From a longitudinal study in the Philippines, regardless of HAZ categories at 6 months (defined as moderate/severe stunting (HAZ < -2), mild stunting (-2 ≤ HAZ < -1), at risk of stunting (-1< HAZ < 0) or normal height (HAZ ≥ 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. In addition, changes in HAZ from 6 to 24 months and changes in HAZ from 24 months to 11 years were also positively associated with cognitive ability at 11 years in the same study (10). These outcomes are similar to the results among children in Bangladesh. In this study, cognitive impairment was associated with poverty, birth condition and postnatal growth that started at 7 months of age and worsened up to 64 months when it became even more substantial (11). The impact of the 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 significantly contributed 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) (13).

Evidence for the impact of underweight and stunting on the development of emotional skills is largely variable across the identified studies. Two meta-analyses that described data from lower- and middle-income countries showed the limited influence of undernutrition on a child's attachment, emotionality, social competence and temperament (5, 7). 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 (14). There is evidence, therefore, that underweight and stunting impact social skill development. Low HAZ and WAZ correlated strongly with children having less schooling or needing a longer time to complete schooling (15), and in later life, with lower income and living in a less conducive environment, such as having a higher number of pregnancies and having the first child at a younger age (16).

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

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

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

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

The importance of interventions in improving cognitive outcomes among undernourished children

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

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

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

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

The impact of overweight/obesity on neurodevelopment and cognition

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

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

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

Factors influencing the impact of suboptimal growth on neurodevelopment and cognition

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

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

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

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

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

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

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

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

Consideration for future research and actions:

1) More studies should be conducted on the impact of nutritional/behavioural interventions in overweight/obese children on neurodevelopment and cognition, especially in low-income countries, as all the currently retrieved literature came from high-income countries. 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). In addition to the negative consequences of undernutrition, an increase in childhood obesity prevalence can lead to adverse long-term consequences on human capital in these countries.

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

3) Optimally, any program or intervention for growth monitoring in the 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 (35). Multidimensional approaches that can improve neuro-cognitive development in children include providing adequate nutrient intakes for catch-up growth among underweight or stunted children, interventions to reduce childhood overweight/obesity as well as socio-economic stimulations, such as improving educational attainment, job security, social welfare, housing and sanitation levels of the population. Actions taken should tackle both undernutrition and overweight/obesity concurrently – not

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

CONCLUSION

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

DECLARATIONS

Acknowledgements

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

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Author contributions

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

Competing interests

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

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

References

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

21. Rosado JL, Lopez P, Garcia OP, et al. Effectiveness of the nutritional supplement used in the Mexican Oportunidades programme on growth, anaemia, morbidity and cognitive development in children aged 12-24 months. Public Health Nutr. 2011;14(5):931-7.
22. Yousafzai AK, Rasheed MA, Rizvi A, et al. Effect of integrated responsive stimulation and nutrition interventions in the Lady Health Worker programme in Pakistan on child development, growth, and health outcomes: a cluster-randomised factorial effectiveness trial. Lancet. 2014;384(9950):1282-93.
23. Morano M, Colella D, Caroli M. Gross motor skill performance in a sample of overweight and non-overweight preschool children. Int J Pediatr Obes. 2011;6 Suppl 2:42-6.
24. Liang J, Matheson BE, Kaye WH, et al. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. International journal of obesity (2005). 2014;38(4):494-506.
25. Reinert KR, Po'e EK, Barkin SL. The relationship between executive function and obesity in children and adolescents: a systematic literature review. J Obes. 2013;2013:820956.
26. Hayes JF, Eichen DM, Barch DM, et al. Executive function in childhood obesity: Promising intervention strategies to optimize treatment outcomes. Appetite. 2018;124:10-23.
27. Walker SP, Chang SM, Younger N, et al. The effect of psychosocial stimulation on cognition and behaviour at 6 years in a cohort of term, low-birthweight Jamaican children. Dev Med Child Neurol. 2010;52(7):e148-54.
28. Nguyen PH, Kim SS, Sanghvi T, et al. Integrating Nutrition Interventions into an Existing Maternal, Neonatal, and Child Health Program Increased Maternal Dietary Diversity, Micronutrient Intake, and Exclusive Breastfeeding Practices in Bangladesh: Results of a Cluster-Randomized Program Evaluation. J Nutr. 2017;147(12):2326-37.
29. Kristjansson E, Francis DK, Liberato S, et al. Food supplementation for improving the physical and psychosocial health of socio-economically disadvantaged children aged three months to five years. Cochrane Database Syst Rev. 2015(3):CD009924.
30. Pimpin L, Kranz S, Liu E, et al. Effects of animal protein supplementation of mothers, preterm infants, and term infants on growth outcomes in childhood: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2019;110(2):410-29.
31. Sjarif DR, Yuliati K, Iskandar WJ. Daily consumption of growing-up milk reduces stunting among Indonesian toddlers. Medical Journal Indonesia. 2019;28:70-6.
32. Lee R, Singh L, van Liefde D, et al. Milk Powder Added to a School Meal Increases Cognitive Test Scores in Ghanaian Children. J Nutr. 2018;148(7):1177-84.
33. Smithers LG, Golley RK, Mittinty MN, et al. Do dietary trajectories between infancy and toddlerhood influence IQ in childhood and adolescence? Results from a prospective birth cohort study. PLoS One. 2013;8(3):e58904.
34. Miller AL, Lee HJ, Lumeng JC. Obesity-associated biomarkers and executive function in children. Pediatr Res. 2015;77(1-2):143-7.
35. Double-duty actions for nutrition. Policy Brief. World Health Organization. 2017.
36. World Health Organization. Global nutrition targets 2025. 2014.
37. Smithers LG, Lynch JW, Yang S, et al. Impact of neonatal growth on IQ and behavior at early school age. Pediatrics. 2013;132(1):e53-60.
38. Aubuchon-Endsley NL, Grant SL, Berhanu G, et al. Hemoglobin, growth, and attention of infants in southern Ethiopia. Child Dev. 2011;82(4):1238-51.
39. Waber DP, Bryce CP, Girard JM, et al. Impaired IQ and academic skills in adults who experienced moderate to severe infantile malnutrition: a 40-year study. Nutr Neurosci. 2014;17(2):58-64.
40. Sudfeld CR, McCoy DC, Fink G, et al. Malnutrition and Its Determinants Are Associated with Suboptimal Cognitive, Communication, and Motor Development in Tanzanian Children. J Nutr. 2015;145(12):2705-14.
41. Ip P, Ho FKW, Rao N, et al. Impact of nutritional supplements on cognitive development of children in developing countries: A meta-analysis. Sci Rep. 2017;7(1):10611.
42. Larson LM, Yousafzai AK. A meta-analysis of nutrition interventions on mental development of children 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> Thu, May 13, 2021 at 7:37 AM
To: "suryawan.ahmad@gmail.com" <suryawan.ahmad@gmail.com>

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

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

Sent from my iPhone

Begin forwarded message:

From: Nutrition Research Reviews <onbehalfof@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:

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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.

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 SD>WAZ< 3 SD) and obesity as WAZ $\geqslant$ 3 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

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

Running title: Malnutrition and cognitive neurodevelopmental consequences

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Abstract

The negative impact of stunting and severe underweight on cognitive neurodevelopment of children is well-documented; however, the effect of overweight/obesity is still unclear. The 2018 Global Nutrition Report reported that stunting and overweight concurrently affect 189 million children worldwide. As existing reviews separately discuss undernutrition from *overweight/obesity*, this scoping review aims to document the impact of mild/moderate and severe underweight, stunting, and overweight/obesity among children aged 0-60 months on their cognitive neurodevelopmental trajectories. Twenty-six articles were analysed to extract significant information from literature retrieved from PubMed and Cochrane databases published from 1 January 2009 to 31 October 2019. Length gain is associated with cognitive neurodevelopment in normo-nourished and stunted children aged under 24 months. Among stunted children, it seems that cognitive and neurodevelopmental deficits can potentially be recovered before 8 years old, particularly in those whose nutritional status *has improved*. The impact of overweight/obesity on cognitive neurodevelopment appears to be limited to attention, gross motor skills and executive control. Parental education level, birth weight/length, breastfeeding duration, and sanitation level are some identifiable factors that modify the impact of undernutrition and overweight/obesity on cognitive and neurodevelopment. In conclusion, *underweight, stunting and overweight/obesity* have a significant impact on cognitive neurodevelopment. *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.*

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

INTRODUCTION

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

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

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

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 SD>WAZ< 3 SD and obesity as WAZ ≥ 3 SD) (3). This combined approach will conceivably allow for a more holistic view of the situation commonly found in many countries across the world.

METHODS

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

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

RESULTS AND DISCUSSION

Descriptive summary of included studies

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

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

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

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

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

From a longitudinal study in the Philippines, regardless of HAZ categories at 6 months (defined as moderate/severe stunting (HAZ < -2), mild stunting (-2 ≤ HAZ < -1), at risk of stunting (-1< HAZ < 0) or normal height (HAZ ≥ 0)), more gain (or less loss) in HAZ after the age of 6 months *was* positively associated with cognitive function at 11 years of age. In addition, changes in HAZ from 6 to 24 months and changes in HAZ from 24 months to 11 years were also positively associated with cognitive ability at 11 years in the same study [11]. These outcomes are similar to the results among children in Bangladesh. In this study, cognitive impairment was associated with poverty, birth condition and postnatal growth that started at 7 months of age and worsened up to 64 months when it became even more substantial [12]. The impact of the 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 [13]. Another study reported that higher HAZ at 4-6 years of age among healthy Malaysian children significantly contributed 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) [14].

Evidence for the impact of underweight and stunting on the development of emotional skills is largely variable across the identified studies. Two meta-analyses that described data from lower- and middle-income countries showed the limited influence of undernutrition on a child's attachment, emotionality, social competence and temperament [6, 8]. 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 temperament *differences,* which were assessed using validated interviewer-administered questionnaire to parents, were small to moderate [15]. There is evidence, therefore, that underweight and stunting impact social skill development. Low HAZ and WAZ correlated strongly with children having less schooling or needing a longer time to complete schooling [16], and in later life, with lower income and living in a less conducive environment, such as having a higher number of pregnancies and having the first child at a younger age [17].

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

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

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

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

The importance of interventions in improving cognitive outcomes among undernourished children

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

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

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

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

The impact of overweight/obesity on neurodevelopment and cognition

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

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

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

Factors influencing the impact of suboptimal growth on neurodevelopment and cognition

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

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

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

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

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

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].

Limitations and strengths of the review

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

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

Consideration for future research and actions:

1) More studies should be conducted on the impact of nutritional/behavioural interventions in overweight/obese children on neurodevelopment and cognition, especially in low-income countries, as the currently retrieved literature all came from high-income countries. 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 [3]. In addition to the negative consequences of undernutrition, an increase in childhood obesity prevalence can lead to adverse long-term consequences on human capital in these countries.

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

3) Optimally, any program or intervention for growth monitoring in the 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 [37]. *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.* Actions taken should

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

CONCLUSION

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

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Author contributions

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

Competing interests

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

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

References

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

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

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

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: • Cognitive • Motor • Socio-emotional	• 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	• 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	• 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		• -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	• Temperament and attention assessed using modified version of the Laboratory Temperament Assessment Battery (Lab-TAB) and MOFPTask at 6 and 9 months	• 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	• 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	• 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	• 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	• At 48 months: social skills competence or 'daily living skills' assessed using VSMS • At 60 months: cognitive functioning assessed using R-DPDQ	• Cognitive functioning • Social skills competence • Fine motor skills	Good
10	Crookston BT, 2013 [16]	• 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: • Schooling average • Mathematics test • Reading comprehension/verbal achievement: Early Grade Reading Assessment • Receptive vocabulary: Peabody Picture Vocabulary Test (PPVT)	• 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 • 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	• Age of starting and leaving school • Highest grade attained	• 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		• 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	• 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	• 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	At 6 to 24 months: • Baseline assessment using revised version of the Bayley Scales of Infant Development • Temperament assessed through an interviewer-administered maternal questionnaire	• 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: • Cognition • Communication (comprising expressive and receptive communication skills) • Motor (comprising fine and gross motor skills)	• 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	• 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	• 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	• 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	• 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	• 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	• 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.	• 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	• 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 • 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	• 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	• Cognitive scales • Language scales • Motor scales	Good

								than control, but at 24 months of age only the language scores remained significantly higher. • 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		

								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	• 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	• 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	• Children who received both vitamin B12 and folic acid had 0.45 (95% CI 0.19, 0.73) and 0.28 (95%	• Gross motor • Problem solving skills	Good

					folic acid) with (1:1:1:1 ratio)			CI 0.02, 0.54) higher SD-units in the domains of gross motor and problem solving functioning, respectively. • 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: • BSID-I, -II or -III—Mental Scale • Griffiths Mental Developmental Scale	• Motor development, but not growth status, effect sizes were significantly associated with mental development in postnatal interventions.	Motor development	Good

							• Fagan Test of Infant Intelligence	• 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	At 72 months: • 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	• 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	• Selective attention • Visual-spatial memory	Poor

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

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

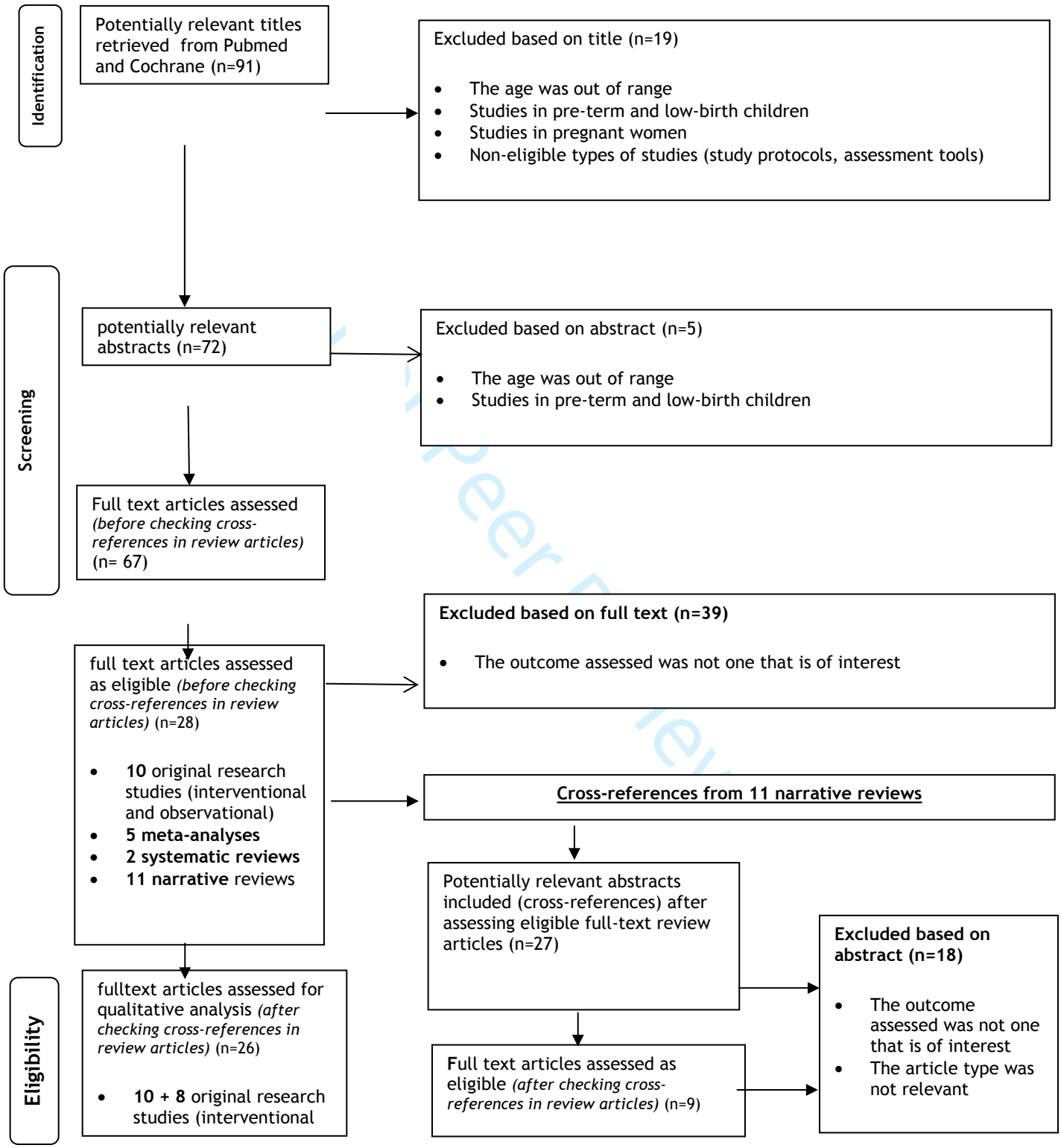
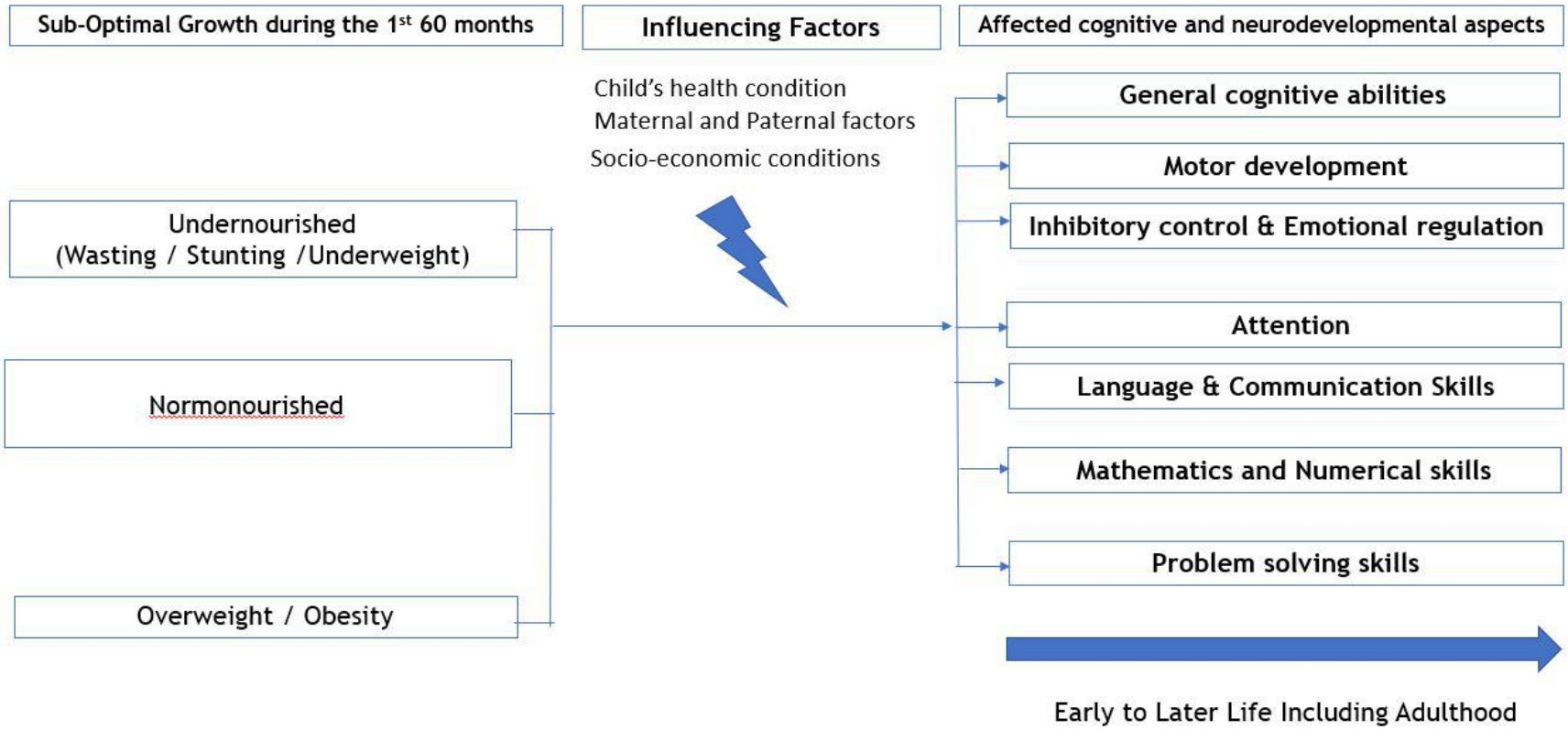


Figure 2. Impact of suboptimal growth in early childhood on developmental-related aspects



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Deputy Dean (Undergraduate Studies)

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

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

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

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

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

09 November 2021
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To whom it may concern,

Confirmation of online publication

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

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

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.

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S R Priyadarshini, J A Moses, C Anandharamakrishnan

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

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

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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. Muhardi

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Modulation of intestinal stem cell homeostasis by nutrients: a novel therapeutic option for intestinal diseases

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

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