Systematic review and meta-analysis found that malnutrition was associated with poor cognitive development

Running title: mal**nutrition and cognitive development**

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ABSTRACT

Background: Malnutrition is a major public health issue that has been associated with high susceptibility for impaired brain development and mental functioning. However, to date studies on this topic have not been collated and appraised. This systematic review and meta-analysis investigated the association between malnutrition and cognitive development.

Methods: We searched the MEDLINE, Scopus, CINAHL, Embase PsycINFO and Cochrane Library databases in English up to 8 December 2020. All studies reporting an association between nutritional status and cognitive development were included. P values of less than 0.05 were considered statistically significant and the results are reported as standardised mean differences (SMD), 95% confidence intervals (95%) and I^2 statistics.

Results: We included 12 studies comprising 7,607 participants aged 1 to 12 years. Children with malnutrition had worse scores than controls for the Wechsler Intelligence Scale (SMD -0.40; 95% CI -0.60 to -0.20; p<0.0001; I^2 77.1%), the Raven's Coloured Progressive Matrices (SMD -3.75; 95% CI -5.68 to -1.83; p<0.0001; I^2 99.2%), visual processing (SMD -0.85; 95% CI -1.23 to -0.46; p 0.009; I^2 11.0%) and short memory (SMD 0.85; 95% CI -1.21 to -0.49; p<0.0001; I^2 0%) tests.

Conclusion: Normal cognitive development requires access to good and safe nutrition.

KEY NOTES

- Until now, no attempt has been made to collate and appraise literature on malnutrition and cognitive development.
- Findings from this review suggest that malnutrition is associated with poor cognitive development.
- It is important to promote access to safe and good nutrition in order to aid in normal cognitive development for children.

Key words: brain development, children, malnutrition, cognitive development, nutrition

INTRODUCTION

Worldwide malnutrition is considered a major public health issue and includes stunting defined as low height for age, wasting defined as low weight for height, underweight defined as low weight for age and micronutrient deficiencies or insufficiencies.[1] It is estimated that around 462 million adults are underweight and 159 million children under the age of 5 are stunted and 50 million are wasted.[1] The major concern in malnourished children is due to the higher risk of nutrition-related death from common diseases such as diarrhea, pneumonia, and malaria.[2] Indeed, an estimated 45% of deaths (3.1 million yearly) of children under five years are linked to malnutrition.[2] The underlying causes of malnutrition are mainly due to poor behavioural practices of food utilisation, poor infant feeding practices, inadequate clean drinking water and sanitation facilities, food insecurity, diseases, limited access to health care services, poor maternal and childcare practices, and illiteracy.[3] Moreover, malnutrition has also been shown to be associated with impaired brain development and, consequently, impaired mental functioning.[4] Importantly, adequate nutrition, especially during pregnancy and infancy, is crucial for normal brain development, laying the foundation for the development of cognitive, motor, and socio-emotional skills throughout childhood and adulthood.[5] Indeed, the brain and cognitive development are the result of several factors combined with nutrition including the amount and quality of stimulation the child receives from the environment, the timing of nutrient deprivation, the degree of nutrient deficiency and the possibility of recovery.[5] Moreover, other important factors have to be considered including poverty, poor maternal education, low access to healthcare, preterm birth, and indeed more generally all social determinants of health.[5] As expected, the majority of settings with insufficient resources, where children are not able to achieve their full growth and developmental potential, are in Africa and Asia.[6] Not surprisingly, most studies that have investigated associations between early malnutrition and poorer intelligence quotient (IQ) levels, cognitive function, and school achievement, as well as greater behavioural problems showed strongest associations in Africa and Asia.[5] This represent a serious threat to public health and limits educational achievements and opportunities for economic development within these two continents.

Indeed, the economic impact associated with child malnutrition particularly underweight and stunted children is significant with far reaching consequences on health, education and productivity, undermining, in turn, the possible growth of the country.

Giving the growing attention to malnutrition and the ambitious targets declared by the World Health Organization in the Sustainable Development Goal 2, by 2030 end all forms of malnutrition,[7] understanding the impact of malnutrition on development cognition is of high importance. Therefore, the aim of this systematic review and meta-analysis was to collate and appraise literature that has examined the association between malnutrition and cognitive development.

MATERIALS AND METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[8] and Meta-analysis Of Observational Studies in Epidemiology[9] statements and followed a structured protocol, available on reasonable request to the corresponding author.

Data sources and literature search strategy

Two investigators (NV and DP) independently conducted a literature search using the MEDLINE, Scopus, CINAHL, Embase PsycINFO and Cochrane Library databases from inception up to 8 December 2020. Any inconsistencies were resolved by consensus with a third author (FT).

In MEDLINE, the following search strategy was used: child OR children OR infant AND nutrition* OR malnourish* AND cognitive OR neurodevelopment OR memory. Conference abstracts and reference lists of included articles were hand-searched to identify any potential additional relevant work.

Study selection

Following the PICOS criteria, we included studies assessing as population children with malnutrition, as comparison children without malnutrition, as outcomes validated cognitive tests, and observational case-control, cross-sectional and cohort studies.

The status of malnutrition was defined following the definition: underweight as weight-for-age $Z < -2$, stunting as height-for-age $Z < -2$ and wasting as weight-for-height $Z < -2$. Cognitive status was assessed through validated tools, as summarised in Table S1. Studies were excluded if they included populations of more than 18 years of age; if the data were not analysable; if they did not clearly report data regarding cognitive status in cases and, or, controls.

Data extraction

For each eligible study, two independent investigators (NV, DP) extracted: name of the first author and year of publication, setting, sample size, mean age of the population, percentage of females, type of study, definition of malnutrition, diagnostic tool used for cognitive status.

Outcomes

The primary outcomes were means and standard deviations (SDs) of the validated tools of cognition, comparing the values of people with malnutrition to controls. If data were reported in other ways, as median and interquartile ranges, they were transformed to means and SD. We also extracted data regarding presence of categorical outcomes, such as number of poor semester achievement and those below IQ average.

Assessment of studies quality

Two independent authors (DP, LS) carried out quality assessment of included studies using the Newcastle-Ottawa Scale (NOS).[10] The NOS assigns a maximum of nine points based on three quality parameters: selection, comparability, and outcome. As per the NOS grading in past reviews, we graded studies as having a high (<5 stars), moderate (5-7 stars) or low risk of bias (≥8 stars).[11]

Data synthesis and statistical analysis

For all analyses, a p-value less than 0.05 was considered statistically significant. The primary analysis compared the values of cognitive tests between participants with malnutrition vs. controls. We calculated the difference between the means of the treatment and control groups using through standardised mean differences (SMD) with their 95% confidence intervals (CIs), applying a random-effect model.[12]

Heterogeneity across studies was assessed by the I^2 metric. Given significant heterogeneity ($I^2 \geq 50\%$ and/or $p<0.05$)[13] and having at least 10 studies for each outcome, we planned to run meta-regression analyses. However, no outcome included 10 studies and so these analyses were not possible. Publication bias was assessed by visual inspection of funnel plots and using the Egger bias test.[14] In case of publication bias, when three or more studies were available, we used the Duval and Tweedie non-parametric trim-and-fill method to account for potential publication bias.[15] Based on the assumption that the effect sizes of all the studies are normally distributed around the centre of a funnel plot, in the event of asymmetries, this procedure adjusts for the potential effect of unpublished (trimmed) studies.[14] However, no outcome had 3 different studies.

RESULTS

As shown in Figure 1, we initially identified 4779 possible eligible papers. After removing 4701 articles, through the title and, or, abstract screening, 78 were retrieved as full-text versions. Of the 78 full-text, 12 satisfied the inclusion and, or, exclusion criteria and were included in the systematic-review and meta-analysis.

As shown in Table 1, the 12 case-control studies included a total of 7,607 participants, with a maximum participant age of 12 years and 48.3% of participants were female. The studies were predominantly carried out in Asia and Africa where five studies were performed in each continent followed by South America and Middle-East with one each. Finally, seven studies were carried out in a school setting.

As shown in **Table 2**, malnutrition was associated with a worse score in Wechsler intelligence scale for children (WISC-IV) (SMD -0.40; 95% CI -0.60 to -0.20; $p<0.0001$; I^2 77.1%) and in Raven's Coloured Progressive Matrices (RCPM) (SMD -3.75; 95% CI -5.68 to -1.83; $p<0.0001$; I^2 99.2%). Finally, malnutrition was associated with worse scores in visual processing (SMD -0.85; 95% CI -1.23 to -0.46; $p=0.009$; I^2 11.0%) and short memory (SMD -0.85; 95% CI -1.21 to -0.49; $p<0.0001$; I^2 0%) tests compared to controls. On the contrary no significant differences were observed for the

IQ and total scores of educational achievement using the Test of Nonverbal Intelligence Third Edition (TONI3) or Bruininks–Oseretsky Test of Motor-Proficiency 2 Short Form (BOT2-SF). Moreover, malnutrition was associated with a higher prevalence of the number of people not reaching semester achievement (OR 3.22; 95% CI 2.12 to -4.91; p<0.0001; I^2 0%), whilst no differences were detected for number of children below average IQ and for Schedule of Growing Skills II (SGS II) in adjusted analyses, as shown in Table 2.

In addition to the studies included in meta-analysis, four out the twelve included in the systematic review showed important findings. A longitudinal study assessing 1674 children by the Peabody Picture Vocabulary Test showed that only one-third of children who were stunted in infancy at 1 year of age, recovered by the time they were 5 years old.[20] In another study the IQ was calculated in 200 children using Kamat's psychological test and 29.3% of those malnourished were classified with below average IQ compared to the 11.5% of children with normal nutritional status.[21] Finally, two studies assessing the IQ by RPCM showed a higher prevalence of malnourished children with below average IQ compared to normal nutritional status (68.7% vs 15.9%) and (83.3% vs 44.3%) respectively.[22,23]

The overall mean score of the studies was 6.5 (range: 5-8), indicating an overall good quality, according to the NOS (Table S2).

DISCUSSION

Findings from this systematic review and meta-analysis show the association between malnutrition and different domains of cognitive development. In particular, significant and worse scores were observed using the WISC-IV tool, the RCPM tool, visual processing, and short memory tests. Moreover, malnutrition was associated with a lower prevalence of the number of people reaching semester achievement. On the contrary, no significant differences were observed in adjusted models between malnutrition and total scores for educational achievement, Bruininks–Oseretsky Test of Motor-Prociency 2 Short Form, number of children below average IQ, and Growing Skills II. These data, on one hand, confirm evidence of an association between malnutrition and poor cognitive development and, on the other hand, reflect both the heterogeneity of assessment and the multifactorial pathogenesis.

Generally, studies comparing malnourished children and controls showed poorer scores in terms of IQ, cognitive functions and school achievement.[29] These findings support literature that has identified malnutrition in early life is associated with more attention problems, lower social status and a lower standard of living in adulthood compared to controls.[30] There are indeed plausible and direct pathways that may explain the relationship between malnutrition and poor cognitive outcomes. For example, malnutrition is associated with both structural and functional pathology of the brain. Structurally malnutrition results in tissue damage, growth retardation, disorderly differentiation, reduction in synapses and synaptic neurotransmitters, delayed myelination and reduced overall development of dendritic arborization of the developing brain.[31]

Importantly, nutrition is only one factor that may influence brain development and others include poverty, poor healthcare and preterm birth.[5] Moreover, children living in poorer settings are often exposed to additional negative factors such as poor sanitation and hygiene, child abuse, and neglect that may heavily affect their development. However, good nutrition should be considered a crucial aspect for normal brain development.[28]

Importantly, when developing interventions and guidelines for children, it should be considered that healthy nutrition starts prior to conception and during pregnancy. Indeed, the mother and fetal nutritional status may induce neural tube disorders, low birth weight and length, and other negative consequences including developmental delays and disabilities.[32] Moreover, breastfeeding plays a crucial role in cognitive development, owing to the rich composition of breastmilk in term of nutrients, and the mother-infant interaction which has been found to be of importance for cognitive and socio-emotional development.[33]

Findings from the present review suggest that there is urgency to implement interventions to reduce malnutrition and, thus, poverty subsequently improving social determinants of health. First, it is necessary to identify programs with efficacy in improving nutrition and developmental outcomes in children. Next, it would be crucial to obtain data about costs and benefits of ongoing programs, preferably integrated programs. It is also necessary to redesign tailored policies for the most affected countries, taking into account social, political and economic contexts and addressing the nutritional issue starting from prenatal period with educational and preventive programs. Finally, social protection should defend the most vulnerable groups providing the necessary means of subsistence and aiming to achieve social inclusion.

The selection of only validated tools for cognitive development assessment and the representativeness of the sample are clear strengths of this meta-analysis. However, findings must be interpreted in light of the study's limitations. First, the use of different measurement tools meant the sample was divided into several groups for analyses reducing the strength of the findings. Finally, the multifactorial nature of both nutrition and cognitive development prohibits determination of cause and effect. The interaction between nutrition, inflammation and neurodevelopment may also be considered as a limitation. When taking a holistic approach also inflammation, both due to infection or other causes, should be considered as a main factor impairing cognition and behaviour in early and adult life.[34] Unfortunately, also considering the limited resources, no included studies assessed inflammation markers, and further comprehensive studies are needed to fill this evidence gap. Finally, we included only observational studies that have inherent limitations such as a high potential risk of bias and confounding factors. For example, eight of the included studies did not report on controlling for covariates in their statistical analyses and the four which did controlled for varying and different correlates. Malnutrition is highly dependent on several factors, including socio-economic determinants and parental education and only two of the four included studies controlled for both these variables. It is important for future studies on the association between malnutrition and cognitive development to adjust analyses accordingly for these important covariates.

CONCLUSION

Findings from this review suggest that it is important to promote access to safe and good nutrition in order to aid in normal cognitive development for children. The achievement of this objective in the near future is unlikely and a strong commitment of all actors involved including governments and the international community is now necessary and urgent.

Conflicts of Interest

The authors declare no conflicts of interest

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None

ABBREVIATIONS

BOT2-SF = Bruininks–Oseretsky Test of Motor-Proficiency 2 Short Form

CI = confidence intervals

IQ = intelligence quotient

NOS = Newcastle-Ottawa Scale

RCPM = Raven's Coloured Progressive Matrices

SD = standard deviation

SGS = Schedule of Growing Skills

SMD = standardised mean differences

TONI 3 = Test of Nonverbal Intelligence Third Edition

WISC-IV = Wechsler intelligence scale for children

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Legend to figure

Figure 1. PRISMA flow-chart.

Tables

Table 1. Descriptive characteristics of the included studies

Author, year	Country	Conti-nent	Setting	Sample size	% girls	Mean age (SD) or range	NOS	Confounders
Al-Mekhlafi, 2011[16]	Malaysia	Asia	School	241	50.3	7 -12	7	Low household income, low mothers' educa-tional level
Ayalew, 2020[17]	Ethiopia	Africa	School	347	50.1	9.45 (1.97)	8	Not reported
Bogale, 2011[18]	Ethiopia	Africa	Outpa-tients	100	NA	5	7	Not reported
Chowdhury, 2011[19]	India	Asia	School	454	NA	5-12	7	Not reported
Crookston, 2009[20]	Perù	South America	Outpa-tients	1305	NA	1	6	Number of sib-lings, area popu-lation, maternal education, wealth
Garkal, 2014[21]	India	Asia	School	200	NA	5-9	7	Not reported
Ghazi, 2012[22]	Iraq	Middle-East	School	529	47.8	7-8	5	Not reported
Ghosh, 2015[23]	India	Asia	School	265	55.8	5-12	7	Not reported
Jimoh, 2018[24]	Nigeria	Africa	Commu-nity	415	45.5	0.5-5	5	Not reported
Li, 2016[25]	China	Asia	Commu-nity	1742	38.5	9.04 (0.78)	6	Age of children, ma-ternal age, sex of children, edu-cational level and occupation of parents, house-hold wealth in-dex, older siblings of chil-dren, school of children, prena-tal supplementa-tion, and gesta-tional weeks
Liu, 2003[26]	Mauritius	Africa	Commu-nity	1193	48.6	3	6	Psycho-social and environ-mental

Pienaar, 2019[27]	South Af-rica	Africa	School	816	48.5	6.78	7	Not reported

Table 2. Meta-analysis of the main outcomes of the investigation

Continuous outcomes						
Test (Ref)	**N of studies**	**N of malnourished**	**N of controls**	**SMD (95%CI)**	**p-value**	**I^2**
Intelligence quotient and total scores of educational achievement (IQ - TONI3)[16]	1	205	287	0.05 (-0.10; 0.20)	0.52	0
Wechsler intelligence scale for children (WISC-IV)[25,26]	2	527	5918	-0.40 (-0.60; -0.20)	<0.0001	77.1
Raven's Coloured Progressive Matrices (RCPM)[19]	1	427	791	-3.75 (-5.68; -1.83)	<0.0001	99.2
Bruininks–Oseretsky Test of Motor-Prociency 2 Short Form (BOT2-SF)[27]	1	130	2318	-0.38 (-0.82; 0.05)	0.12	82.7
Visual processing[18]	1	41	59	-0.85 (-1.23; -0.46)	0.009	11.0
Short memory[18]	1	41	59	-0.85 (-1.21; -0.49)	<0.0001	0
Dichotomous outcomes						
Outcome	**N of studies**	**N of events/ n total malnourished**	**N of events/ n total controls**	**OR (95% CI)**	**p-value**	**I^2**
N poor semester achievement[17]	1	169/879	28/478	3.22 (2.12-4.91)	<0.0001	0
N of below average IQ[24]	1	12/70	156/1175	1.32 (0.70-2.51)	0.39	0

Growing Skills II (SGS II) (adjusted analyses)[24]	1	12/70	156/1175	1.36 (0.80-2.32)	0.26	0

Supplementary Table 1. List and description of validated tools used for the cognitive status assessment

Tools	**Function**	**Brief description**
Intelligence quotient and total scores of educational achievement	Academic performance	The psychological variables exposed relate in some way to the level of learning of reading, writing and calculating, useful for identifying any specific learning disorders, which can only be diagnosed in the presence of a normal IQ. In some cases the achievement of basic skills is based on the semester of attendance.
IQ by Kamat's psychological tests and Wechsler intelligence scale for children (WISC-IV)	Intelligence	The used tests are batteries which in turn include numerous subtests, which could be divided into as many cognitive domains if desired. However, authors reported global scores without sub-dimensions division.
Raven's Colored Progressive Matrices (RCPM) and Cognitive Development Assessment CDA-Quantitative	Non-verbal reasoning	In this category we included tests only assessing non-verbal intelligence.
Growing Skills II (SGS II)	Quotient development	The multi-domain tool is used with very young children, observed in interaction with the external environment, stimuli, family members, educational agents, etc. It allows to intercept specific delays in development. It is a very versatile tool, consisting of several areas: passive postural, active postural, locomotor, manipulative, visual, hearing and language, speech and language, interactive, self-care.
Peabody Picture Vocabulary Test (PPVT)	Language	PPVT is used to evaluate vocabulary skills and listening comprehension. It is a commonly used measure for evaluating cognitive development in both high- and low-income countries.

Bruininks – Oseretsky Test of Motor-Prociency 2 Short Form (BOT2-SF)	Visual motor skills	The BOT2-SF is used to assess motor proficiency. It consists of 14 items and evaluates motor skills in four area com ponents which each consist of two sub-items: fine motor precision and fine motor integration, manual dexterity and bilateral coordination, balance and running speed and agility, upper limb coordination and strength.
KABC-II	Visual processing	In this case the visual processing activity was assessed by three subtests of KABC-II drum kit (Triangles, Conceptual Thinking, Pattern Reasoning) that are included for the evalu ation of this function.
KABC-II	Short-term memory	The short-term memory was assessed by three other subtests of the KABC-II battery: Word Order, Number Recall, Hand Movements.

IQ = intelligence quotient

Supplementary Table 2 The quality of the studies according to the Newcastle - Ottawa assessment Scale adapted for cross-sectional studies.

	1	2	3	4	5	6	7	Tot
Al-Mekhlafi, 2011	1	1	1	1	1	1	1	7
Ayalew, 2020	1	1	1	1	2	1	1	8
Bogale, 2011	1	1	1	1	1	1	1	7
Chowdhury, 2011	1	1	1	1	1	1	1	7
Crookston, 2009	1	1	0	1	1	1	1	6
Garkal, 2014	1	1	1	1	1	1	1	7
Ghazi, 2012	1	1	0	1	0	1	1	5
Ghosh, 2015	1	1	1	1	1	1	1	7
Jimoh, 2018	1	1	0	1	0	1	1	5
Li, 2016	1	1	0	1	1	1	1	6
Liu, 2003	1	1	0	1	1	1	1	6
Pienaar, 2019	1	1	1	1	1	1	1	7