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Education and health as social determinants: the econeurobiology of brain development

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Education and health as social determinants: the econeurobiology of brain development

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Editorial: Education and health as social determinants: the econeurobiology of brain development

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Editorial on the Research Topic
Education and health as social determinants: the econeurobiology of brain development

Introduction

The development of the human brain is a dynamic and complex process, profoundly influenced by the surrounding environment during childhood. Early life experiences and educational enrichment play a crucial role in brain development, highlighting the interplay between genetic and environmental factors (1). The field of econeurobiology provides an essential framework for understanding how these factors interact to shape neurobiological development. This perspective is particularly significant in recognizing how education and health function as critical social determinants that influence cognitive and behavioral outcomes in children.

This Research Topic of Frontiers in Public Health brings together a collection of studies that explore these interactions in depth, emphasizing the key factors that impact brain development and the long-term effects on children's behavior and academic performance. The research underscores the profound influence of early-life experiences—from the positive effects of supportive educational environments to the harmful consequences adverse childhood experiences (ACE), toxic stress and trauma (2).

By focusing on the concepts of developmental neuroplasticity and brain connectivity, these studies offer valuable insights into the mechanisms by which environmental conditions shape the developing brain. Moreover, the integration of Gardner's multiple intelligences into educational strategies is emphasized as a means to enhance cognitive and emotional resilience (3). Collectively, the articles in this Research Topic provide essential knowledge for educators, policymakers, and healthcare professionals dedicated to fostering optimal development in children.

Key factors shaping brain development

The studies in this Research Topic demonstrate that the environment plays a crucial role in brain development, significantly influencing cognitive and behavioral outcomes.

Mualem et al. emphasize six critical factors in brain development: a nurturing environment, adequate nutrition, physical activity, music, sleep, and brain connectivity as explained by Gardner's multiple intelligences. The study highlights how these elements promote cognitive and emotional growth, while also noting the detrimental effects of trauma and deprivation on long-term health and learning outcomes.

Tian et al. explore the relationship between life-course household wealth mobility and adolescent health in rural China. Key findings show that upward wealth mobility, especially during early childhood, is associated with better physical growth, cognitive development, and lower behavioral problems, underscoring the critical role of socioeconomic conditions in shaping long-term health and development outcomes.

Sánchez-Ferrer et al. examine the emotional impact of COVID-19 home confinement on children in Spain. Findings indicate that nearly 40% of children experienced poor emotional states, including fear, sadness, and irritability. Factors such as sleep disturbances, lack of outdoor access, and parental anxiety exacerbated these effects, while creative communication and having pets mitigated emotional distress.

Mucignat-Caretta and Soravia review how environmental factors, both positive and negative, influence human brain development. Music training is highlighted as a beneficial factor that enhances cognitive and motor skills through brain plasticity, while stress is shown to negatively impact brain structure and function. The findings underscore the significant role of environmental inputs in shaping cognitive and emotional development.

Liu et al. systematically review the relationship between fundamental movement skills (FMS) and health-related fitness in children and adolescents. They find strong evidence linking FMS with better cardiopulmonary function, muscle strength, and endurance, while also showing a negative correlation with body composition. The review underscores the importance of developing FMS for overall physical health and fitness.

Melby et al. examine the associations between adolescents' physical literacy, sport and exercise participation (SEP), and wellbeing. Findings reveal that higher physical literacy correlates positively with SEP and various aspects of wellbeing, including self-esteem and life satisfaction. These associations are particularly strong among girls, suggesting that physical literacy is crucial for enhancing adolescents' emotional and social wellbeing.

Lapidot et al. investigate the connection between the gut microbiome and cognitive development in school-aged children, finding that greater microbial diversity is positively linked to higher cognitive function as reflected in IQ scores. Recent research highlights how dietary preferences, particularly traditional vs. processed foods, affect cognitive performance and social behavior in kindergarten children, underscoring nutrition's vital role in early development (4). Socioeconomic status also significantly influences gut microbiome composition and cognitive outcomes.

Ba et al. examine the prevalence and determinants of meeting minimum dietary diversity (MDD) among children aged 6–23 months in three sub-Saharan African countries (Gambia, Liberia, and Rwanda). The findings reveal that only 23.2% of children meet MDD, with significant variations by country, socioeconomic status, maternal education, and access to healthcare, highlighting critical disparities in child nutrition.

Elhady et al. identify multiple barriers to providing adequate nutrition care for child malnutrition in a low-resource setting. Key barriers include insufficient training for healthcare providers, a shortage of nutritional supplements, inadequate patient education materials, and systemic issues like workforce shortages. These challenges hinder effective nutrition care, emphasizing the need for targeted improvements in resources, training, and health system management.

Posner and Rothbart discuss how understanding and strengthening brain networks can enhance elementary education. Key insights include the role of brain networks in reading, writing, number processing, attention, and motivation. Strengthening these networks through targeted educational strategies can improve learning outcomes and foster a growth mindset, highlighting the importance of neuroscience-informed teaching practices in early education.

You et al. identify elevated plasma levels of CCL5 as a potential risk factor for developing tic disorders in children. Elevated CCL5, along with other cytokines like PDGF-AA, was significantly associated with tic disorder development, though not with tic severity. These findings suggest CCL5 could serve as a biomarker for predicting the onset of tic disorders.

Finally, in a key article, Mualem et al. illustrate the influence of neural pathways on classroom learning, using the example of story writing. The optimal development of these connections is vital for fostering both quick, intuitive thinking and more deliberate analysis, leading to what is referred to as the "optimized brain." Additionally, the article introduces the "Econeurobiology of the Brain for Healthy Child Development" model, showing how a child's ecological environment affects neurological development. This interaction shapes cognitive abilities, emotional regulation, and overall wellbeing, underscoring the importance of a supportive and enriching environment for optimal brain development.

Conclusion

In conclusion, this Research Topic provides a comprehensive exploration of how environmental and social determinants, particularly education and health, play a pivotal role in brain development. The insights offered in these articles underscore the importance of a multidisciplinary approach to fostering optimal cognitive and emotional growth in children, emphasizing the critical need for supportive environments that enhance brain connectivity and overall wellbeing.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prevalence and determinants of meeting minimum dietary diversity among children aged 6–23 months in three sub-Saharan African Countries: The Demographic and Health Surveys, 2019–2020

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Background: Dietary diversity is an indicator of nutritional adequacy, which plays a significant role in child growth and development. Lack of adequate nutrition is associated with suboptimal brain development, lower school performance, and increased risk of mortality and chronic diseases. We aimed to determine the prevalence and determinants of meeting minimum dietary diversity (MDD), defined as consuming at least five out of eight basic food groups in the previous 24-h in three sub-Saharan African countries.

Methods: A weighted population-based cross-sectional study was conducted using the most recent Demographic and Health Surveys (DHS). MDD data were available between 2019 and 2020 for three sub-Saharan African countries (Gambia, Liberia, and Rwanda). The study population included 5,832 children aged 6–23 months. A multivariable logistic regression model was developed to identify independent factors associated with meeting MDD.

Results: Overall, the weighted prevalence of children who met the MDD was 23.2% (95% CI: 21.7–24.8%), ranging from 8.6% in Liberia to 34.4% in Rwanda. Independent factors associated with meeting MDD were: age of the child (OR) = 1.96, 95% CI: 1.61, 2.39 for 12–17 months vs. 6–11 months], mothers from highest households' wealth status (OR = 1.86, 95% CI: 1.45–2.39) compared with the lowest**,** and mothers with secondary/higher education (OR = 1.69, 95% CI: 1.35–2.12) compared with those with no education. Mothers who were employed, had access to a radio, and those who visited a healthcare facility in the last 12 months were more likely to meet the MDD. There was no significant association between the child's sex and the odds of fulfilling the MDD.

Conclusions: There is substantial heterogeneity in the prevalence of MDD in these three sub-Saharan African countries. Lack of food availability or affordability may play a significant role in the low prevalence of MDD. The present analysis suggests that policies that will effectively increase the prevalence of meeting MDD should target poor households with appropriate materials or financial assistance and mothers with lower literacy. Public health interventions working with sectors such as education and radio stations to promote health education about the benefits of diverse diets is a critical step toward improving MDD in sub-Saharan Africa and preventing undernutrition.

KEYWORDS

sub-Saharan Africa, dietary diversity, children, nutrition, DHS

Introduction

Undernutrition has decreased globally but remains endemic in several regions such as southeastern Asia and sub-Saharan Africa (SSA) (1, 2). Between 2000 and 2020, the number of children affected by stunting under age 5 worldwide declined from 203.6 million to 149.2 million (3). However, during the same time, the numbers have increased at an alarming rate in SSA—from 22.8 million to 29.3 million (3). Child undernutrition is an important cause of preventable disease burden of public health significance affecting children, specifically those living in SSA (4). Lack of adequate nutrition is associated with inadequate brain development, lower school performance, increased risk of mortality, and chronic diseases (5). According to the United Nations Children's Fund (UNICEF), about 3.1 million children die from undernutrition each year (6). Globally, in 2020, approximately 45.4 million children under age 5 were wasted and 38.9 million were overweight (7). According to the WHO, the risk of a child dying before reaching 5 years of age in Africa is nearly 8 times higher than in Europe (76.5 per 1,000 live births vs. 9.6 per 1,000 live births) (8). Child dietary diversity has been shown to be positively associated with the mean micronutrient adequacy of the diet (9, 10). Therefore, the minimum dietary diversity (MDD) can be effective in assessing a population-level picture of infant and young child diet quality and appropriate complementary feeding practices in low resource settings such as SSA. Enhanced child feeding practices by providing adequately diversified food such as meeting MDD can result in improved energy and nutrient intake, which can lead to better nutritional status and children's overall health and well-being (11).

The MDD score is a population-level indicator developed by the World Health Organization (WHO) to assess diet diversity as part of infant and young child feeding (IYCF) practices among children 6–23 months old (12). The WHO has recommended that a child consumes the MDD of $\geq$ 5 of 8 pre-defined food groups during the previous 24-h to meet daily energy and essential nutrients requirements (13). Diversified diet assists children to have the proper nutrients needed to maintain optimal child growth and development during critical periods (14, 15). A diverse diet is more likely to meet both macro-and micronutrient needs for human health (16).

According to previous studies, sociodemographic-economic factors such as household wealth index (17–20), maternal age (20), maternal education (18, 20, 21) maternal employment status (20, 22, 23), contact with health care facility (21), place of residence (22, 24), and exposure to mass media such as radio (17, 18, 20) have been suggested to affect MDD among children aged 6–23 months in low-and middle-income countries (LMICs) including SSA. In addition, child factor such as age has also been associated with MDD in SSA (19, 20, 24). To improve the proportion of children fed with a diet meeting MDD in SSA, it is essential to fully understand regional and country-specific variations in the prevalence of MDD and associated factors. Such knowledge will assist in putting in place regional initiatives to prioritize intervention strategies for the most at-risk countries in SSA and assist stakeholders to adequately identifying potential contributing factors for the low prevalence of meeting MDD. However, these estimates are lacking because most previous studies that have examined the determinants of meeting MDD in SSA such as access to media, level of education, and wealth status were mainly limited to individual countries such as Ethiopia (17, 25, 26). Thus, we aimed to fill this critical gap in our knowledge by conducting a multi-country population-based cross-sectional study of the prevalence of meeting MDD in three combined SSA countries; and examining the associated socio-demographic-economic factors using the available and most recent Demographic and Health Surveys (DHS) data from 2019–2020.

Methods

Data source and participants

For the present cross-sectional study, we included all SSA countries that participated in the DHS most recent years (2019–2020) and collected data on MDD among children aged 6–23 months old. There was a total of three countries that had conducted DHS surveys in the years since 2019 and had asked mothers about the types of food their child had consumed during the day or night before the interview. These countries included Gambia, Liberia, and Rwanda. The mean response rate across surveys was 97.9% (range, 99–97.7%). This study followed the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE) reporting guideline (27). Each host country collected data in coordination with ICF International, a global consulting technology services company located in Rockville, MD (28). The DHS surveys are nationally representative household surveys supported by the US Agency for International Development (USAID) for over 30 years. The DHS surveys data included over 300 surveys conducted in more than 90 World Bank-defined LMICs worldwide.

The surveys used multistage cluster sampling and a stratified sampling design to collect detailed information such as sociodemographic characteristics, health behaviors, child's health and nutrition indicators, HIV and AIDS, and reproductive health (29, 30). The first stage involves dividing the country into geographic regions. Then within these regions, populations are stratified either by urban or rural areas. The primary sampling units (PSUs) were selected with a probability proportional to the size within each stratum. All households within the cluster were listed in the second stage of sampling, and approximately 25 households were randomly selected for an interview using equal probability systematic sampling.

The children's records or kid's records (KR) DHS datasets were used for the present study. According to the DHS guideline for assessing MDD among children (https://dhsprogram.com/data/Guide-to-DHS-Statistics/Minimum_Dietary_Diversity.htm), the present weighted analysis was limited to the last-born children aged 6–23 months who were living with their mothers and fed with an MDD during the day or night preceding the survey ($n = 5{,}832$).

Study variables

Outcome variables

The MDD is a population-level indicator designed by the WHO to assess diet diversity among children 6–23 months old. This indicator is one of the eight IYCF indicators developed by the WHO to provide simple, valid, and reliable metrics for determining IYCF practices (31). MDD data are collected from a questionnaire administrated to the child's mothers or caregivers as part of the IYCF module. Based on June 2017 expert consultation, the WHO updated the version of MDD-7 (7 food groups) to MDD-8 to reflect the inclusion of breast milk as an 8th food group. Therefore, the criterion for meeting MDD changed from 4 of 7 groups to 5 of 8 groups (32). The outcome of interest for the present study was the proportion of children's diets meeting MDD during the previous day. According to the most recent WHO (13) and DHS (33), we defined meeting MDD among children aged 6–23 months as at least 5 out of 8 food groups fed during the day or night preceding the survey. The components of the 8 food groups included: (1) breastmilk, (2) grains, roots, and tubers, (3) legumes and nuts, (4) dairy products (infant formula, milk, yogurt, cheese), (5) flesh foods (meat, fish, poultry, and liver/organ meats), (6) eggs, (7) vitamin A-rich fruits and vegetables, (8) other fruits and vegetables. The response options for each food group were 1 for "consumed" and 0 for not "consumed." A cumulative score was calculated by combining the scores of all the food groups. A binary outcome variable for meeting an MDD was created by assigning "1" for children who consumed $\geq$ 5 out of 8 food groups and "0" for those who consumed $<$5 food groups (18).

Explanatory variables

We selected country of residence, and child and maternal factors as potential determinants because they have been shown to be correlated with MDD (17, 18, 34). The child's factors included the child's age and sex. The maternal factors included age, antenatal care visits (ANC), household wealth index status, educational status, marital status, place of residence, employment status, household owning a radio, household owning a television, and if visited a healthcare facility in the last 12 months. Both child and maternal factors were collected through self-report questionnaires. Wealth index quintiles were determined using a principal component analysis approach of household assets (household ownership of several items such as television, car, radio, and other wealth-related characteristics). Detailed information on determining wealth index quintiles has been described elsewhere (35). The wealth index was recategorized from quintiles into three categories by combining the poorest and poorer into one category (called "lowest"); middle wealth level into the second category (called "middle"); and richer and richest into the third category (called "highest"), as done in previous studies (36–38). We also recategorized maternal age from a continuous scale into three groups for this study (15–29, 30–39, and 40–49 years old).

Statistical analysis

We performed statistical analyses using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Consistent with the DHS guideline for analyzing the DHS data and to ensure that the estimates were nationally representative, all analyses were conducted using appropriate survey weights, clustering, and stratification to account for the complex sampling design (39). Univariable analyses were performed using frequency distributions for categorical variables to describe the characteristics of the study participants. The prevalence of meeting MDD was calculated as the number of children who met the MDD divided by the total number of children in that category multiplied by 100%. Multivariable logistic regression models (proc surveylogistic; SAS institute) were used to examine each independent factor's association with meeting MDD. A stratified analysis was also conducted to examine the prevalence of each of the 8 nutrient-rich food groups described above by country. In addition, to better understand between-country differences, we also analyzed each demographic/social factor of MDD stratified by country. A Variance Inflation Factor (VIF) was performed to measure the degree of multicollinearity among independent variables, which did not indicate any substantial multicollinearity from the full adjusted model, with VIF values of 3 or less. Among our selected factors, 8 participants had missing data for ANC visits, 157 participants for access to a radio, and 157 participants for access to a TV. Considering that the proportion of missing data was very low (2.6%), a complete case analysis approach was adopted. To test the robustness of our results, we also conducted a sensitivity analysis using a multivariable binomial regression in which the outcome variable was the number of food groups (numerator) divided by eight (denominator). Descriptive statistics are presented as the weighted prevalence of meeting MDD, and the multivariable logistic regression results are presented as adjusted odds ratios (OR) with 95% confidence intervals (CIs). Statistical tests were reported as significant at p-values <0.05, and all p-values were 2-sided.

Ethical considerations

Each country's procedures and questionnaires for standard DHS surveys were reviewed and approved by the ICF International Institutional Review Board (IRB) and the IRBs of each host country. Before the survey, written or oral informed consent was obtained from each participant or proxy. Survey participants were not coerced into participation (40), and all data are completely de-identified with no names or household addresses in the data files. Thus, no further IRB approval was needed by the authors' institutions of the present manuscript. Details on the ethical matters are described in the DHS methodology, protecting the Privacy of DHS Survey Respondents (41).

Results

Sociodemographic characteristics of the participants

A total of 5,832 children aged 6–23 months from three SSA who live with their mothers were included in this analysis (Table 1). The mean age (SE) of the children was 14.2 (0.01) months. The majority of the children were between 6–11 months and were males (51.0%). More than one-half of these children's mothers were younger (15–29 years old) (54.5%), had four or more antenatal care visits than <4 (69.7%), and were mostly from the lowest household wealth index status (44.1%) than the middle and highest. In addition, more than one-half of mothers had access to a radio (51.0%), visited a healthcare facility in the last 12 months (82.5%), lived in rural areas (57.4%), and were employed (63.6%) (Table 2).

Prevalence of meeting MDD in these SSA countries

Overall, the weighted prevalence of children who met the MDD was 23.2% (95% CI: 21.7%-24.8%), ranging from 8.6% in Liberia to 34.4% in Rwanda (Table 1). The prevalence of meeting MDD among children fed during the day or night preceding the survey was higher among older children aged 12–17 months (26.7%) and 18–23 months (27.2%) compared to aged 6–11 months (16.5%) and males (23.6%) compared to female (22.9%). In addition, maternal factors such as older (40–49 years old) age (26.7%), higher wealth status (31.8%), secondary/higher education (28.7%), employment, access to a radio, and visited healthcare facility in the past 12 months had the highest prevalence of meeting MDD (Table 2).

Country-stratified analysis (Supplementary Table 1) indicated that the prevalence of meeting MDD also varied widely between countries in relation to different maternal factors such as ANC visits, household wealth status, education level, marital status, employment status, access to a radio, and visited healthcare facility in the last 12 months. For all countries, children whose mothers had four or more ANC visits, had the highest household wealth status, were married/living with a partner, were currently employed, had access to a radio, and visited a healthcare facility in the last 12 months had the highest prevalence of meeting MDD consistently. Liberia and Gambia had the highest prevalence of meeting MDD among mothers with secondary/higher education regarding the educational level. For Rwanda, mothers with primary education had the highest prevalence of fulfilling the MDD. For all countries, children aged 12–17 months consistently had the highest prevalence of meeting MDD.

TABLE 1 Background characteristics of the weighted survey participants, the prevalence of meeting minimum dietary diversity by country and survey year ($N = 5{,}832$).

			All participants	Minimum dietary diversity
Countries	**Survey year**	**Response rate (%)**	N^a ($\%^b$)	N^c (%)
Overall			5,832	1,356 (23.3)
Liberia	2019–2020	99	1,360 (23.3)	117 (8.6)
Gambia	2019–2020	97	2,109 (36.2)	425 (20.2)
Rwanda	2019–2020	97.7	2,363 (40.5)	814 (34.4)

N^a, Weighted sample size of the combined dataset that is represented by that survey for each country.
$\%^b$, The % of the combined dataset represented by that survey.
N^c, Prevalence of minimum dietary diversity.

Figure 1 shows the prevalence of each of the 8 nutrient-rich food groups included in the MDD stratified by country. There was disparity regarding the 8 nutrients-rich food groups across countries. Rwanda had the highest prevalence of breastmilk, legumes/nuts, and vitamin A-rich fruits/vegetable consumption. Interestingly, the prevalence of receiving protein sources (eggs), dairy products, and other fruits/vegetables was lower in all countries than breastmilk, legumes/nuts, flesh foods, grain/roots/tubes, and vitamin A-rich fruits/vegetables that contribute to low MDD. In addition, eggs were the least food group consumed in all countries. Breastmilk consumption and grains/roots/tubes were consistently higher in all countries than in other food groups (Figure 1).

Factors associated with meeting MDD

The babies aged 12–17 months were almost 2 times more likely to meet MDD (OR = 1.96; 95% CI: 1.61, 2.39, $p < 0.001$) and aged 18–23 months (OR = 1.92; 95% CI: 1.58, 2.33, $p < 0.001$) when compared to those aged 6–11 months (Table 2). The respondents from the households whose wealth index were middle (OR = 1.45; 95% CI: 1.16, 1.81, $p = 0.001$) and highest (OR = 1.86; 95% CI: 1.45, 2.39, $p < 0.001$) had greater odds to meet MDD than those from the lowest (Table 2). The babies whose mothers had secondary/higher were almost 2 times more likely to meet MDD (OR = 1.69; 95% CI: 1.35, 2.12, $p < 0.001$) compared to those with no formal education (Table 2). Furthermore, the babies whose mothers had employment had higher likelihood to achieve MDD (OR = 1.20; 95% CI: 1.01, 1.44, $p = 0.04$) than those from mothers who had no employment (Table 2). The babies whose mothers had a radio in the households had higher odds to meet MDD (OR = 1.30; 95% CI: 1.09, 1.56, $p = 0.004$) than those who did not have a radio (Table 2). Lastly, children whose mothers visited a healthcare facility in the last 12 months were almost 2 times more likely to meet MDD (OR = 1.57; 95% CI: 1.27, 1.92, $p < 0.001$) (Table 2). Interestingly, we did not observe a significant association between the child's sex and the odds of fulfilling the MDD. These results remained consistent in the sensitivity analysis using multivariable binomial regression.

Discussion

The purpose of this study was to conduct a population-based cross-sectional study to determine the prevalence of meeting MDD in three combined SSA countries and the associated socio-demographic-economic factors. Our pooled results showed that the mean of the weighted prevalence of children 6–23 months who met the MDD was low (23%) in these three SSA countries and exhibited substantial between-country variation. The low prevalence of meeting MDD among children in these low-resource countries is concerning and has the potential to increase the risk of mortality and chronic diseases in the future. Disparities due to wealth are significant, and children's diets are more likely to meet MDD in wealthier households. More importantly, children whose mothers had more education, were employed, had access to a radio, and visited healthcare facilities in the last 12 months were more likely to meet the MDD. The child's age was also significantly associated with meeting MDD. We found a similar non-significant trend for access to a TV, which could be due to a smaller proportion of households owning a TV. Conversely, we did not observe any significant associations between a child's sex and the odds of meeting MDD. This study showed disparity regarding the 8 nutrients-rich food groups across these three SSA countries. Protein sources such as eggs were the least food group consumed in all countries.

The observed low prevalence of meeting MDD in this study is consistent with a previous study conducted in Ethiopia (17). Lack of food availability or affordability may play a significant role in the low prevalence of meeting MDD observed in this study. Our finding agrees with previous studies that also indicated a significant positive association between a child's age and meeting MDD (18, 42, 43). A potential explanation for

TABLE 2 Background characteristics of the weighted survey participants, the prevalence of meeting minimum dietary diversity, and the multivariable-adjusted odds ratio ($N = 5,832$).

	All participants	Minimum dietary diversity	Multivariable-adjusted analysis	
Characteristics	N^a ($\%^b$)	N^c (%)	(OR) (95% CI)	*p*-value
Child characteristics				
Age of child				
6–11 months	2,070 (35.5)	342 (16.5)	ref.	
12–17 months	2,020 (34.6)	539 (26.7)	1.96 (1.61, 2.39)	<0.001
18–23 months	1,742 (30.0)	474 (27.2)	1.92 (1.58, 2.33)	<0.001
Sex of child				
Male	2,958 (50.7)	697 (23.6)	ref.	
Female	2,874 (49.3)	658 (22.9)	0.97 (0.83, 1.15)	0.75
Maternal factors				
Age groups				
15–29	3,176 (54.5)	675 (21.3)	ref.	
30–39	2,173 (37.3)	551 (25.4)	1.05 (0.88, 1.25)	0.57
40–49	483 (8.3)	129 (26.7)	1.16 (0.87, 1.55)	0.32
ANC visits				
<4	1,768 (30.4)	491 (27.8)	ref.	
≥4	4,059 (69.7)	864 (21.3)	0.97 (0.81, 1.17)	0.78
Wealth index status				
Lowest	2,572 (44.1)	412 (16.0)	ref.	
Middle	1,177 (20.2)	281 (23.9)	1.45 (1.16, 1.81)	0.001
Highest	2,083 (35.7)	662 (31.8)	1.86 (1.45, 2.39)	<0.001
Place of residence				
Urban	2,486 (42.6)	576 (23.2)	ref.	
Rural	3,346 (57.4)	779 (23.3)	0.90 (0.71, 1.14)	0.37
Maternal education				
No education	1,617 (27.7)	230 (14.2)	ref.	
Primary	2,294 (39.3)	573 (25.0)	1.14 (0.91, 1.43)	0.24
Secondary/Higher	1,921 (32.9)	552 (28.7)	1.69 (1.35, 2.12)	<0.001
Marital status				
Never married	700 (12.0)	131 (18.7)	ref.	
Married/Living with partner	4,848 (83.1)	1,161 (23.9)	1.09 (0.81, 1.47)	0.55
Widowed/Divorced/Separated	284 (4.9)	63 (22.2)	1.13 (0.71, 1.78)	0.61
Maternal employment				
No	2,125 (36.5)	423 (19.9)	ref.	
Yes	3,707 (63.6)	932 (25.1)	1.20 (1.01, 1.44)	0.04
Household has radio				
No	2,790 (49.1)	560 (20.1)	ref.	
Yes	2,887 (50.9)	765 (26.5)	1.30 (1.09, 1.56)	0.004
Household has television				
No	3,887 (68.5)	851 (21.9)	ref.	
Yes	1,791 (31.5)	474 (26.5)	1.00 (0.78, 1.29)	0.99
Visited healthcare facility last 12 months				
No	1,020 (17.5)	169 (16.6)	ref.	
Yes	4,812 (82.5)	1,186 (24.6)	1.57 (1.27, 1.92)	<0.001

ANC, Antenatal care.
N^a, Weighted sample size of the combined dataset.
$\%^b$, The % of the combined dataset.
N^c, Prevalence of meeting minimum dietary diversity.
Ref, reference.
Model fully adjusted for country of residence, age of the child (categorical), sex of child (male/female), age of mother (categorical), antenatal care visits (< 4/≥ 4), education status (categorical), marital status (categorical), wealth index status (categorical), place of residence (urban/rural), employment status (yes/no), household having a radio (yes/no), household having a television (yes/no), visited health care facility in the last 12 months (yes/no).

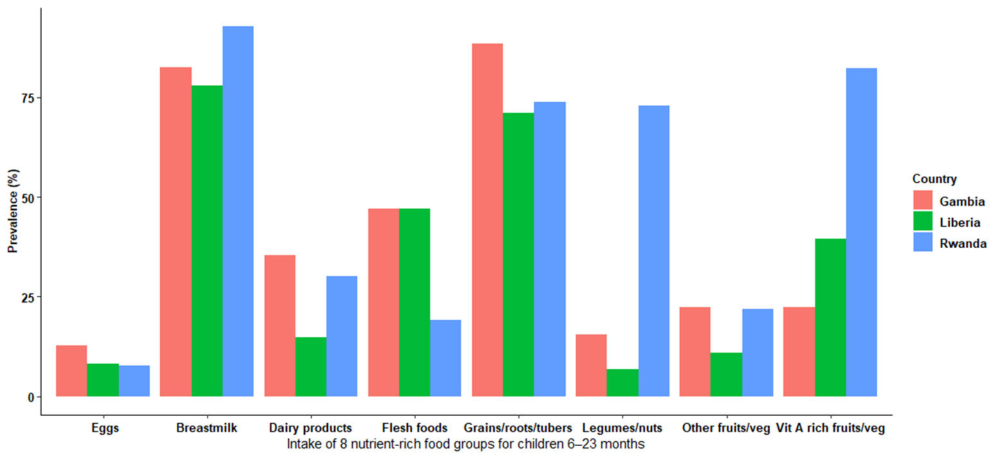

FIGURE 1
Weighted prevalence of intake of 8 nutrient-rich food groups for children 6–23 months.

this association could be due to older children's willingness to accept diverse foods with different tastes and textures and their familiarity with foods than younger children (18, 44). The positive association between wealthier households and meeting MDD observed in this study is consistent with the findings from previous studies conducted in Ethiopia (17) and Indonesia (18). Consistent with earlier studies from other LMICs (18–20, 42), we found that mothers with higher educational levels were more likely to feed their children with more diversified foods. Socioeconomic inequalities represent a major threat to optimal feeding practices (45). It postulated that poorer households' factors and lack of maternal education regarding an adequate diet for young children could drive these disparities in complementary feeding practices. Therefore, closing the gap in dietary inequalities between countries is critical to preventing long-term socioeconomic and health inequalities. Highly educated mothers might have access to more resources that promote the benefits of a diversified diet and a better understanding of nutritional health education messages (18). This study also found that respondents who had exposure to mass media (radio) had greater odds of achieving MDD. The media such as national radio stations are usually considered to be a reliable source of health and nutrition-related information in low-resource countries, thus its messages are more likely to be embraced (20, 46). This is a similar finding to a study conducted in Ethiopia (17). Additionally, our finding of a significant association between maternal employment and meeting MDD is consistent with previous studies (20–22). Lastly, our observed positive association between mothers who visited a healthcare facility in the last 12 months and the odds of meeting MDD is also consistent with a previous study conducted in Nigeria (21).

Public health recommendations

The Sustainable Development Goals, part of the call for action toward appropriate diets for children, aim to address goals 2 (zero hunger) and 3 (good health and well-being) (47). Implementing policies and programs to reduce wealth-related inequalities is essential for optimal child nutrition. Recent estimates suggest that more than 11 million cases of stunting could have been averted if the proportion of children's diets meeting MDD was 90% (48). However, in the present study from these three SSA countries, the rates of meeting MDD did not reach the threshold of 50%. Previous studies have observed the critical role of dietary diversity in impacting the relationship with child anthropometry (49, 50).

MDD is a simple yet valid and reliable population-level indicator of IYCF practices and is critical for assessing national and subnational comparisons, and is relevant for identifying populations at risk and targeting interventions. Our current analysis suggests that policies that will effectively increase the prevalence of meeting MDD should target poor households with appropriate materials or financial assistance and mothers with lower literacy. In a recent pooled analysis of 80 low- and middle-income countries, dietary diversity was higher when absolute household income exceeded ∼US$20,000 (51). Additionally, public health interventions working with other sectors such as education and radio stations to promote health education about the benefits of diverse diets (18), especially among teenage girls, are critically needed. Targeting teenage girls with nutrition-related interventions before becoming pregnant may significantly increase the prevalence of meeting MDD. More importantly, providing financial assistance to poorer households or the availability of food pantries may also play an essential role in ensuring each child consumes adequately diverse foods to meet their nutritional requirements (34).

Study strengths and limitations

The strength of this study is the analysis of a nationally representative sample of children aged 6–23 months from three SSA countries using 2019–2020 DHS data. To the best of our knowledge, this is one of the few comprehensive studies to investigate the prevalence and determinants of meeting MDD using the most recent DHS data across multiple SSA countries with high response rates. In addition, we used the most updated MDD indicator with eight food groups, which is a valid and reliable metric for assessing IYCF feeding practices at the population level developed by the WHO (9).

Notwithstanding, the present study has a few limitations that are worth mentioning. First, the cross-sectional nature of the survey does not allow for determining causality. Secondly, almost all low-income countries are found in SSA. Most recent MDD data was limited to only three of the 48 countries in SSA, and thus, our findings may lack external validity for other SSA low-income countries. Moreover, MDD was based on maternal recall, which may be subject to recall bias and social desirability (18, 25). Additionally, this study did not adjust for total energy due to a lack of data on calorie consumption from the DHS database. Lastly, a single 24-diet recall is not considered to be representative of habitual diet at an individual level. Because it doesn't account for day-to-day variation.

Conclusions

In this study using three SSA countries, few children were fed a diet that met MDD on the day of recall. Interestingly, the prevalence of eggs, dairy products, and other fruits/vegetables being consumed remained very low in all countries. Maternal education, household wealth status, employment status, access to a radio, visited healthcare facilities in the last 12 months, and age of the child was the significant determinant of meeting the WHO recommended feeding practice indicator of MDD among the youngest children in these three SSA countries. We did not observe a significant association between the child's sex and the odds of fulfilling the MDD. The findings highlighted the need to target mothers, especially those with low education and lower household wealth status, through health education about the importance of adequately diversified foods and financial assistance to ensure optimal child growth in these low-resource countries and prevent undernutrition.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://dhsprogram.com/data/.

Author contributions

Designed research (project conception, development of overall research plan, and study oversight) and analyzed data, or performed statistical analysis: DB. Wrote the first draft of the manuscript: DB and PS. All authors reviewed and commented on subsequent drafts of the manuscript and have read and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.846049/full#supplementary-material

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Emotional impact on children during home confinement in Spain

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Introduction: The COVID-19 pandemic has brought about important changes. On March 14, 2020, a strict home confinement was decreed in Spain. Children did not attend school and were not allowed to leave their homes. The aim of this study was to determine the emotional state of these children, as well as associated factors.

Material and methods: A cross-sectional descriptive study was conducted using an online questionnaire sent by cell phone. This survey includes sociodemographic items and questions concerning the emotional impact of the lockdown. With the questions on emotions, two categories of emotional state were established with the variables fear, irritability, sadness and somatization: those who were less or more emotionally affected. A multivariate logistic model was used to estimate the associations between the variables.

Results: A total of 3,890 responses were obtained. The mean age of the children was 6.78 years (range 0 to 16). A score indicating poor emotional state was reported by 40.12%. The multivariate logistic model for poor emotional state was directly associated with having less appetite, sleep disturbances, and with parents' beliefs that their child will have difficulties returning to normal life after lockdown. A better emotional state was associated with being an only child, access to outdoor spaces at home, having pets, and parents informing their children about the pandemic using creative explanations.

Conclusions: During strict home confinement, a considerable emotional impact was observed in children as described by their parents. Specific elements were associated with a better or poorer emotional state.

KEYWORDS

confinement, COVID-19, emotional impact, sadness, irritability, children

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first reported in Wuhan, China, in December 2019, had a tremendous impact initially in China and subsequently throughout the world. While most patients infected with SARS-CoV-2 had mild illness, about 5% of patients experienced severe lung injury or multi-organ dysfunction, resulting in a 1–4% case fatality rate (1).

Restrictive measures in the general population were necessary to reduce the rate of virus transmission. Quarantines and pandemic disasters have demonstrated negative psychological effects, including confusion, anger, and post-traumatic distress (2, 3).

During the first outbreak in Europe in March 2020, a strict lockdown took place in Spain with the population confined to their homes. Only essential work was permitted, and the population was allowed to leave their homes only for basic activities. In Spain, this strict lockdown was declared as of March 13, 2020. In addition to schools being closed, children were not allowed to leave their homes under any circumstances (except to go to the doctor or to accompany their parents for essential activities if they would have been left at home alone). As of April 26, children were allowed to leave their homes for a reduced period of time. Prior to COVID-19, a review in The Lancet on quarantines revealed their broad and potentially long-lasting negative psychological consequences (3). Another general population study compared mental health during the pandemic period and in the same time period 3 years prior. A clear psychological deterioration was found, with an increase in depression that was more pronounced in young adults (4).

Confinements have produced an emotional impact on the entire population (5) and children (6). The effects of the lockdown on emotional well-being have been perceived as negative (3, 7), with increased stress, anger, fear, and confusion (8). In children, it has also been shown that the COVID-19 pandemic has had a significant psychological impact (9). Children are frightened, nervous, sad, bored, and angry but also feel safe, calm, and happy to be with their families (10). Nonetheless, these negative feelings have been more prevalent and can affect the entire family (11). In adolescents, this has been associated with depression and anxiety (12).

During the confinement, daily routines have been altered, such as sleep habits (13, 14). These changes may have long-term emotional effects (15). Other habits, such as eating patterns, have also undergone changes in this period (16). In addition, activities that help improve the emotional health of young people, such as exercise (17), physiotherapy, relaxation, and academic performance, were restricted (18).

The emotional impact depends on many biological and sociodemographic factors that must be taken into account (19). The degree to which parents are affected also influences their children (20, 21). These effects on the family and children, as well as their needs during the first outbreak, were not taken into consideration (22, 23).

Studies on emotional health in children during the COVID-19 pandemic have been conducted mainly in the Chinese population (24). There are many methodological limitations in the studies carried out, such as small sample sizes or being performed after the period of confinement with the resulting recall bias, among other limitations (12).

The studies in children during this period of confinement are highly relevant because of the great emotional impact described and because they enable us to determine the sociodemographic characteristics of the children at greatest risk. In addition, there are variables that may involve a greater emotional impact on children, such as the direct or indirect consequences of COVID in the family (23), the presence of some type of disability (24) or having parents who are essential workers during the pandemic (25). On the other hand, variables such as having pets (26) or having outdoor access at home can be protective (17). This information is important in order to be able to implement measures to limit the effects of future confinement on the emotional health of children.

The aim of this study was to assess the degree of emotional impact on children as perceived by their parents during the strict lockdown and to identify the factors associated with emotional state.

We analyzed the most common sociodemographic variables, paying special attention to housing conditions (due to the situation of confinement) and examined several dimensions that may be associated with emotional state, such as communication with the children, parental perception of after effects, the effect on illnesses or the physical repercussions on the children.

Materials and methods

Participants

A cross-sectional descriptive study was carried out through a questionnaire that was sent by instant messaging via cell phone to parents for completion. There was no sample selection. The inclusion criteria were residing in Spain and agreeing to complete the questionnaire. The questionnaire was available from April 22, 2020 to April 26, 2020. A total of 3,890 questionnaires were collected during the study period.

A panel of local experts met to construct a specific questionnaire to study the effect of the pandemic on children. Given the exceptional nature of the situation, with strict confinement, the previously validated questionnaires were considered unsuitable. To construct the questionnaire and select the possible variables related to emotional states, previous questionnaires that assess fear, anxiety and sadness were consulted, such as the KIDSCREEN (27, 28), the Liebowitz social anxiety scale (29), the Spielberger State-Trait Anxiety Inventory (STAI) (30, 31) or the Emotional Eating Scale Adapted for Children and Adolescents (EES-C) (32). Given the relationship of this emotional situation with somatization (3, 33) it was also included as an emotional variable. The presence of somatization signs was also included in the measurements due to its relationship with the emotional state.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Variables

The first part includes the following variables: Age (years), Sex (boy/girl), Autonomous community (Spanish province), Do you have other children at home? (yes/no), Number of children at home (number), Number of adults at home (number), Location of home (no answer/urban/rural), Size of home (no answer/less 60 m^2/60–120 m^2/more 120 m^2), Outdoor space at home (no answer/yes/no), Average academic grade (no answer/excellence/very good/satisfactory/unsatisfactory), Educational support (yes/no), Parents are health sector workers (yes/no), Parents are law enforcement workers (yes/no), Parents are other essential workers (yes/no), Have had Covid-19 (yes/no), Pets in the home (yes/no), and Underlying disease (yes/no).

Questionnaire

The questionnaire for families, developed by a local group of experts, was divided into 5 dimensions with several questions in each:

Communication: Do you feel that you have given your child age-appropriate information (in words he/she can understand) about what is happening? (yes/no/I am not sure), To what extent have you given information to your child? (honest including negative aspects/honest avoiding negative aspects/no information), How have you approached the information given to your child? (realistic information/information by embellishing or misrepresenting the negative aspects/creative information/no information).

Normality during and after the pandemic: Do you feel that your child has accepted and adapted to the current situation? (yes/no/I am not sure), Do you think your child might have trouble returning to "normal" daily activities? (yes/no/I am not sure).

Control of disease: Only answer this question if your child has a medical condition. How do you think the confinement has affected the condition? (negative/positive/no changes), During this period, did you need to consult a medical professional because you were concerned about any aspect of your child's health? (yes/no).

Non-emotional involvement: Do you feel that your child is having trouble falling asleep or is sleeping worse than usual? (yes/no/I am not sure), Do you think there have been changes in your child's appetite? (yes/no/I am not sure), Regarding nutrition, do you feel that there have been changes in the quality of the diet during this period? (improved/worse/no changes/I am not sure), With regard to the time spent in front of screens (video consoles, television, electronic tablets, cell phones, etc.), indicate the average time spent daily by your child (in relation to the current situation) (1/1–2/2–3/3–4/more than 4 h/does not use).

Emotional involvement: Do you think your child has ever felt sad (in relation to the current situation)? (yes/no/I am not sure), Do you think your child has ever felt afraid (in relation to the current situation)? (yes/no/I am not sure), Do you think your child is more irritable? Example: more temper tantrums, less obedient, more sensitive (yes/no/I am not sure), During the confinement period, has your child had symptoms such as headache, abdominal pain, musculoskeletal pain, tiredness, etc. for no apparent reason and without this type of pain being usual previously? (somatization) (yes/no/I am not sure).

As a response variable, the dimension of emotional state was constructed from 4 items (sadness, fear, irritability and somatization) in the following way: A value of 1 is given to the response "yes" and 0 to the response "no" in each of the items. The total score for the response variable is the sum of all the items, ranging between 0 and 4, with 4 being the worst emotional state. It was grouped as scores of 3–4 vs. 0–2.

Statistical analysis

A descriptive analysis of all the variables was performed by calculating frequencies for qualitative variables and minimum, maximum, mean, and standard deviation for quantitative variables. The factors associated with emotional state and type of information given to the child were analyzed using contingency tables applying the chi-squared test for qualitative variables and comparison of the mean values for quantitative variables using Student's *t*-test.

To estimate the magnitude of the associations with poor emotional state, multivariate logistic models were fitted. The total sample without missing data in the variables (n = 1,501) was randomly split into a training sample and a test sample at a ratio of 2/3 and 1/3. The model was adjusted in the training sample to arrive at an optimal model, applying the Homer-Lemeshow calibration test. Odds ratios (OR) were estimated,

TABLE 1 Values of the variables analyzed in the total sample (abbreviated table).

Variable	N (%); mean ± SD
Mean age of children (years)	6.78 (3.24)
Sex (Male)	772 (51.4)
Only child	338 (22.5)
Mean number of children in the family	1.93 (0.78)
Mean number of adults	2.03 (0.48)
Urban housing	3,108 (85.6)
Living area > 120 m^2	1,061 (29.2)
Home with garden	1,732 (47.7)
Pets	1,152 (39.9)
Chronic illness	422 (10.8)
Sleep (worse)	1,689 (44.7)
Good emotional state (0–2)	1,349 (59.9)

N = 1,501.
*Table of the complete description of all the variables analyzed in Supplementary materials 1, 2.

together with their 95% confidence intervals. A stepwise variable selection procedure based on the Akaike information criterion was performed. A validation process was conducted on the test sample, calculating the area under the ROC curve and its 95% confidence interval, Alpha level 0.05. All analyses were performed using R version 4.0.2.

Results

The general characteristics of the sample are shown in Table 1. Women made up 48.6% of the sample, with a mean age of 6.78 years. Most of the respondents were preschool-age (36.3%) and school-age children (51.3%). The sample was primarily urban (77.7%) but almost half of the sample owned a house with a garden. Concerning the emotional state of the children, 44.9% were afraid, 67.5% sad, 64.2% irritable, and 29.6% experienced somatization of an illness. According to the constructed variable "emotional state," in 33.8% this was poor (presence of 3 or 4 variables) (abbreviated Table 1 and complete tables in Supplementary materials 1, 2).

Certain variables were significantly associated ($p < 0.05$) with a poorer emotional state, such as not being an only child, having sleep disturbances, not having a terrace or garden, parents believing that they will have problems returning to normal life after the pandemic, and giving honest information about the situation were significantly related to a worse emotional state. These variables are shown in Table 2 (abbreviated Table 2 and complete tables in Supplementary materials 3, 4).

The multivariate logistic model performed to explain poor emotional state is shown in Table 3. Receiving information through creative explanations (OR 0.22, CI 0.073–0.70), having a home with a garden (OR 0.578, CI 0.35–1.00), being an only child (OR 0.68, CI 0.45–0.98), children not asking about the pandemic situation (OR 0.34, CI 0.24–0.48) or not having sleep disturbances (OR 0.41, CI 0.30–0.57) are elements that were associated with a better emotional state In contrast, not having pets (OR 1.44, CI 1.04–1.97), having less appetite (OR 2.30, CI 1.45–3.65), or parents who believe that life will not return to normal after the pandemic (OR 2.72 CI 1.79–4.15) were associated with a poor emotional state.

The model has an area under the ROC curve in the test sample of 0.812 (95% CI: 0.773–0.850), good calibration (Homer-Lemeshow test: p-value 0.713), and a success rate in the test sample of 75.4% (95% CI: 0.773–0.850) (Table 3).

Discussion

The results of this study reveal the considerable emotional impact on children during the lockdown, identifying factors associated with a poor emotional state. Giving children information using creative explanations, living in a home with a garden, being an only child, and having pets were factors associated with less emotional distress. Conversely, having less appetite, disturbed sleep, or a parent who believes that the situation will not return to normal after confinement were associated with a greater impact on the emotional state of the child.

The period of strict home confinement of children in Spain in the spring of 2020 was one of the longest experienced. Children were unable to leave their homes for 6 weeks.

We sought to quantify this impact by means of a questionnaire for parents, in which they assessed the emotional situation of their child as well as providing various medical and sociodemographic variables. The start date of the survey was just 4 days before the end of the lockdown (following 38 days without leaving the home and up to the time when the lockdown officially ended).

Emotional experience was subjectively assessed by the parents through the items concerning their child's perception of sadness, fear, irritability, and physical symptoms. These values were answered dichotomously (Yes or No). With these data, we defined the emotional state as "good" (score 0–2) or "poor" (score 3–4). The findings indicate that confinement had an important effect, with 40.1% having a poor emotional state, with feelings of sadness and irritability experienced by approximately two-thirds of the children. These data are data are consistent with the existing literature (8, 9), with no gender differences found.

The emotional impact of the COVID-19 lockdown has also been described in children, and in all cases the effects are similar to our results (10, 11, 21, 25, 26). These effects have also been studied in adolescents and adults (7) as well as in parents (20).

TABLE 2 Summarized bivariate analysis of the variables analyzed with respect to emotional state (good 0–2 negative emotions or bad 3–4 negative emotions, including sadness, fear, irritability, and physical symptoms)**.

		0–2 negative emotions		3–4 negative emotions		
		n	%	*n*	%	*p*-value
Information adapted to the age of the children	I have tried to be honest with them	931	65.2%	496	34.8%	<0.001
	I have preferred not to give information	63	85.1%	11	14.9%	
Situation will normalize after the pandemic	Yes	922	72.3%	354	27.7%	<0.001
	No	72	32.0%	153	68.0%	
Only child	No	719	64.0%	405	36.0%	0.001
	Yes	275	72.9%	102	27.1%	
Type of information given to the children	Realistic information	695	65.2%	371	34.8%	<0.001
	Information misrepresenting the negative aspects	172	60.6%	112	39.4%	
	Creative explanations	62	83.8%	12	16.2%	
	No information	65	84.4%	12	15.6%	
Information adapted to the age of the children	Yes	931	65.2%	496	34.8%	<0.001
	No	63	85.1%	11	14.9%	
Sleep disturbances	Yes	284	47.9%	309	52.1%	<0.001
	No	710	78.2%	198	21.8%	
Return to activity after pandemic	Yes	261	51.3%	248	48.7%	<0.001
	No	733	73.9%	259	26.1%	
Outdoor access at home (garden or terrace)	Yes	501	71.9%	196	28.1%	<0.001
	No	405	60.7%	262	39.3%	

N = 1,501.
**Table of the complete bivariate analysis of all variables analyzed in Supplementary materials 3, 4.

Most of these studies show a negative emotional impact that is greater in the younger population (5) and relatively smaller at older ages.

Multivariate analysis indicated that having siblings in the home increased emotional risk during the pandemic and could be explained by greater parental stress and household turmoil (21). Decreased appetite and sleep disturbances were also associated with a poor emotional state (13, 14, 27). Both of these elements are known to affect emotional well-being (28).

Similarly, parents' beliefs that their child may not be able to return to normal life after the pandemic could be associated with greater emotional distress, since it is the parents themselves who value their children emotionally and are aware of the difficulties they may have readapting to normal life after the lockdown.

By contrast, the existence of a garden at home was linked to a better emotional state in children in that they can "leave" the house to take a walk or to be in the sun, both elements traditionally associated with happiness, as well as increased access to physical exercise (18). In addition, having a garden was associated with another key element for the protection of mental health, namely, having greater economic resources (19). It is of note that the size of the house showed no significant association.

The connection observed between children having a good emotional state and parents providing creative explanations

TABLE 3 Multivariate logistic model for poor emotional state (presence of 3–4 negative items).

		Betha	OR*	CI 95%	*p*-value
Type of information given to the child	Realistic information	0	1		
	Information misrepresenting the negative aspects	0.05372	1.055	(0.712–1.565)	0.789
	Creative explanations	−1.48621	0.226	(0.073–0.700)	0.009
	No information	−0.58049	0.560	(0.227–1.378)	0.206
Appetite	Has more	0	1		
	No change	−0.30185	0.739	(0.510–1.072)	0.111
	Has less	0.83570	2.306	(1.454–3.658)	0.001
Home with garden	No answer	0	1		
	Yes	−0.54739	0.578	(0.335–1.000)	0.049
	No	−0.10606	0.899	(0.525–1.542)	0.699
Sleep disturbance	No	−0.88301	0.414	(0.300–0.570)	<0.001
Parent believes situation will not normalize	No	1.00382	2.729	(1.791–4.157)	<0.001
Only child	Yes	−0.40418	0.668	(0.453–0.983)	0.040
Pets in the home	No	0.36440	1.440	(1.047–1.979)	0.024
Children ask about what is happening	No	−1.06831	0.344	(0.243–0.485)	<0.001
Return to activity	No	−0.43769	0.646	(0.464–0.898)	0.009
Age		0.04036	1.041	(0.986–1.100)	0.148
Sex (Female)		0.16531	1.180	(0.867–1.605)	0.292

Training sample $n = 1,000$; test sample $n = 501$; number of children with a poor emotional state (3–4 items) in the training sample = 347; area under the ROC curve in the test sample = 0.812 (95% CI 0.773–0.850). Homer-Lemeshow p-value = 0.713; accuracy rate in the test sample = 75.4%. Nagelkerke's $R^2 = 0.339$. Likelihood ratio chi-squared test = 281.8 ($p < 0.001$).
*Model adjusted for control of disease.

about the coronavirus could be could be due to the age of these children. Younger children would normally be given imaginative stories, while older children are given factual information and would be more affected. This coincides with studies demonstrating a greater impact on older children. In our study, the mean age of the children who did not receive information was 2.26 years and those who did receive information was 6.76 years, with a significant difference ($p < 0.001$). Finally, having pets in the home was associated with a good emotional state. Research postulates that animals provide greater social competence (29), which would be helpful to children in this context. In our paper, the physical activity is not studied. It is interesting that in other studies this physical activity (34) does not affect the emotional state (30). On the other hand, Cognitive-Behavioral Therapy in adolescents with low academic performance decreased their stress (31).

Recognizing that confinement can have a detrimental effect on mental health, especially in certain conditions such as the ones described above, provides incentives for measures to limit this effect, such as increased communication with parents, information about the disease with age-appropriate information and, of course, early access to mental health services (32). Public health authorities must take into consideration these emotional effects, not prolonging the confinement or quarantine for longer than necessary (3).

Further research in this area can help to better understand the factors associated with home confinement and the degree of emotional impact on children, which can be instrumental in identifying those at higher risk and to implement interventions to enhance emotional well-being in this more vulnerable group and even to introduce preventive measures for potential future home confinements, as proposed by the Chinese government (30). We believe it is of great interest to examine the consequences of the recent lockdown through follow-up of the child population during the post-pandemic period in the long term.

As potential limitations of the study, it should be mentioned that since this was an online questionnaire and there was no statistical sampling, the sample may not accurately represent the general pediatric population due to possible selection bias, although the large sample size may reflect a wide variability in the population. Moreover, the cross-sectional design prevents establishing causal relationships. Another limitation is that the scales used have not been validated in the pediatric population. The authors did not believe that in the situation of strict pandemic confinement, the anxiety, depression or irritability scales were appropriate, since they were validated in a context other than strict pediatric confinement. The questionnaire was developed by an *ad hoc* panel of experts. Based on information from other studies (33, 35–41), and the opinion of the expert panel, the different dimensions were constructed to obtain a questionnaire that would meet the objective of our study in this particular context. Thus, the "emotional state" scale was created from the emotions reported by the parents to each of the questions in a dichotomous manner, which allows for simplicity in the responses of the parents since the survey was online, but it can be a limitation because it does not collect response gradient as a Likert scale does. And so, the yes/no dichotomy can lead to a loss of information.

As strengths, we highlight the large sample size and that the data collection was carried out at the very end of the lockdown, which limits recall bias and focuses responses on the real experiences of the families during the lockdown.

Conclusions

During home confinement in Spain, an elevated percentage of children experienced important emotional effects as perceived by their parents. The factors associated with greater or lesser emotional impact on children during strict home confinement that should be taken into account to reduce these negative effects in future confinements are described.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the San Juan de Alicante University Hospital Ethics Committee. Verbal consent was obtained from the participants legal guardian/next of kin. Written informed consent from the participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

EC-G, JQ, CG-M, AN-R, FS, and EC-C: conception and design of the study, data collection, analysis, interpretation, drafting and critical revision of the manuscript, with important intellectual contributions, and approval of the final draft for publication. All authors having revised and discussed the manuscript, take responsibility, and serve as guarantors for the accuracy and integrity of the report.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.969922/full#supplementary-material

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Associations between life-course household wealth mobility and adolescent physical growth, cognitive development and emotional and behavioral problems: A birth cohort in rural western China

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Background: Parental household wealth has been shown to be associated with offspring health conditions, while inconsistent associations were reported among generally healthy population especially in low- and middle- income countries (LMICs). Whether the household wealth upward mobility in LMICs would confer benefits to child health remains unknown.

Methods: We conducted a prospective birth cohort of children born to mothers who participated in a randomized trial of antenatal micronutrient supplementation in rural western China. Household wealth were repeatedly assessed at pregnancy, mid-childhood and early adolescence using principal component analysis for household assets and dwelling characteristics. We used conditional gains and group-based trajectory modeling to assess the quantitative changes between two single-time points and relative mobility of household wealth over life-course, respectively. We performed generalized linear regressions to examine the associations of household wealth mobility indicators with adolescent height- (HAZ) and body mass index-for-age and sex z score (BAZ), scores of full-scale intelligent quotient (FSIQ) and emotional and behavioral problems.

Results: A total of 1,188 adolescents were followed, among them 59.9% were male with a mean (SD) age of 11.7 (0.9) years old. Per SD conditional increase of household wealth z score from pregnancy to mid-childhood was associated with 0.11 (95% CI 0.04, 0.17) SD higher HAZ and 1.41 (95% CI 0.68, 2.13) points higher FSIQ at early adolescence. Adolescents from the household wealth Upward trajectory had a 0.25 (95% CI 0.03, 0.47) SD higher HAZ and 4.98 (95% CI 2.59, 7.38) points higher FSIQ than those in the Consistently low subgroup.

Conclusion: Household wealth upward mobility particularly during early life has benefits on adolescent HAZ and cognitive development, which argues for government policies to implement social welfare programs to mitigate or reduce the consequences of early-life deprivations. Given the importance of household wealth in child health, it is recommended that socioeconomic circumstances should be routinely documented in the healthcare record in LMICs.

KEYWORDS

birth cohort, household wealth mobility, adolescent, physical growth, cognition, behavioral health

1. Introduction

The national economic growth in low- and middle- income countries (LMICs) has been rapidly developing for decades, potentially resulting in the improvement of child health. According to country-level data, the global under-five mortality rate substantially decreased by 53%, from 90.6 in 1990 to 42.5 deaths per 1,000 livebirths in 2015 (1). In general population, individual households have varying patterns and/or degrees of household wealth mobility. Based on demographic and health surveys in 39 LMICs, Winskill et al. (2) reported that children in the poorest households had a higher probability of co-occurring fever, acute respiratory infection, diarrhea and wasting. However, a study using data of 121 demographic and health surveys in 36 LMICs between 1990 and 2011 observed a quantitatively very small to null association between increases in per-head gross domestic product and reductions in early childhood malnutrition (3).

These discrepancies may be explained by the single-time point measurement of household wealth and cross-sectional nature of demographic and health surveys among these studies, which are unable to capture the mobility of individual household wealth. We only noted two studies conducted in high-income countries that measured socioeconomic status (SES) at multiple-time points, which, however, manually categorized the sample into subgroups by merging the low-, medium-, and high-SES at single-time point in an un-nuanced manner. They both reported that upward shift of household SES from baseline had benefits on later cardiovascular health (4, 5). However, household wealth as the largest contributor to child health among individual SES measures (6, 7), the associations between household wealth mobility and child heath remain unclear. Besides, household wealth can vary by years as compared to stable parental education and occupation. In addition, as the theory of Developmental Origins of Health and Disease describes that exposures to deprivations during early life may lay the foundations for long-term health (8), it remains unclear whether the upward mobility of postnatal household wealth would buffer against the negative effects of prenatal disadvantaged environment on child long-term health (4). Finally, household wealth and its mobility may exert positive or negative effects on child and adolescent specific health outcome (9).

In this study, we used data from a birth cohort in rural western China where national economy has been rapidly developing for decades. In our village setting, individual families have wider range and higher diversities of household wealth as compared to those in eastern metropolitan cities in last decade, i.e., during our study period, providing the unique opportunity to assess the household wealth mobility. We prospectively followed participants at birth, mid-childhood (7–9 y) and early adolescence (10–14 y) and repeatedly assessed household wealth at each visit. We aimed to examine the associations of household wealth at single-time point, conditional increase between two single-time points and life-course relative mobilities (trajectories) from pregnancy to early adolescence with adolescent multiple health outcomes, including physical growth, cognitive development, and emotional and behavioral problems.

2. Materials and methods

2.1. Study design and participant

We conducted a prospective birth cohort of children born to mothers who participated in a cluster-randomized, double-blind trial in rural western China conducted between August 2002 and February 2006 (ISRCTN08850194) (10). Briefly, all pregnant women from every village in two counties were eligible to enroll in this trial and were randomized to take a daily capsule of folic acid, iron/folic acid, or multiple micronutrients until delivery. Among 4,488 singleton live births eligible to enroll in long-term follow-up after excluding birth defects, and/or deaths (online Supplementary Figure 1), we followed 1,744 children at mid-childhood (age 7–10 years) between 2012 and 2013, and among them, 1,188 were followed at early adolescence (age 10–14 years) between June-December 2016. The procedure details of the parent trial and follow-up studies were described elsewhere (10–12). The trial and follow-up evaluation protocols were approved by the Ethics Committee in Xi'an Jiaotong University Health Science Center. Written informed consent was obtained from the biological parents or caregivers, and verbal consent was obtained from all the participants depending on their age.

2.2. Household wealth index

We repeatedly assessed household wealth at enrollment of parent trial (<28 gestational weeks), mid-childhood and early

Abbreviations: BAZ, body mass index-for- age and sex z score; CI, confidence interval; FSIQ, full-scale intelligent quotient; HAZ, height-for- age and sex z score; LMIC, low- and middle- income country; MUAC, mid-upper arm circumference; PRI, perceptual reasoning index; PSI, processing speed index; SD, standard deviation; SES, socioeconomic status; VCI, verbal comprehension index; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; WMI, working memory index.

adolescence, which was derived from principal component analysis for household assets and dwelling characteristics. The following items were included at pregnancy: (i) goods, bicycle, motor, orchard, radio, TV/VCD, refrigerator, washer, poultry, goat/sheep/pig, cattle/cow and car/tractor; (ii) characteristics of the house, house types (soil cave-dwelling, brick-cave dwelling, soil wall, brick/concrete wall, and apartment), materials for the floor, and availability of electricity, running water and household toilet. In addition to these, phone, computer, air conditioner and automatic water heater were included at mid-childhood and early adolescence. Briefly, household assets and dwelling characteristics were classified into Having/Yes and Not having/No. The household wealth index was priorly constructed and locally validated (13). We categorized the household wealth index to indicate low-, medium- and high-wealth households by its tercile.

2.3. Measurements of adolescent health at adolescence-stage visit

2.3.1. Physical growth

All anthropometric measures were taken by the same filed worker following standardized procedures in a local school classroom. Standing height was measured to 1 mm precision using a stadiometer (SZG-210, Shanghai JWFU Medical Apparatus Corporation) and weight after losing heavy clothes was measured to nearest the 0.1 kg (BC-420, Tanita Corporation, Tokyo, Japan). Height-for-age and sex *z* score (HAZ) and body mass index-for-age and sex *z* score (BAZ) were derived using World Health Organization growth standards (14). Adolescent stunting and overweight/obesity was defined as HAZ < -2 standard deviation (SD) and BAZ $> +1$ SD, respectively. Body mass index (kg/m^2) was calculated as weight in kilograms divided by the square of height in meters.

2.3.2. Cognitive development

We used a validated Chinese version of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (15). The full-scale intelligent quotient (FSIQ) was derived to represent adolescent general cognitive development. Besides, other aspects of adolescent cognitive development including verbal comprehension (VCI), perceptual reasoning (PRI), working memory (WMI), and processing speed index (PSI) were derived.

2.3.3. Emotional and behavioral problems

Adolescents actively completed the scale of the Chinese version of Achenbach Youth's Self-Report (2001 version) under the guidance of field workers (16). Three continuous scores were derived, with lower scores indicating better emotional and behavioral outcome. Internalizing score was composed of withdrawn, anxious/depressed and somatic complaints, externalizing score was composed of delinquent/rule-breaking and aggressive behavior, and the total behavioral problem score was composed of all symptoms above and social problem, thought problem and attention problem. Both of the cognitive development and emotional and behavioral problem assessments were administrated in a local school meeting room free of distraction.

2.4. Other covariables

We collected the following covariables by face-to-face interview using standard procedures in the parent trial. We included parent age (continuous), education ($<$3 years, primary, secondary, $\geq$high school) and occupation (farmer, others), antenatal randomized regimens with durations (folic acid or folic acid plus iron $<$180 days, folic acid plus iron $\geq$180 days, multiple micronutrients $<$180 days, and multiple micronutrients $\geq$180 days) accounting for prior findings (12), maternal parity (0, $\geq$1), maternal mid-upper arm circumference at enrollment ($<$21.5 cm, $\geq$21.5 cm), and birth outcomes [small-for-gestational age by $<$10th centile by INTERGROWTH (17) and sex].

2.5. Statistical analyses

To assess the conditional increase of household wealth, we calculated the conditional gains of household wealth index between two single-time points, which was the standardized residual of regressing household wealth index at prior time point on household wealth index at later (18). To assess the life-course relative mobility of household wealth from pregnancy to early adolescence, we performed group-based trajectory modeling that assigned individuals with similar features of household wealth mobility trajectories into distinct, exclusive subgroups (19), using the "traj" command implemented in Stata software. Models with two or more subgroups were conducted after accounting for the varying trajectory shapes of linear, quadratic and/or cubic terms. Data-based parameters and principles were applied to decide the final subgroups (19), including (i) Bayesian and Akaike information criterion value, (ii) average of the posterior probabilities of group membership for individuals assigned to each group $>$0.7, (iii) odds of correct classification based on the posterior probabilities of group membership $>$5, and (iv) minimizing overlap in confidence intervals (CIs) and capturing the distinctive features of the data as parsimonious as possible.

We took adolescent HAZ, BAZ, FSIQ, and scores of total behavioral problems, externalizing and internalizing behavioral problems as primary outcomes, and other aspects of cognitive development and emotional and behavioral problems as secondary outcomes, respectively. We performed generalized linear regressions with Gaussian distribution and identity link to examine the associations of household wealth mobility indicators with adolescent health outcomes separately. The adjusted mean differences with their 95% CIs were estimated after including the covariables above. In addition, we performed stratified analyses by parental education (low and high educational level) and adolescent sex (male and female) after obtaining the interaction *P*-values that were estimated from likelihood ratio tests comparing models including and excluding the interaction terms.

For sensitive analyses addressing the lost to follow-up, we conducted inverse probability weighting, and randomly sampled the lowest and highest 80% wealth households at pregnancy and repeated the analyses for primary outcomes. The weight of each participant is given by the inverse of the predicted probability for followed participant in a logistic regression model, which included parental education, occupation and age, maternal parity and mid-upper arm circumference, randomized regimens by duration, small-for-gestational age, and adolescent sex and age. In addition, we used E-value approach to assess the impact extent of potential unmeasured confounder on affecting the estimates above (20). All statistical analyses were conducted in Stata 15.0 (Stata Corp, College Station, Texas, USA). A two-sided *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Background characteristics

Among 1,188 adolescents included in the final analyses (Table 1), 59.9% were male, and the mean age was 11.7 (SD, 0.9) years old. Majority of their parents had secondary education and lived on farming. The percentage of adolescent stunting and overweight/obesity was 2.3% (27/1,181) and 14.2% (166/1,167), respectively. The mean (SD) of adolescent HAZ, BAZ, FSIQ, total behavioral problem score, internalizing and externalizing score was 0.07 (1.07), −0.27 (1.15), 97.2 (12.4) points, 49.0 (24.1) points, 11.2 (7.6) points, and 8.4 (7.1) points, respectively. Adolescents born to parents who had higher education level, were non-farmers and came from high-wealth households were more likely to be lost to follow-up (Table 1). However, the characteristics of birth outcomes between adolescents followed and those lost to follow-up were balanced.

3.2. Household wealth mobility and adolescent health

3.2.1. Household wealth at single-time point

As shown in Table 2, per SD increase of household wealth index at pregnancy was associated with 0.09 (95% CI 0.04, 0.14) SD higher HAZ, 0.71 (95% CI 0.11, 1.31) points higher FSIQ, and −1.54 (95% CI −2.84, −0.24) points lower scores of total behavioral problems and −0.47 (95% CI −0.85, −0.09) points lower scores of externalizing behavioral problems at early adolescence. Similar results were observed for household wealth index at mid-childhood and early adolescence, and for other aspects of adolescent cognitive development (Supplementary Table 1). While, we observed null associations of household wealth at mid-childhood and early adolescence with adolescent socioemotional scores, respectively (Table 2 and Supplementary Table 2).

3.2.2. Conditional increase of household wealth between two single-time points

We observed positive associations of conditional increase/gain of household wealth between two single-time points, i.e., quantitative increase of household wealth, with adolescent HAZ and cognitive development, while null associations for BAZ and scores of emotional and behavioral problems in Table 3 and Supplementary Tables 1, 2. Specifically, per SD of household wealth conditional increase from pregnancy to mid-childhood was associated with 0.11 (95% CI 0.04, 0.17) SD higher HAZ and 1.41 (95% CI 0.68, 2.13) points higher FSIQ at early adolescence, respectively. Similar associations between conditional increase of household wealth from mid-childhood to early adolescence and adolescent HAZ and cognitive development (FSIQ and other aspects) were observed.

3.2.3. Life-course trajectories (relative-scale mobility) of household wealth and adolescent health

We identified four distinct life-course trajectories of household wealth, which could be characterized as: (i) Consistently low (53.8% of the sample), (ii) Upward (11.4%), (iii) Downward (22.2%), and (iv) Consistently high (12.6%) (Supplementary Figure 2). The parameters of deciding the final trajectories were summarized in Supplementary Table 4 while accounting for the distinctive features of the data as parsimonious as possible.

Adolescents from the Upward subgroup had a 0.25 (95% CI 0.03, 0.47) SD higher HAZ than those in the Consistently low subgroup, while adolescents from the Downward subgroup had a −0.31 (95% CI −0.55, −0.07) SD lower HAZ as compared to those in the Consistently high subgroup (Table 4). The corresponding estimates were 4.98 (95% CI 2.59, 7.38) and −4.03 (−6.66, −1.41) points for adolescent FSIQ. Similar positive associations were observed for other aspects of adolescent cognitive development (Supplementary Table 1), while null associations for adolescent BAZ and scores of emotional and behavioral problems (Table 4 and Supplementary Table 2).

3.2.4. Stratified analyses by parental education and adolescent sex

The *P*-values of interactions between parental education and adolescent sex and household wealth mobility indicators were presented in Supplementary Table 4, most of which were beyond 0.05. Further, we performed stratified analysis by maternal education (Supplementary Tables 5, 6), paternal education (Supplementary Tables 7, 8), and adolescent sex (Supplementary Tables 9, 10). The benefits of household wealth increase on adolescent HAZ and cognitive development were more pronounced among adolescents from households with higher maternal and paternal education. In addition, the benefits were doubled among adolescent females as compared with males.

3.3. Sensitivity analyses

Finally, the sensitivity analyses accounting for the lost to follow-up showed comparable results (Supplementary Tables 11–13) to those in Tables 2–4. The results of E-value approach indicated that an unmeasured confounder with strong strength would be required to explain away the observed associations (Supplementary Table 14), suggesting the robustness of our results.

4. Discussions

We observed that household wealth upward mobility particularly during early life was associated with adolescent higher HAZ and better cognitive development in a birth cohort in an undeveloped setting. Further, adolescents from wealthier households at pregnancy had lower (better) scores of emotional and behavioral

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TABLE 1 Comparison of background characteristics between adolescents followed and those lost to follow-up in a birth cohort in rural western China.

Factors	Adolescents followed from pregnancy through mid-childhood into early adolescence/number (%)	Adolescents lost to follow-up /number (%)	*P*-values
n	1,188 (100.0)	3,300 (100.0)	
Maternal age years/mean (SD)	24.8 (4.5)	24.6 (4.3)	0.18
Maternal education			<0.001
<3 years	77 (6.5)	173 (5.3)	
Primary	371 (31.3)	798 (24.3)	
Secondary	600 (50.6)	1,811 (55.1)	
High school and above	137 (11.6)	503 (15.3)	
Maternal occupation			<0.001
Farmer	1,030 (87.1)	2,710 (82.7)	
Others	152 (12.9)	565 (17.3)	
Paternal age (years)/Mean (SD)	28.0 (4.2)	27.8 (4.1)	0.10
Paternal education			<0.001
<3 years	20 (1.7)	40 (1.2)	
Primary	188 (15.9)	387 (11.8)	
Secondary	735 (62.0)	2,033 (61.9)	
High school and above	243 (20.5)	824 (25.1)	
Paternal occupation			<0.001
Farmer	951 (80.3)	2,400 (72.9)	
Others	234 (19.7)	890 (27.1)	
Household wealth index at pregnancy/enrollment[a]	−0.14 (1.4)	0.09 (1.5)	<0.001
Low (Q1)	412 (34.7)	1,021 (30.9)	0.003
Medium (Q2)	429 (36.1)	1140 (34.6)	
High (Q3)	347 (29.2)	1,139 (34.5)	
Parity at enrollment			0.19
0	757 (63.7)	2,172 (65.8)	
≥1	431 (36.3)	1,128 (34.2)	
Maternal MUAC (cm)			0.341
<21.5	225 (19.1)	582 (17.9)	
≥21.5	953 (80.9)	2,678 (82.1)	
Randomized regimens			0.12
Folic acid	732 (34.6)	853 (36.0)	
Folic acid plus iron	676 (32.0)	795 (33.5)	
Multiple micronutrient	707 (33.4)	725 (30.5)	
Offspring sex			<0.001
Male	712 (59.9)	1,773 (53.7)	
Female	476 (40.1)	1,527 (46.3)	
Birth weight (gram) /Mean (SD)	3,205 (416)	3,194 (416)	0.46
Gestational weeks at delivery /Mean (SD)	39.8 (1.6)	39.8 (1.7)	0.63
Preterm (<37 gestational weeks)	50 (4.2)	158 (4.8)	0.42
Low birth weight (<2,500 g)	47 (4.1)	99 (3.2)	0.14
Small-for-gestational age (<10th)	138 (12.4)	374 (12.4)	0.99
Age at adolescence (years)/mean (SD)	11.7 (0.9)	11.7 (0.9)	0.55

SD, standard deviation; MUAC, mid-upper arm circumference.
[a]Household wealth at enrollment was derived from principal component analysis for household assets and dwelling characteristics, and was further categorized by its terciles.

TABLE 2 Associations between household wealth index at single-time point and adolescent HAZ, BAZ, cognitive development, and emotional and behavioral problems in a birth cohort in rural western China (n = 1,188).

Household wealth index	Z scores of physical growth[a]		Cognitive development[a]	Scores of emotional and behavioral problems[a]		
	HAZ	BAZ	FSIQ	Total problem	Internalizing	Externalizing
Pregnancy/per SD	0.09 (0.04, 0.14)	0.03 (−0.03, 0.09)	0.71 (0.11, 1.31)	−1.54 (−2.84, −0.24)	−0.31 (−0.73, 0.10)	−0.47 (−0.85, −0.09)
Low (Q1)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium (Q2)	0.06 (−0.09, 0.22)	−0.02 (−0.19, 0.15)	0.01 (−1.67, 1.68)	−3.09 (−6.69, 0.51)	−0.46 (−1.62, 0.69)	−0.60 (−1.65, 0.45)
High (Q3)	0.24 (0.06, 0.42)	0.12 (−0.08, 0.32)	2.43 (0.41, 4.45)	−5.24 (−9.62, −0.87)	−1.30 (−2.70, 0.10)	−1.75 (−3.02, −0.47)
Mid-childhood/per SD	0.10 (0.06, 0.15)	0.03 (−0.02, 0.08)	1.18 (0.70, 1.67)	−0.002 (−1.07, 1.07)	−0.11 (−0.45, 0.23)	−0.06 (−0.37, 0.25)
Low (Q1)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium (Q2)	0.16 (0.01, 0.31)	0.10 (−0.07, 0.27)	0.14 (−1.54, 1.81)	0.46 (−3.19, 4.12)	0.08 (−1.09, 1.24)	0.12 (−0.94, 1.19)
High (Q3)	0.38 (0.22, 0.55)	0.07 (−0.12, 0.25)	3.37 (1.53, 5.21)	−0.32 (−4.36, 3.72)	−0.50 (−1.79, 0.80)	−0.23 (−1.41, 0.95)
Early adolescence/per SD	0.11 (0.06, 0.16)	0.05 (0.003, 0.11)	1.48 (0.97, 1.99)	−0.48 (−1.60, 0.64)	−0.28 (−0.64, 0.08)	−0.14 (−0.47, 0.19)
Low (Q1)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium (Q2)	0.22 (0.07, 0.37)	0.24 (0.08, 0.41)	1.14 (−0.48, 2.75)	−2.12 (−5.66, 1.43)	−0.99 (−2.13, 0.14)	−0.04 (−1.08, 1.00)
High (Q3)	0.34 (0.17, 0.51)	0.14 (−0.05, 0.33)	5.16 (3.27, 7.05)	−1.68 (−5.84, 2.48)	−1.12 (−2.46, 0.21)	−0.48 (−1.69, 0.74)

HAZ, height-for- age and sex z score; BAZ, body mass index-for- age and sex z score; FSIQ, full-scale intelligent quotient.

[a]Data are presented with adjusted mean differences and their 95% confidence intervals. The adjustments included parental education, occupation and age, maternal parity and mid-upper arm circumference, randomized regimens by duration, small-for-gestational age, and adolescent sex and age.

problems. Although the interaction P-values did not reach statistical significance, the benefits of household wealth increase on adolescent HAZ and cognitive development were more pronounced among households with higher maternal or paternal education level. Furthermore, the corresponding benefits were doubled among female adolescents as compared with their counterparts.

We used household assets and dwelling characteristics to construct household wealth index, which is a robust measure in LMICs as compared to income and consumption, suffering from information bias. Our study is one of the few studies to comprehensively assess the mobility and trajectories of household wealth from pregnancy to early adolescence, evaluate adolescent health in multiple domains and examined their relationships in a nuanced manner. Our results show that postnatal household wealth conditional increase could confer the benefits to adolescent HAZ and cognitive development after accounting for the influence of household wealth at pregnancy. Besides, the effect size of household wealth conditional increase between pregnancy and mid-childhood seems to be larger than that between mid-childhood and early adolescence, although with confidence interval overlapping. This finding is in line with the hypothesis that the plasticity of child development is larger during early life, particularly during the first 1,000 days. Another explanation was that school education may have relatively larger impact on adolescent cognitive development as compared to household wealth mobility after mid-childhood/primary school age, given the national strategy of 9-year compulsory education well-implemented in China. In the meantime, some nutritional intervention programs were conducted among school, e.g., the Yingyangbao strategy widely covered in rural areas in China (21), which potentially buffer against the health consequences of disadvantaged families. In addition, on the relative scale (position change) of household wealth in our sample from pregnancy to early adolescence, our trajectory results show the consistency of wealth-driven health disparities in LMICs (22). Of note, adolescents from Upward household wealth trajectory had comparable HAZ and cognitive development to those from Consistently high household wealth trajectory. These results suggest that postnatal household wealth upward mobility may have long-lasting benefits on adolescent health, particularly for household wealth increase during early life. Majority of studies considered that the household wealth was a proxy of offspring access to health care, optimal diets, clean water and sanitation, home environment and other resources (23). Nevertheless, mediation analyses reported that the mediators above could not completely explain the associations between household wealth and health outcomes at later life (24–26). Among adults, Zhang and colleagues reported that healthy lifestyle only mediated a small proportion (3.0% to 12.3%) of the association between low SES and higher risk of mortality and cardiovascular diseases (27). These results suggest that poor household wealth at early life may have a direct or causal link to suboptimal life-course health outcomes, which may result from persistent structural changes due to deprivations during pregnancy (28). Our results that household wealth at pregnancy was associated with adolescent HAZ, cognitive development and emotional and behavioral health agree well with this hypothesis. Taken together, to improve child health and development in public health practices, much efforts should be made as early as practicable to lay the foundation and target the high-risk population in disadvantaged households. In public health implications, we suggested that deprived families

TABLE 3 Associations between conditional gains of household wealth among periods and adolescent HAZ, BAZ, cognitive development and emotional and behavioral problems in a birth cohort in rural western China ($n = 1,188$).

Household wealth	Z scores of physical growth[a]		Cognitive development[a]	Scores of emotional and behavioral problems[a]		
	HAZ	BAZ	FSIQ	Total problem	Internalizing	Externalizing
Gains from pregnancy to mid–childhood/per SD	0.11 (0.04, 0.17)	0.03 (−0.05, 0.10)	1.41 (0.68, 2.13)	0.69 (−0.90, 2.28)	−0.02 (−0.53, 0.49)	0.12 (−0.34, 0.59)
Low (Q1)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium (Q2)	0.04 (−0.11, 0.19)	0.07 (−0.10, 0.23)	0.87 (−0.79, 2.53)	0.47 (−3.18, 4.12)	−0.17 (−1.33, 1.00)	−0.10 (−1.17, 0.96)
High (Q3)	0.21 (0.05, 0.37)	0.06 (−0.12, 0.24)	2.82 (1.08, 4.57)	0.98 (−2.83, 4.79)	−0.23 (−1.45, 0.99)	0.24 (−0.87, 1.36)
<=0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>0	0.24 (0.11, 0.37)	0.05 (−0.09, 0.19)	1.98 (0.55, 3.41)	1.6 (−1.53, 4.73)	0.19 (−0.82, 1.19)	0.45 (−0.47, 1.36)
Gains from mid–childhood to early adolescence/per SD	0.06 (−0.01, 0.12)	0.05 (−0.02, 0.12)	1.07 (0.38, 1.76)	−0.43 (−1.93, 1.07)	−0.26 (−0.74, 0.22)	−0.08 (−0.52, 0.36)
Low (Q1)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium (Q2)	0.17 (0.02, 0.32)	0.28 (0.12, 0.45)	0.64 (−1.03, 2.30)	0.35 (−3.27, 3.97)	−0.02 (−1.18, 1.14)	0.11 (−0.95, 1.17)
High (Q3)	0.19 (0.04, 0.34)	0.19 (0.01, 0.36)	2.58 (0.87, 4.28)	0.01 (−3.71, 3.73)	−0.46 (−1.65, 0.73)	0.29 (−0.79, 1.38)
<=0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>0	0.11 (−0.02, 0.23)	0.12 (−0.02, 0.26)	1.69 (0.30, 3.07)	−0.53 (−3.56, 2.51)	−0.23 (−1.20, 0.74)	−0.17 (−1.06, 0.71)
Gains from pregnancy to early adolescence/per SD	0.11 (0.04, 0.18)	0.06 (−0.01, 0.14)	1.74 (1.00, 2.47)	0.06 (−1.56, 1.67)	−0.24 (−0.76, 0.28)	0.03 (−0.44, 0.50)
Low (Q1)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Medium (Q2)	0.14 (−0.005, 0.29)	0.23 (0.07, 0.39)	0.58 (−1.04, 2.19)	−0.99 (−4.54, 2.55)	−0.57 (−1.70, 0.57)	0.24 (−0.79, 1.28)
High (Q3)	0.29 (0.13, 0.45)	0.17 (−0.01, 0.35)	3.92 (2.14, 5.70)	−0.76 (−4.66, 3.13)	−0.91 (−2.16, 0.34)	−0.27 (−1.41, 0.87)
<=0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>0	0.15 (0.03, 0.28)	0.12 (−0.02, 0.26)	1.95 (0.55, 3.36)	−1.25 (−4.34, 1.83)	−0.76 (−1.75, 0.23)	−0.48 (−1.38, 0.42)

HAZ, height-for- age and sex z score; BAZ, body mass index-for- age and sex *z* score; FSIQ, full-scale intelligent quotient.

[a]Data are presented with adjusted mean differences and their 95% confidence intervals. The adjustments included parental education, occupation and age, maternal parity and mid-upper arm circumference, randomized regimens by duration, small-for-gestational age, and adolescent sex and age.

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TABLE 4 Associations between life-course household wealth trajectories and adolescent HAZ, BAZ, cognitive development, and emotional and behavioral problems in a birth cohort in rural western China (n = 1,188).

Household wealth	Z scores of physical growth[a]		Cognitive development[a]	Scores of emotional and behavioral problems[a]		
	HAZ	BAZ	FSIQ	Total problem	Internalizing	Externalizing
Upward vs. Consistently low	0.25 (0.03, 0.47)	−0.01 (−0.25, 0.24)	4.98 (2.59, 7.38)	0.18 (−5.15, 5.52)	−0.56 (−2.27, 1.15)	0.08 (−1.47, 1.64)
Downward vs. Consistently low	0.19 (0.02, 0.36)	−0.03 (−0.23, 0.16)	2.62 (0.74, 4.51)	−1.47 (−5.67, 2.73)	−0.75 (−2.09, 0.60)	−0.47 (−1.70, 0.76)
Consistently high vs. Consistently low	0.49 (0.25, 0.73)	0.10 (−0.17, 0.37)	6.66 (4.00, 9.32)	−3.67 (−9.64, 2.30)	−1.07 (−2.98, 0.84)	−1.52 (−3.26, 0.22)
Upward vs. Consistently high	−0.24 (−0.52, 0.04)	−0.11 (−0.42, 0.21)	−1.67 (−4.76, 1.41)	3.86 (−3.17, 10.88)	0.51 (−1.74, 2.76)	1.60 (−0.45, 3.65)
Downward vs. Consistently high	−0.31 (−0.55, −0.07)	−0.13 (−0.40, 0.13)	−4.03 (−6.66, −1.41)	2.20 (−3.80, 8.20)	0.32 (−1.60, 2.24)	1.05 (−0.70, 2.80)
Upward vs. Downward	0.08 (−0.16, 0.32)	0.01 (−0.27, 0.30)	2.28 (−0.34, 4.90)	1.05 (−4.93, 7.03)	0.04 (−1.93, 2.00)	0.40 (−1.34, 2.14)

HAZ, height-for- age and sex z score; BAZ, body mass index-for- age and sex z score; FSIQ, full-scale intelligent quotient.
[a]Data are presented with adjusted mean differences and their 95% confidence intervals. The adjustments included parental education, occupation and age, maternal parity and mid-upper arm circumference, randomized regimens by duration, small-for-gestational age, and adolescent sex and age.

should be included in social welfare programs at the beginning of pregnancy.

In addition, the potential benefits of household wealth increase over time may differ by specific health outcome. We observed consistent significance for adolescent HAZ and cognitive development which may result from the appropriate infant feeding, diets, stimulation, and home environment among higher wealth households, all of which have been shown to be causes of child linear growth and development (29). Prior study reported lower (better) scores of emotional and behavioral problems among children from wealthier households (30). Our study further contributes to the literature that higher household wealth at pregnancy but not postnatal household wealth increase has benefits on adolescent socioemotional outcomes. In addition, the transition of overweight/obesity from the wealthy to the poor along with the national economy increasing was documented in other LMICs (31). We only observed statistically positive associations of adolescent BAZ with household wealth at early adolescence, suggesting the likely minimal impact of household wealth mobility at early life on adolescent weight. However, we could not provide more details on the underlying mechanisms linking household wealth to a specific outcome, and mediation analyses examining corresponding mediators are needed in future. Overall, postnatal household wealth increase has some long-term benefits on adolescent health particularly for adolescents being born and raised in consistently wealthy families, which argue for government policies to implement social welfare programs such as cash transfer and health insurance to mitigate or reduce the consequences of early-life deprivations (32).

Furthermore, we examined the modifications of parent education and offspring sex on the relationship between household wealth mobilities and adolescent health, although majority of these interaction P-values were not statistically significant. In the present study, the benefits of postnatal household wealth increase on adolescent health were more pronounced among adolescents from households with higher parental education. Similarly, prior study reported that higher maternal education might buffer against the negative effects of higher household wealth on child overweight/obesity (33). Besides, Conger and colleagues reported that higher parent education level would increase their family investments on child care and consequently lead to the improvement of child health (34). We hypothesized that households with higher parental education were more likely to take advantage of the wealth and transfer resources into appropriate practices of child care, consequently improving adolescent health (35). As for the sex modification, the benefits of household wealth increase on adolescent health were observed both among female and male adolescents, but the effect sizes particularly for cognitive development were doubled among adolescent females. Prior study reported that adolescent females relate to males were more likely to follow the parenting on healthy life styles (36). Similarly, we previously reported a statistically significant interactions of maternal education and sex for adolescent anemia (37). In addition, the relationship of household wealth at pregnancy and adolescent emotional and behavioral health was only observed among males in the present study, which may be due to the statistical power, and/or that adolescent males had higher prevalence of externalizing behavioral problems as compared to females (38). However, the sex modification of the relationship between SES and children emotional and behavioral outcomes were not consistent in the literature (39), warranting confirmations in future studies.

Our findings have a few limitations. Firstly, adolescents were born to mothers who had participated in an antenatal micronutrient supplementation trial which might limit the generalization. However, this community-based trial enrolled all eligible pregnant women in every village and we adjusted for randomized regimens in all analyses. Besides, this micronutrient intervention strategy would be expected to weaken the tie between household wealth and adolescent health for its ability to reduce the wealth-driven equity (40). Secondly, as with other cohorts with long-term follow-up periods, loss of participants may lead to the selection bias. Households with higher parental education and wealth are more likely to move out of study area into cities and thus be lost to follow, resulting in the underestimates in our study. We have partly addressed this by performing inverse probability weighting and repeating analyses among the lowest and highest 80% wealth households at baseline, all of which showed comparable results. Thirdly, the household wealth index derived from assets and dwelling characteristics might be country-specific, although it was commonly used in LMICs. Besides, the wealth mobility defined by household wealth index may not indicate the actual increase of inflation-adjusted family income, which however mainly suggested wealth positional change among our participants. Finally, residual confounding was always possible due to the nature of observational design, and causal inference could be pursued under the counterfactual outcome framework in future studies as the reviewer suggested. However, our sensitivity analyses of E-value approach suggested that the contribution of unmeasured confounding to biasing our results was likely minimal.

Higher prenatal household wealth and postnatal household wealth increase particularly during early life had wide benefits on adolescent HAZ and cognitive development, and possibly socioemotional outcomes. To improve adolescent health and human capital outcomes, public health programs targeting at all life-course stages are warranted and should be accompanied by strategies to reach the most vulnerable populations at the beginning of pregnancy. Given the importance of household wealth and other related SES indicators in child health, it is recommended that socioeconomic circumstances should be routinely documented in the healthcare record.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee in Xi'an Jiaotong University Health Science Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YC, LZ, and ZZ designed the study. JT, SL, LW, QQ, QD, AA, ME, and ZZ conducted the study. JT, YZ, and ZZ analyzed data and interpreted results. JT, YZ, and ZZ wrote the paper. LZ and ZZ had primary responsibility for final content. All authors reviewed, revised, and approved the final paper.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1061251/full#supplementary-material

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Cross-sectional associations between adolescents' physical literacy, sport and exercise participation, and wellbeing

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Background: Adolescence is a significant period in one's development of positive emotional and social wellbeing. Physical literacy (PL) is considered a determinant of physical health and wellbeing and is thought to be the foundation for an individual's engagement in physical activities. Yet, limited evidence exists on PL's association with adolescents' health and physical activity behavior. This study aims to (1) explore the associations between Danish adolescents' PL and their emotional and social wellbeing, (2) examine whether these associations are mediated by sport and exercise participation (SEP), and (3) consider if the associations differ across sex.

Methods: Cross-sectional data from a national population survey were collected in 2020. The sample consisted of 1,518 Danish adolescents aged 13–15 years. PL was assessed with the validated MyPL questionnaire. The weekly time engaged in sports and exercise was self-reported. Self-esteem, life satisfaction, body satisfaction, and loneliness were measured with items from the standardized HBSC questionnaire, and a wellbeing composite score was calculated from these four measures. We constructed structural equation models with PL and sports and exercise participation as independent variables and the five aspects of wellbeing as dependent variables.

Results: Positive associations were observed between PL and SEP ($\beta = 0.33$, $p < 0.001$) and between PL and the five aspects of wellbeing with β-values between 0.19 and 0.30 ($p < 0.001$). These associations were greater among girls. The association between PL and four of the five wellbeing outcomes were partly mediated by SEP with indirect effects (β) between 0.03 and 0.05.

Conclusions: Results from this study support the hypotheses that PL is important for children and adolescents' wellbeing and physical activity behavior.

KEYWORDS

mental health, SEM, youth, quality of life, children, physical literacy, sport participation, exercise participation

Background

Adolescents' emotional and social wellbeing has been in a worrying decline over recent years (1) and is currently considered one of the greatest disease burdens among adolescents (2). Additionally, the prevalence of issues in emotional and social well-being are more common among adolescent girls compared to boys (3, 4). This is unfortunate, as adolescents' emotional and social wellbeing is crucial to their academic, cognitive, and social development (5, 6), and low wellbeing is connected to increased risks of non-communicable diseases (7, 8) and mortality (9). Wellbeing promotes mental health and alleviates related issues (2), and the World Health Organization (WHO) has declared that emotional and social wellbeing combine to form the foundation of well-functioning individuals and communities (10).

Emotional and social wellbeing, also commonly referred to as mental health (11), are associated with individual, social, and environmental factors (12), including lifestyle factors such as physical activity and sport participation (13–15). Numerous personal aspects are thought to be closely related to wellbeing, such as self-esteem (16), life satisfaction (17), body satisfaction (18), and loneliness (19). Self-esteem is defined as an individual's feelings and thoughts about their own importance and worth and is an essential part of one's self-concept (20). Self-esteem has shown to be associated with mental health in adolescence and adulthood (16). Life satisfaction is defined as an individual's cognitive appraisal of life quality from their own set of criteria (21) and is as an essential component within positive mental health (17). Body satisfaction, an aspect of body image, is defined as an individual's appraisal of their physical appearance and body based on their thoughts, feelings, and attitudes toward their body (22). Body satisfaction is seen as an element in mental health that has increased importance during adolescence (18). Loneliness is a negative feeling produced by disagreement between an individual's desired and existing social relations (23) and is associated with mental health problems (24).

Adolescence is a life-stage with increased vulnerability to mental health problems, which makes it a significant period in the development of positive mental health (25). Promoting positive mental health and preventing health problems, especially in early life-stages, is generally more effective than treating diseases (26, 27), and thus it is important to identify factors related to positive mental health in children and adolescents.

A concept that has gained increased attention for its potential in promoting physical health and wellbeing is that of physical literacy (PL) (28, 29). PL describes important individual attributes and prerequisites in engaging in and adhering to physical activities throughout life (30) and is therefore thought to be a determinant of health (31). While various definitions exist, most include the elements cardiovascular fitness, strength, motor competence, motivation, confidence, knowledge, and understanding, which are encompassed in three overall domains: physical, affective and cognitive. It has been argued that PL "can make significant contributions to quality of life" [(30), p. 32] and that higher levels of PL will lead to self-esteem, an important part of psychological well-being in physical activities (30). Further, drawing on findings in self-determination theory research, it has been previously suggested that PL could be a determinant of overall well-being (32, 33). This belief stems from the positive relation between autonomous motivation and contextual wellbeing (34), which both are strengthened by the perception of competences (i.e., the PL element of confidence), and from the fact that wellbeing in physical activities can transfer to other contexts (35) and may also transfer to overall wellbeing (36). Two recent studies have found positive correlations between PL and aspects of mental health in children and young adolescents (32, 33).

PL is thought to lay the foundation of engagement in sports and other physical activities (30, 31) that can positively affect children's and adolescents' wellbeing (13–15). A recent systematic review found that the extant evidence demonstrates a positive association between PL and physical activity (37), with emerging longitudinal evidence supporting the assumption that PL is important for physical activity later in life (37, 38). However, most studies have investigated PL and its associations with health and physical activity among children up to the age of 12 years, with only a few studies focusing on adolescents (39) and young adults (40). These studies observed similar associations as those found among children.

Therefore, our objectives are to (a) investigate the associations between PL and aspects of emotional and social wellbeing among adolescents aged 13–15 years, (b) explore to what degree these associations are mediated by sport and exercise participation (SEP), and (c) investigate how these associations differ among boys and girls. We hypothesized that adolescents' PL would be associated with their SEP and their wellbeing and that the relationship would differ between the sexes. We further hypothesized that the relationship between PL and aspects of well-being would be partly mediated by SEP (see the hypothesized paths in Figure 1).

Methods

Study population

Our data came from a large-scale national survey conducted between October 29 and December 21, 2020 by Rambøll Management Consulting for the Danish Institute for Sports Studies (41). The sample of adolescents aged 13–15 years old was randomly drawn by the Danish Health Data Authority.

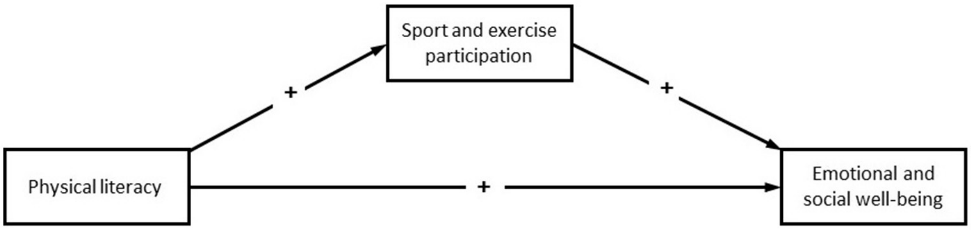

FIGURE 1
Hypothesized associations between study variables. This figure illustrates the theorized structural equation model, with aspects of emotional and social wellbeing serving as the outcomes.

A slightly different questionnaire was sent to the age-groups 7–12 years old and 13–15 years old. An invitation with a weblink to the online survey was sent *via* digital mail to the parents/guardians of 9,000 children and adolescents aged 7–15 years. Two reminders were sent *via* parents/guardians' digital mail to the adolescents who had not yet completed the survey. In parallel, telephone follow-ups with the parents/guardians were conducted, encouraging the adolescents and children to participate in the survey. During the call and in the e-mails, parents/guardians could also provide the adolescents or children's private e-mail address, allowing Rambøll Management Consulting to send the invitation directly to the adolescent or child. The survey links were accessible for ∼2 months. By then, 4,379 children and adolescents aged 7–15 years (48.7 % of those invited) had completed the survey, of which 1,518 were adolescents aged 13–15 years and thus included for analysis in this study. All completed answers had full data.

Measurements

Measurement of physical literacy

We measured PL with the MyPL questionnaire, a context-specific questionnaire suitable for population survey, developed by the authors of this study and validated in the same sample of this study. The MyPL is a PL assessment tool that strives to account for how PL differs across different social and physical environments for physical activity, as described in the conceptualization by Whitehead (30), and to ensure that PL items will be interpreted similarly across respondents, compared to other PL assessment tools wherein participants are probed on their generic relationship toward physical activity. Confirmatory factor analysis of the model showed good fit indices (CFI = 0.938; TLI = 0.925; RMSEA = 0.065 (90% CI 0.062–0.068); SRMR = 0.055). The MyPL also showed good internal consistency and reliability for the total PL scale was 0.778 (Cronbach's alpha) and 0.783 (McDonald's Omega). The results of development and initial validation of the MyPL questionnaire is unfolded in a study be Elsborg et al. entitled "From global domains to physical activity environments: development and initial validation of a questionnaire-based physical literacy measure designed for large-scale population surveys," which is prepared for submission. The questionnaire items and responds methods can be found in Appendix 1.

The 21-item PL scale consisted of 5 subscales: a PL for ball- and running-based activities (7 items), which consist of the elements autonomous motivation and confidence for ball and running activities combined with the physical competences of ball skills, endurance, and strength; a PL for playground-based activities (5 items) consisting of autonomous motivation and confidence for skating and climbing activities, as well as the physical competence of balance; a PL for gymnastic-based activities (4 items) consisting of autonomous motivation and confidence for gymnastics, along with physical competences for gymnastic and skipping; a PL for water-based activities (3 items) consisting of autonomous motivation and confidence for water activities combined with physical competences for swimming; and a general (not environment-specific) knowledge and understanding PL domain [3 item from the CAPL-2 (42)], which consisted of knowledge about the transfer of skills between different sports, knowledge about the importance of daily physical activity, and conceptual knowledge of strength and health.

Measurement of sport and exercise participation

Weekly time spent on SEP was measured with the question "How many hours do you normally use on sport/exercise per week (not counting time used on transportation)?" Participants typed in hours and minutes. Answers above 20 h were not included to minimize the risk of participants mistaking hours with minutes.

Measurement of aspects of mental health

Self-esteem

We assessed self-esteem with three items measuring participants' conceptions of others' thoughts about them and their positive self-conceptions. The participants responded to the prompts "I like myself," "I am good enough as I am," and "Others my age like me" using a five-point Likert scale from strongly agree to strongly disagree. The self-esteem score was calculated as the mean of the three items. The three-item self-esteem scale has showed good reliability ($\alpha = 0.89$) in similar population (43) and is used in the standardized HBSC questionnaire (44).

Life satisfaction

We assessed life satisfaction with the Cantril Ladder (45), which is based on the above definition. Participants were presented with a ladder from zero to ten and asked to indicate "Where on the ladder do you feel you stand at the moment?" with zero indicating the worst possible life and 10 indicating the best possible (46). The Cantril Ladder has demonstrated good reliability and convergent validity (45) and is widely used, such as in the HBSC study [e.g., (47)]. Furthermore, it has shown to be related to psychological wellbeing, mood, emotions, and self-perception (48) and thus seems to be a suitable indicator of life satisfaction among adolescents.

Body satisfaction

We measured body satisfaction with a single item from the Body Investment Scale (49), which reflects the above definition. Participants are asked "How satisfied are you with your body (physical appearance)?" and using a 5-point Likert scale from very dissatisfied to very satisfied.

Loneliness

We measured global loneliness with a single item. Participants responded to the question "Do you feel lonely?" using a four-point Likert scale from "Yes, very often" to "No." A high score reflects minor to no feelings of loneliness and is thus a positive emotional health indicator. The single-item measure of global loneliness has shown a significant relationship with the UCLA Loneliness Scale, which is an indirect multi-item scale to measure loneliness (19).

Wellbeing composite score

To better compare results to other studies, we decided to use a wellbeing composite score, which is the mean of the self-esteem scale (the mean of the three items) and the three single-item scores for life satisfaction, body satisfaction, and loneliness.

Data analysis

Descriptive statistics and reliability coefficients were calculated in SPSS 25.0 (IBM Corp, Armonk, NY, USA). We used Cronbach's alpha and McDonald's omega (50) to examine the reliability of the psychometric subscales and combined scales. We considered values above 0.7 acceptable (51). For scales measuring psychological constructs with fewer than five items (i.e., self-esteem and mental health), values above 0.6 were considered acceptable (52). The values of all variables were normalized into a zero to one range to avoid high variation in the structural equation models (SEMs).

We used R studio and the lavaan packages (53) to perform an SEM with each of the aspects of wellbeing as the outcome and PL and SEP as the predictor and mediator, respectively (see the hypothesized model in Figure 1). We adjusted all models for age, and the models with the total sample were also adjusted for sex. We allowed all exogenous variables to covariate. To estimate missing values, we applied a maximum-likelihood estimation with robust standard error (MLR) values. Study variables were normally distributed (see Skewness and Kurtosis in Table 1). To inspect the model-fit indexes, we followed recommended cut-off criteria: the Tucker-Lewis index (TLI > 0.95), the comparative fit index (CFI > 0.95), and the root mean square error of approximation (RMSEA < 0.06) (54). Significance tests were two-tailed, and we considered P-values below 0.05 statistically significant. We only report standardized coefficients.

Results

Descriptive statistics

The sample size was 1,518, with 51.3% being girls and a mean age of 14 years. The mean scores, standard deviations, minimum, maximum, skewness, and kurtosis for all scales and variables are reported in Table 1.

Reliability

The internal consistency of the scales where evaluated with Cronbach's alpha and McDonald's omega (55) and are presented in Table 1. The reliability coefficients for the mental health and self-esteem scale were all above our minimum requirements. Reliability coefficients for the PL scale and the PL subscales were acceptable to good, except for the cognitive domain, where Ω-was below acceptable and α was almost zero.

Association between physical literacy, sports and exercise participation, and aspects of wellbeing

The unadjusted intercorrelations (Pearson's R or r) among all study variables are presented in Table 2. In the total sample, PL correlated with SEP ($r = 0.29$, $p < 0.001$) and with all

TABLE 1 Sample descriptive and scale reliability.

	Mean	SD	Min.	Max.	Skewness	Kurtosis	α	Ω
Competitive activities (7 items)	0.62	0.18	0.00	1.00	−0.28	−0.33	0.78	0.79
Playground activities (5 items)	0.55	0.18	0.00	1.00	−0.20	−0.19	0.68	0.68
Gymnastic-based activities (3 items)	0.48	0.27	0.00	1.00	0.14	−0.89	0.78	0.78
Water-based activities (3 items)	0.63	0.22	0.00	1.00	−0.39	−0.37	0.66	0.66
Cognitive domain (3 items)	0.75	0.23	0.00	1.00	−0.46	−0.45	0.06	0.54
Physical literacy (21 items)	0.60	0.12	0.13	0.92	−0.27	−0.09	0.84	0.73
SEP (hours/week)	5.26	3.49	0.00	19.00	1.03	0.82		
Life satisfaction (1 item)	0.73	0.17	0.00	1.00	−0.83	0.71		
Body satisfaction (1 item)	0.66	0.23	0.00	1.00	−0.58	0.17		
Loneliness (1 item)	0.85	0.22	0.00	1.00	−1.48	2.12		
Self-esteem (3 items)	0.72	0.20	0.00	1.00	−0.89	1.11	0.86	0.87
Wellbeing composite (6 items)	0.74	0.16	0.17	1.00	−0.83	0.66	0.75	0.76

Min, Minimum; Max, Maximum; SD, Standard deviation; α, Cronbach's alpha; *Ω*, Omega (ML).

wellbeing outcomes with r-values between 0.14 and 0.20. SEP correlated with wellbeing outcomes with r-values between 0.07 and 0.14.

SEMs were conducted for each wellbeing outcome—life-satisfaction, body satisfaction, loneliness, self-esteem, and the wellbeing composite score—and performed by total sample separately for boys and girls. The standardized regression coefficients (β), standard error (SE), and *p*-values for each of the models are presented in Table 3. The path from PL to SEP is included in all models. All models showed good fits (for all five models: CFI = 1.000, TLI = 1.000, and RMSEA = 0.000).

The SEMs showed that PL was significant and positively associated with SEP (β = 0.33, $p < 0.001$) and with all aspects of mental health. Table 3 and Figure 2 show information about path coefficients from the five structural equation models. We observed significant positive associations between PL and all wellbeing outcomes for the total sample: wellbeing composite score (β = 0.24, $p < 0.001$), self-esteem (β = 0.24, $p < 0.001$), life satisfaction (β = 0.19, $p < 0.001$), loneliness (β = 0.23, $p < 0.001$), and body satisfaction (β = 0.30, $p < 0.001$). We found that SEP was associated with all aspects of wellbeing except for self-esteem, and only partly and to a small extent mediated the association between PL and the wellbeing composite score (indirect effect: β = 0.03, $p < 0.001$), life-satisfaction (indirect effect: β = 0.04, $p < 0.001$), loneliness (indirect effect: β = 0.03, $p < 0.05$), and body-satisfaction (indirect effect: β = 0.03, $p < 0.05$).

Sex differences in the associations

The SEMs conducted separately for boys and girls showed that PL was found to be significantly associated with all wellbeing outcomes for both sexes, with β-coefficients ranging from 0.10 to 0.23 among boys and 0.27 to 0.36 among girls. In boys, SEP was associated with all wellbeing outcomes except self-esteem, with β-coefficients between 0.09 and 0.13. In girls, SEP only correlated with the wellbeing composite score (β = 0.10, $p < 0.05$) and life satisfaction (β = 0.14, $p < 0.01$).

We observed higher β-coefficients for the direct association between PL and wellbeing measures among girls compared to boys in all models (boys/girls)—wellbeing composite score: β = 0.16 / β = 0.31; life satisfaction: β = 0.10 / β = 0.29; loneliness: β = 0.16 / β = 0.29; body satisfaction: β = 0.23 / β = 0.36; and self-esteem: β = 0.16 / β = 0.33. Among boys, we observed a significant association between SEP and the wellbeing composite score (β = 0.09, $p = 0.011$), life satisfaction (β = 0.10, $p = 0.000$), loneliness (β = 0.10, $p = 0.050$), and body satisfaction (β = 0.13, $p = 0.014$) but no significant association with self-esteem. Among girls, SEP was significantly associated with the wellbeing composite score (β = 0.10, $p = 0.016$) and life satisfaction (β = 0.14, $p = 0.001$) but not with the other aspects.

Discussion

The results of this study indicate that PL is positively associated with SEP. In the total sample, we observed an association b between PL and SEP, with a β-value of 0.33. This finding is in accordance with previous studies of cross-sectional design. Choi et al. (39) observed an adjusted association between self-reported PL and self-reported time spent in physical activities among 1945 Chinese adolescents (12–18 years of age) with a β-value of 0.23 (39), Coyne et al. (56) observed an adjusted association between PL and pedometer measured physical activity among 1,000 Canadian children (8–12 years of age) with a β-value of 0.18 (56), Melby et al. (33) found an adjusted association between PL and accelerometer measured physical activity among 647 Danish children (7–13 years of

TABLE 2 Variable intercorrelation matrix (Pearson's R).

		1	2	3	4	5	6	7
1. Age								
2. Physical literacy		**−0.09**						
	Boys	−0.08*						
	Girls	**−0.11**						
3. SEP		0.03	**0.29**					
	Boys	0.06	**0.26**					
	Girls	0.00	**0.33**					
4. Life satisfaction		**−0.07**	**0.16**	**0.14**				
	Boys	−0.06	**0.11**	**0.11**				
	Girls	−0.09*	**0.23**	**0.16**				
5. Body satisfaction		−0.07*	**0.17**	**0.09**	**0.47**			
	Boys	−0.08*	**0.17**	**0.08***	**0.38**			
	Girls	−0.06	**0.20**	**0.08***	**0.50**			
6. Loneliness		**−0.07**	**0.14**	**0.07**	**0.46**	**0.31**		
	Boys	−0.08*	**0.12**	0.07	**0.42**	**0.21**		
	Girls	−0.07	**0.17**	0.07	**0.46**	**0.33**		
7. Self-esteem		−0.03	**0.15**	**0.09**	**0.49**	**0.53**	**0.41**	
	Boys	−0.03	**0.11**	0.04	**0.43**	**0.42**	**0.35**	
	Girls	−0.03	**0.21**	**0.11**	**0.51**	**0.58**	**0.42**	
8. Wellbeing composite		**−0.08**	**0.20**	**0.12**	**0.77**	**0.77**	**0.72**	**0.79**
	Boys	−0.09*	**0.18**	**0.10**	**0.74**	**0.70**	**0.70**	**0.76**
	Girls	−0.08*	**0.26**	**0.13**	**0.77**	**0.80**	**0.72**	**0.81**

Bold text indicates a p-value under 0.01; * indicates a p-value under 0.05.

age) with a β-value of 0.39 (33), Yli-Piipari et al. (57) found that physical literacy explained 29% of their overall physical activity participation among 450 Finnish 11-year-old children (57), and, in a sample of 2,879 Canadian children (8–12 years of age), Belanger et al. (58) found that children scoring above the recommended levels of PL had higher odds of meeting physical activity guidelines (58).

The results of this study indicate that PL is positively associated with important aspects of adolescent's wellbeing. In the total sample, we observed an association between PL and emotional and social wellbeing, with β-values ranging from 0.23 to 0.30. This result is in line with previous studies. A study by Jefferies et al. (59) found an unadjusted association between PL and resilience among 227 Canadian children (9–12 years of age) with a β-value of 0.21, a study by Caldwell et al. (60) observed a positive association between PL and health-related quality of life among 222 Canadian children (mean age 10.7 years), a study by Blain et al. (32) found an unadjusted associations between PL and positive and negative affect among 187 young adolescents (mean age 12.8 years) with β-values of −0.25 and 0.38 ($p < 0.05$), and a study by Melby et al. (33) found adjusted associations between PL and four aspects of wellbeing among 647 Danish children (7–13 years of age) with β-values of 0.21–0.38. However, only few studies have investigated the association between PL and wellbeing outcomes.

Stratifying the sample by sex, we observed more pronounced associations between PL and wellbeing among girls compared to boys, with approximately double-sized β-values. The transition into adolescence is a vulnerable period (25), and girls may be particularly vulnerable to developing mental health issues (1, 61). The strong relationship between PL and emotional and social wellbeing among girls is therefore noteworthy, as it indicates that PL could potentially mitigate or reduce mental health issues among adolescents, especially amongst girls.

To our knowledge, this is the first study to investigate sex differences in the association between PL and wellbeing. Previous studies have found sex differences in the associations between SEP and wellbeing, reporting that girls have greater benefits compared to boys, especially in team sports (62, 63). However, in this study, among girls, we only observed associations between SEP and loneliness and the wellbeing composite score, which means that, when including PL in the models, SEP's relation to adolescent girls' body satisfaction, loneliness, and self-esteem were not significant. Further, β-values of the associations between PL and wellbeing outcomes were greater than those of SEP and wellbeing. In sum, the results of this study indicate that PL is more important for adolescent

TABLE 3 Regression coefficients for the models with aspects of emotional mental health as outcomes.

	All			Boys			Girls		
Paths	**Std B**	**SE**	***P***	**Std B**	**SE**	***P***	**Std B**	**SE**	***P***
PL → Sport (all models)	0.33	0.03	0.000	0.32	0.04	0.000	0.34	0.04	0.000
1. Wellbeing composite score									
PL→ Wellbeing (direct)	0.24	0.03	0.000	0.16	0.05	0.000	0.31	0.05	0.000
Sport → Mental health	0.10	0.03	0.006	0.09	0.04	0.011	0.10	0.04	0.016
Indirect effect	0.03	0.01	0.001	0.03	0.01	0.013	0.03	0.02	0.020
Total effect	0.27	0.03	0.000	0.19	0.04	0.000	0.34	0.05	0.000
2. Life satisfaction									
PL→ Life satisfaction (direct)	0.19	0.04	0.000	0.10	0.05	0.042	0.27	0.06	0.000
Sport→ Life satisfaction	0.12	0.03	0.000	0.10	0.04	0.000	0.14	0.04	0.001
Indirect effect	0.04	0.01	0.000	0.03	0.01	0.020	0.05	0.02	0.003
Total effect	0.23	0.04	0.000	0.14	0.05	0.006	0.32	0.05	0.000
3. Loneliness									
PL→ Loneliness (direct)	0.23	0.05	0.000	0.16	0.07	0.022	0.29	0.08	0.000
Sport→ Loneliness	0.09	0.04	0.019	0.10	0.05	0.050	0.08	0.06	0.167
Indirect effect	0.03	0.01	0.021	0.03	0.02	0.053	0.03	0.02	0.170
Total effect	0.26	0.05	0.000	0.19	0.07	0.005	0.31	0.07	0.000
4. Body satisfaction									
PL→ Body satisfaction (direct)	0.30	0.05	0.000	0.23	0.07	0.000	0.36	0.08	0.000
Sport→ Body satisfaction	0.10	0.04	0.014	0.13	0.05	0.014	0.08	0.06	0.224
Indirect effect	0.03	0.01	0.015	0.04	0.02	0.016	0.03	0.02	0.227
Total effect	0.33	0.05	0.000	0.27	0.06	0.000	0.39	0.07	0.000
5. Self-esteem									
PL→ Self-esteem (direct)	0.24	0.05	0.000	0.16	0.07	0.015	0.32	0.07	0.000
Sport→ Self-esteem	0.07	0.04	0.071	0.04	0.05	0.423	0.10	0.06	0.093
Indirect effect	0.02	0.01	0.075	0.01	0.02	0.427	0.03	0.02	0.101
Total effect	0.26	0.04	0.000	0.17	0.06	0.006	0.35	0.06	0.000

Standardized regression coefficient (Std B), standard error (SE), and p-values for structural equation models with aspects of emotional mental health as the outcomes. Controlled for age and sex.

girls' emotional and social wellbeing than SEP. Among boys, SEP was associated with all aspects of wellbeing except self-esteem, and the β-values of the associations between PL and the wellbeing outcomes were similar (i.e., equal or a little higher) to those of SEP and wellbeing. These findings suggest that both PL and SEP are important for adolescent boys' emotional and social wellbeing.

The minimal or non-significant indirect effects of SEP on the association between PL and wellbeing demonstrate that PL is more relevant to adolescent's wellbeing than SEP. Since previous studies have found positive associations between SEP and emotional wellbeing (64–66), we wonder if the type of sport or exercise contributes to whether or not participation impacts wellbeing positively, as demonstrated in other studies that have shown that traditional team sports have a higher impact on wellbeing outcomes compared to self-organized exercise or individual sports (62, 63). This could also explain why we observed a stronger relationship between SEP and wellbeing among boys compared to girls, as boys more commonly engage in team sports, while girls engage more commonly in self-organized exercise (41). This could also explain why previous studies observed mixed findings, such as the study of Caldwell et al. (60), that found no mediating effect of accelerometer-measured physical activity on the association of PL and health-related quality of life (60) and the study of Melby et al. (33) that found a mediating effect of physical activity in the relationship between PL and one out of five investigated aspects of wellbeing (33).

The observed positive associations between PL and wellbeing could also be understood and explained through the lens of self-determination theory (34). Higher PL increases the possibility that one's basic psychological needs are satisfied in terms of experiencing competence during SEP and, accordingly, wellbeing in the activity (67). Similarly, an individual with low PL will be more likely to experience competence frustration, which will accordingly have a negative effect on their sense of wellbeing in the activity (68, 69). According to basic psychological needs theory, which has been formulated

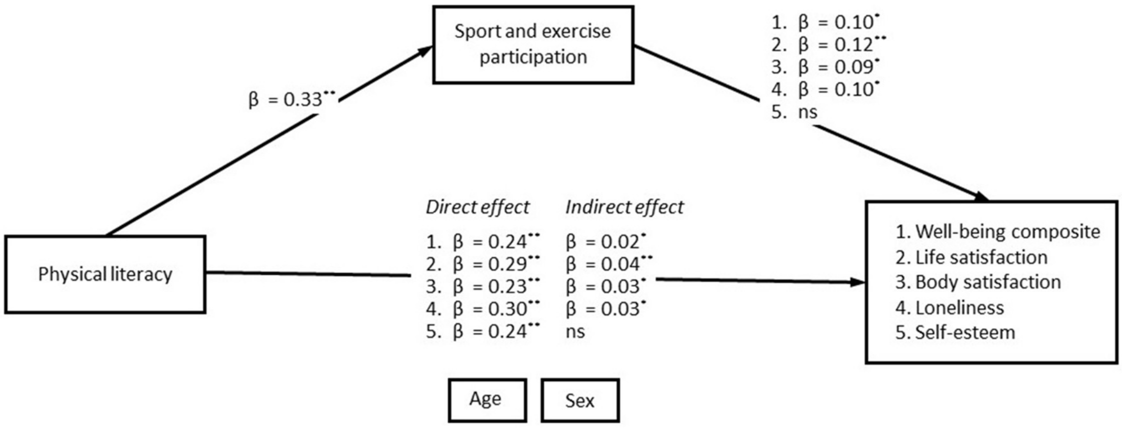

FIGURE 2
Path coefficients of the significant mediation analysis. This figure shows path coefficients of the adjusted structural equation models with aspects of wellbeing as the outcomes. All the shown parameters (β) are standardized and statistically significant. Covariation between all exogenous variables was allowed. **indicates a *p*-value under 0.01; *indicates a *p*-value under 0.05; ns, non-significant association.

and supported in self-determination theory research, only engagement in SEP that fosters need satisfaction will positively impact overall wellbeing. Thus, SEP's impact on wellbeing strongly depends on how the SEP is delivered. This might explain why sport-based interventions exhibit mixed effects on mental health (70). One study found that the association between levels of physical activity and overall wellbeing in children was mediated by their perception of the three basic psychological needs (autonomy, competence, and relatedness) in physical activity environments (71). This result supports our theoretical assumption, outlined in the background section—namely, that wellbeing in contexts of physical activity (i.e., experiencing satisfaction of basic psychological needs) can transfer to other contexts and, ultimately, to the global level (35, 36).

Collectively, the results from this study suggest that it is critical to identify how SEP and physical activities are delivered in a way that fosters wellbeing. In this regard, supported by the observed positive association between PL and mental health in this study, it is useful to take a PL pedagogical perspective, supported by principles of the basic psychological need satisfaction, when delivering sport- or physical-activity-based interventions to increase adolescents' emotional and social wellbeing. Emerging evidence on interventions, driven by the theory of PL and aimed at increasing participation in physical activities in children up to young adulthood, has shown promise in this regard (72–74).

Implications for practice, policy, and research

First, this study contributes to the limited evidence on the association between PL and health, supporting the assumption that PL is important for adolescents' participation in physical activities and their wellbeing. Secondly, the finding that PL has a more significant effect than SEP suggests that focus should be directed away from the current narrow focus on increasing the amount and intensity of physical activity here and now. Instead, the focus should be on supporting the development of the prerequisites for physical activity participation, i.e., the elements of PL. This so-called PL perspective seems to be more advantageous for long-term physical and mental health, including a lifelong engagement in physical activities. Those working with the physical activity of children and adolescents (e.g., physical education teachers, sport coaches, parents, and school principals) should consider how to support the development of PL by considering all of its elements and should accordingly avoid hindering one or more of these said elements. One way to achieve this is to provide appropriate challenges and demand that matches the level of participants' competence to enable experiences of need satisfaction (i.e., the need for competence), resulting in a sense of mastery and contextual wellbeing and hence autonomous motivation and confidence. Creating a task-solving/-learning environment for physical activity contexts—instead of a result-oriented or competitive environment has shown to be an effective way to this and has also shown to be beneficial for the participants' contextual wellbeing and autonomous motivation, as well as the coaches/teachers' facility of a social learning climate with a high degree of autonomy (75, 76).

Policy makers should consider including a PL perspective in addition to national guidelines on physical activity so that they contain recommendations on how best to foster the PL elements of motivation, confidence, physical competences, and knowledge and understanding that enables children and adolescents to engage in physical activities.

Strength and limitations

A clear strength of this study was its use of a large and randomly recruited sample. It was not possible to check for representability in terms of socio-economic status in the sample of 7–15-year olds, or control for socio-economic status, which should be considered a limitation, as most health problems follow a social gradient (77, 78).

The single-item indicators of three of the aspects of wellbeing (life satisfaction, body satisfaction, and loneliness) reduced the reliability of these latent measures compared to multi-item measures. However, some of these measures have been used in similar samples and have been validated against commonly used multiple-item scales (19). Nevertheless, using the five different aspects of wellbeing added valuable information to the investigated relationships.

There was a limitation connected to the self-reported measures of this study. First, SEP was measured with a single item that prompted for the frequency of generic SEP. Secondly, self-reported measures of children's and adolescents' physical activities, such as SEP, may be considered less reliable compared to objective measures (e.g., accelerometery). Thirdly, PL was measured with a newly developed 21-item questionnaire, the MyPL questionnaire, which assessed motivation, confidence, and physical competences connected to various disciplines and contexts. The self-assessment of one's physical competences should especially be considered a limitation compared to studies using more objective direct measures/tests. On the other hand, we consider physical-activity-environment-specific prompting in the MyPL questionnaire a strength, as it deals with challenges connected to generically asking about motivation and confidence, making it further in line with the theory of PL (30).

The main limitation was the cross-sectional design, which presented vagueness about the direction of the investigated associations and put a restrain on making claims about causality. Future research should investigate the associations between PL, physical activity/SEP, and wellbeing using longitudinal and experimental designs and control for socioeconomic status.

Conclusion

This study expands on the scarce evidence on PL's association with health. The study brings novel knowledge on the association between adolescents' PL, SEP, and emotional and social wellbeing and the mediating role of SEP in the association between PL and wellbeing. In accordance with our hypothesis, we found that PL was positively associated with SEP and all investigated aspects of emotional and social wellbeing. We found stronger associations between PL and emotional and social wellbeing among girls compared to boys, indicating that PL is particularly beneficial for adolescent girls' wellbeing. We found mixed results on the mediating role of SEP in the association between PL and the five aspects of emotional and social wellbeing. Results from this study indicate that PL likely contribute to adolescents' emotional and social wellbeing beyond its association with SEP. Implications of these results suggest focussing on supporting children's and adolescents' prerequisites for physical activity participation (i.e., the elements of PL), instead of the narrow focus on cumulative physical activity (i.e., amount and intensity).

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: The dataset has been submitted to the National Archives with the serial number: FD.50354.

Ethics statement

According to a recent Danish legislation of The Danish Data Protection Agency, it is no longer required to collect consent and register the research project to the data review Centre, when the objectives of the research is in society's interest (i.e., to improve society) (79). Thus, this survey did not need to apply or register for ethical approval at the Center of data review. All procedures and handling of data were carried out based on this legislation.

Author contributions

The study was conceptualized and manuscript was drafted by PM, PE, PB, and GN. Data management were conducted by PM and PE. All authors revised and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Barriers to adequate nutrition care for child malnutrition in a low-resource setting: Perspectives of health care providers

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Introduction: Several studies in developing countries found that more need-based training is required for health care providers (HCPs) in child malnutrition management.

Methods: An exploratory cross-sectional study was conducted to explore barriers to providing adequate nutrition care as perceived by the healthcare providers (HCPs) in the child malnutrition clinic at a Children's University Hospital in Egypt. Participants were selected using the purposive sampling technique. Five out of seven HCPs in the clinic were included (two male physicians, one female physician, and two female nurses). Qualitative data were collected through in-depth interviews. The interview guide consisted of semi-structured open-ended questions. Quantitative data were the resulting scores from the scoring system used to assess the understandability and actionability of the patient education materials (PEMs) that are available in the clinic. The Patient Education Materials Assessment Tool for Printable Materials (PEMAT-P) for the scoring. Statistical analysis: The thematic content analysis technique was employed for qualitative data. The percent score was generated for the PEM actionability and understandability for quantitative data.

Results: Most common child malnutrition conditions encountered by HCPs were nutritional deficiencies. Barriers to the delivery of adequate nutrition care to children were physician-centered: limited nutrition education in the medical school, health system-centered: an insufficient number of HCPs, lack of nutritional supplements, lack of patient education materials (PEMs) that suit the characteristics of the served community, lack of updated standard of practice (SOP) and guidelines, inadequate nutrition training of HCPs, and insufficient time for each patient, and caregivers-centered: the low socioeconomic status and false cultural, nutritional beliefs.

Conclusion: There are different barriers to adequate nutrition care for child malnutrition in low-resource healthcare settings. Mainly nutritional deficiencies. Most of the barriers were health system-related in the form of insufficient resources (shortage of workforce; concerning the high caseload, nutritional supplements, and PEMs) and inadequate management of resources (lack of skill-based training, lack of updated SOP and guidelines, and lack of properly designed PEMs that facilitate communication with the target caregivers).

KEYWORDS

malnutrition, low-resource healthcare settings, skill-based training, updated standard of practice, guidelines, nutritional supplements, patient education materials

Introduction

Malnutrition during infancy and childhood may lead to impaired growth, delayed and improper social and cognitive development, low academic achievement, and later in life, reduced productivity (1).

Globally, malnutrition is still a significant cause of death and disease among children, especially those under 5 years (U5Y) of age. Undernutrition type of malnutrition is associated with 45% of child deaths.[1] Most of those deaths take place in low- and middle-income countries that also have rising rates of childhood obesity (see text footnote 1).[2] In 2020, 38.9 million children U5Y of age were overweight worldwide, 45.4 million were wasted, and 149.2 million were stunted (see text footnote 2). Stunting, which is defined by the World Health Organization (WHO) as a height that is more than two standard deviations below the median child's growth standards, is largely irreversible[3] and associated with extremely high health and economic costs[4] (2). Stunting is the impact of chronic malnutrition afflicting the child during the first 1,000 days of life. The number of stunted children is declining in all world regions except Africa (see text footnote 4).

Children's nutritional status is a powerful and sensitive indicator for assessing child health, food security, and the need to improve economic, environmental, and health policies (see text footnote 1). Although Egypt has achieved remarkable progress in child health in the past two decades, the country's U5Y child mortality rate in 2013 was below the Millennium Development Goal (MDG) 44 (see text footnote 4), (2) and far below Sustainable Development Goal (SDG) 2 (3)[5]. The prevalence of child malnutrition in Egypt is predominantly high, with 11% of infants born with a low birth weightweight (see text footnote 2), and 9.5% of children U5Y of age are underweight, which is higher than the average for Africa (6.0%), and 22% are stunted, which is the largest prevalence of stunting in the Middle East (see text footnote 4), (2, 3). Furthermore, stunted growth is a public health problem that has persisted in Egypt for a long time, as reported in EDHS 2014 (percent of stunted U5Y children was reported as 23, 23, 29, and 22% in the years 2000, 2005, 2008, and 2014, respectively) (3).

Educating the caregivers of children has been proven in many studies to not only increase their knowledge but also improve the health outcomes of these children (4–6). A systematic review to explore factors associated with successful nutrition education interventions for children showed that engaging parents through face-to-face education and identification of specific child's or parent's behaviors that needed to be modified were fundamental factors (7). Thus, the role of health care providers (HCPs) in educating caregivers is crucial to overcoming child malnutrition (8). Several studies in developing countries found that there is a need for more in-service, need-based, and skill-based training of HCPs involved in child malnutrition management.

The main objective of the present study was to explore barriers to providing adequate nutrition care services in the child malnutrition clinic to inform future service delivery strategies for managing child malnutrition, particularly in low-resource healthcare settings.

Materials and methods

Design and context of the study

The current study is a clinic-based exploratory cross-sectional study that used a qualitative approach. The study was conducted in the Center of Social and Preventive Medicine (CSPM) Malnutrition Clinic, Faculty of Medicine, Cairo University, Egypt, among HCPs (physicians and nurses) of the clinic.

The study was performed in accordance with the Consolidated Criteria for Reporting Qualitative Research CORE-Q (9).

Sampling technique and sample size

Participants were selected *via* a purposive sampling technique (10). The interviews were continued until they reached data saturation, where no new themes, subthemes, or explanations emerged from the interviews (11). ***Eligibility criteria*** were any HCPs (physicians and nurses) working in the CSPM malnutrition clinic during the study duration who were willing to participate. Out of seven HCPs, participants were five HCPs (two male physicians, one female physician, and two female nurses) because no new data were added starting from the third interview and

1 Available online at: https://www.who.int/news-room/fact.sheets/detail/malnutrition (accessed June 2, 2021).

2 Available online at: https://www.who.int/publications/i/item/9789240025257 (accessed September 12, 2021).

3 Available online at: https://www.who.int/publications/i/item/WHO-NMH-NHD-14.3 (accessed December 20, 2021).

4 *UNICEF Report*. (2021). Available online at: https://www.who.int/publications/i/item/9789240025257 (accessed December 20, 2021).

5 Available online at: https://egypt.un.org/en/sdgs/2 (accessed May 21, 2022).

saturation was achieved at the fifth interview. The interviewed physicians graduated between 1995 and 2001, and the interviewed nurses graduated in 1985 and 1990. One physician was a general practitioner; the other two were continuing their postgraduate studies in family medicine and pediatrics, respectively. The median number of working years mentioned by the HCPs was 6 years, ranging from 8 to 20 years.

Data types and collection tools

Qualitative data were collected through in-depth, audiotaped face-to-face interviews (each lasting up to 45 min) conducted by one of the researchers, who has experience conducting interviews and has worked on many qualitative studies. The interview guide (Appendix 1), which was pilot-tested beforehand, consisted of semi-structured, open-ended questions. The interview guide was developed following systematic literature reviews (3, 4, 6, 8, 12). A trained note-taker assisted the investigator in recording the sessions using a voice recorder and written notes. ***Quantitative data*** were the scoring system results used to assess the understandability and actionability of the educational leaflets distributed to caregivers by HCPs. For scoring, researchers used the Patient Education Materials Assessment Tool for Printable Materials (PEMAT-P) (13). The tool provides two scores for each material: a score for understandability and a separate score for actionability. The researchers scored the education material on each item of the material content, excluding the non-applicable (NA) items. Each item was given either 1 point (agree) or 0 points (disagree) (Tables 1A, B). First, the total points for the material items were summed up to calculate the score. Then, the sum was divided by the total possible points: the number of items on which the material was rated, excluding the items classified as NA. After that, the result was divided by 100 to get a percentage (%). This percentage score is the understandability score or the actionability score of the material on the PEMAT; the more understandable or actionable the material, the higher the score (13).

Statistical analysis

For qualitative data

Data processing was based on the thematic content analysis technique (14, 15), which aims to get descriptions of the message content using a systematic and objective procedure. The thematic analysis is a three-stage analysis. The *first stage* involves understanding the idea through comprehensive and repeated readings of the data transcripts. *The second stage* is material exploration, which involves selecting the participants' statements and organizing them into categories (themes). *The third stage* deals with the processing and interpretation of results. The participants' quotations were used to clarify the meaning of the themes and summaries. Two investigators carried out the analysis. They read the transcript multiple times, made meaningful statements, and created themes and sub-themes.

For quantitative data

The PEMAT-P tool provides two scores for each material: a score for understandability and a separate score for actionability.

TABLE 1A Assessment of printed patient education materials provided to caregivers in CSPM (using PEMAT-P): understandability.

Health education items: Response options (rating): Agree: 1 Disagree: 0	Rating
Contents	
1. The material makes its purpose completely evident.	0
2. The material does not include information or content that distracts from its purpose	1
Word choice and style	
3. The material uses common everyday language.	0
4. Medical terms are used only to familiarize the audience with the terms and are defined if used.	1
5. The material uses the active voice.	0
Use of numbers	
6. Numbers appearing in the material are clear and easy to understand. (If no number = NA)	1
7. The material does not expect the user to perform calculations.	1
Organization	
8. The material breaks or "chunks" information into short sections. (Very short material = NA)	1
9. The material's sections have informative headers (very short material = NA)	1
10. The material presents information in a logical sequence.	1
11. The material provides a summary. (Very short material = NA)	0
Layout and design	
12. The material uses visual cues (e.g., arrows, boxes, bullets, bold, larger font, highlighting) to draw attention to key points.	NA
Use of visual aids	
13. The material uses visual aids whenever they could make content more easily understood (e.g., illustration of healthy portion size).	0
14. The material's visual aids reinforce rather than distract from the content. (No visual aids =NA)	NA
15. The material's visual aids have clear titles or captions. (No visual aids = NA)	NA
16. The material uses illustrations and photographs that are clear and uncluttered (No visual aids = NA)	NA
17. The material uses simple tables with short and clear row and column headings. (No Tables = NA)	0
Total points = 17; Total possible points = 13; Total achieved points = 7 Understandability score= 7/13= 54%	

The researchers scored the education material on each item of the material content, excluding the non-applicable (NA) items. Each item was given either 1 point (agree) or 0 points (disagree) (Tables 1A, B). First, the total points for the material items were summed up to calculate the score. Then, the sum was divided by the total possible points: the number of items on which the material was rated, excluding the items classified as NA. After that, the result was divided by 100 to get a percentage (%). This percentage score is the understandability score or the actionability score of the material on the PEMAT; the more understandable or actionable the material, the higher the score (13).

TABLE 1B Assessment of printed patient education materials provided to caregivers in CSPM (using PEMAT-P): actionability.

Health education items: Response options (rating): Agree: 1 Disagree: 0	Rating
1. The material clearly identifies at least one action the user can take.	1
2. The material addresses the user directly when describing actions.	0
3. The material breaks down any action into manageable, explicit steps	0
4. The material provides a tangible tool (e.g., menu planners, checklists) whenever it could help the user take action.	1
5. The material provides simple instructions or examples of how to perform calculations. (No calculations = NA)	NA
6. The material explains how to use charts, graphs, tables, or diagrams to take action. (No charts, graphs, tables, or diagrams = NA)	NA
7. The material uses visual aids as much as possible rendering it easier to act on the instructions.	0
Total points = 7; Total possible points = 5; Total achieved points = 2 Actionability score = 2/5 = 40%	

Ethical considerations

The study protocol was revised and approved by the Medical Research Committee in the Public Health and Community Medicine Department. All the study participants were treated according to the Helsinki Declaration of biomedical ethics (16). Written informed consent from each participant was obtained after proper orientation regarding the study objectives. Data confidentiality and informant privacy were upheld throughout the whole study. For each participant, we used "I" (interviewee) followed by a number per the chronological order of the interviews (I01, I02, I03..., etc.). The necessary municipal and federal authorities approved the study to be carried out. Using the voice recorder was authorized, and transcriptions of the recordings were performed.

Results

Qualitative data analysis results

By analyzing the qualitative data derived from the interviews, the researchers came up with the following themes:

- Views of HCPs toward malnutrition problems

HCPs mentioned that *"**the most frequent malnutrition problems that come to seeking medical advice were rickets, parasitism, underweight, kwashiorkor, and failure to thrive.**"*

Physicians mentioned that *"**laboratory investigation was the best method to assess the nutritional status.**"*

To improve the child's nutritional status, all HCPs confirmed the importance of *"**nutrition education, counseling, and provision of supplements such as iron and vitamin D**"* during infancy.

- Barriers to providing nutrition care to children

HCPs affirmed that there are three types of barriers that restrict providing quality medical nutrition care.

Physician-centered barriers

- Limited opportunities for applied/clinical nutrition education in medical schools

Physicians mentioned that *"**limited nutrition education in medical school and even in postgraduate studies (namely master's degree)**"* is the major challenge for gaining an adequate medical knowledge. Physicians said that "***they learned the biochemistry of nutrition but not the basic nutrition knowledge needed to share with the patients.***" They expressed dissatisfaction with their medical school education "***We believe that we are ill-qualified to provide nutrition advice in the clinical setting.***"

Furthermore, physicians explained that the nutrition course they received was not applicable to patients. As a result, they were not prepared to counsel caregivers. Some HCPs felt their clinical rotations did not prepare them for the prevention or management of childhood malnutrition from the nutritional aspect due to the limited experience of tutors in clinical nutrition.

Health system-centered barriers

These include barriers related to the resources and process components of the health system.

- Inadequate capacity building of HCPs in the workplace

Physicians expressed their views of inadequate nutrition training programs for physicians: *"**Training prepared us inadequately for work in low-resource settings.**" One* physician delineated his participation in training programs at the Faculty of Medicine, Cairo University. He said the first hospital training course started in June 2009 and included six sessions taught over 1 week. The training approach included theoretical educational sessions, practical training, demonstration exercises, group-based exercises, and case studies about breastfeeding. Another HCP received a nutrition course at the Ministry of Health in 2004, including four sessions taught over 2 days about growth monitoring. However, all respondents affirmed that they do not have access to regular refresher courses to reinforce their learning, provide practice demonstrations, and keep them up to date. In addition, they identified specific areas that are not satisfactorily covered in their nutrition education: nutrition counseling, infant and young children feeding, breastfeeding, and nutritional treatment of micronutrient deficiencies.

HCPs mentioned that training is significantly **infrequent**; that they hadn't received any nutrition care training in the past year. The most recent source of information they had about the contemporary infant feeding issues was the patients' handouts from the National Nutrition Institute. The only topic in which HCPs received training was exclusive breast feeding (EBF) where physicians and nurses have had similar exposure to training. Nurses attended more training than physicians. However, there is a rapid turnover of physicians and nurses, which makes such training needed continuously.

- Insufficient time to provide quality nutrition care

Physicians ascertained that they could not provide quality nutrition counseling in the CSPM malnutrition clinic due to the **high caseload** for the **small number of physicians and nurses**. Thus, they do not have enough time for growth monitoring or caregiver education on EBF, infant nutrition, sick children's nutrition, and pregnant women's nutrition. In addition, they added that there are too many patients per day, patient contact time is roughly 20–25 min long, and there are around 40 patients every day, except on Saturdays, on which there are even more patients.

Three HCPs said local women are always interested in hearing them talk and demonstrate rather than watching or reading visual materials independently. HCPs explained that with so little time spent with patients in the clinic, nutrition counseling is quite challenging. One physician said, "***In my opinion, there are relatively few things that doctors can do to help set up the malnutrition clinic because malnutrition is a complex problem that necessitates behavioral intervention. However, there is not enough time for that***," *and* "***Physicians focus on immediate medical concerns instead of the more long-term concern of childhood nutrition.***"

- Shortage in the workforce and lack of motivation

HCPs cited a shortage in staffing as a barrier to meeting their clients health and nutrition needs. They all mentioned, "***There has been no new recruitment of residents and nurses, no incentives or support in recognition of our hard work.***" On the other hand, the low salary (1200 LE per month), insufficient opportunities for financial growth, and the lack of professional advancement increased the turnover rate of the already-appointed residents. Temporary contracts were used to hire all new doctors. The consensus among HCPs was that "***There is a need for more service providers.***"

- Shortage in logistics and supplies

HCPs demarcated the scarcity of **visual PEM**, **resources for demonstrations** for nurses regarding infant feeding, especially breastfeeding charts, posters (particularly those showing local foods in food groups and demonstrating proper hygienic practices), information leaflets, booklets, and picture information cards. In general, the availability of PEM for caregivers was suboptimal for all areas of child health except for child feeding starting at 6 months up to 9 years of age.

Weighing scales (for babies and pregnant women), stature measuring boards (for length and height), oral rehydration solution (ORS), and infant formula milk for infants in particular categories (6–24 months) were available. However, **nutritional supplements** such as iron, zinc, folic acid, and vitamin A were suboptimal and coupled with a marked shortage of **PEM addressing micronutrient deficiencies**.

There were no CSPM-**specific guidelines** or national **protocols** for the nutritional management of malnourished children. Only educational and instructional leaflets from the National Nutrition Institute for complementary feeding are available.

Caregivers-centered barriers

- Low socioeconomic status (SES)

HCPs recognize that "***childhood malnutrition is a complicated problem influenced by numerous factors.***" This concept makes HCPs understand that there are barriers facing caregivers face in trying to comply with nutritional advice. The most obvious barrier is the low SES status with subsequent limited access to healthy food and inability to recall the detailed medical advice provided.

Physicians mentioned that caregivers usually have limited nutrition knowledge, preventing them from selecting and preparing healthy complementary food. One HCP said, "***Many parents who are unaware of what is and is not healthy for their children.***"

- Culture and context:

Recognizing that people had prior **specific cultural or traditionally-rooted beliefs is critical**. This included the belief that breastfeeding after getting pregnant could cause kwashiorkor in the breastfed child. The potential conflict between health workers' counseling and cultural beliefs and perceptions is more general, extending beyond nutrition issues, and has been well known.

Suggestions of HCPs to improve performance in the malnutrition clinic

- Updating knowledge by continuing medical education (CME)

HCPs demanded more nutrition education, saying it could be provided through periodic rotations and seminars. One physician said, "***We are provided periodic lectures on asthma; why we do not have lectures on nutritional therapy for malnutrition? Not only to teach us about malnutrition epidemiology, but to show us some of the techniques and resources we could need in the future, as well as to instruct us on how to deal with patients in the real world.***"

One physician said, "***To help parents improve their infants' nutrition, doctors must be aware of the specific advice they can give the caregivers regarding their infants' feeding—what, when, and how to feed***." HCPs expressed a need for specific hints on preparing healthy food that could be shared with patients. HCPs stated that they required evidence-based nutrition expertise in addition to patient-friendly information. They valued recommendations based on scientific literature.

HCPs mentioned the most needed topics to emphasize in education: "breastfeeding, complementary feeding for 6- to 24-month-old children, counseling skills, and communication skills."

They recommended getting continuous support and training through nutrition seminars and the introduction of software programs on nutrition counseling to facilitate and ensure proper quality performance of HCPs in malnutrition management, such as history taking, diagnosis, and nutrition education and counseling, including standardization of the nutrition counseling process. In addition, the curriculum of undergraduate training for medical and nursing students should include applied nutrition.

- Counseling skills

HCPs affirmed the need for "***more capacity-building in nutrition counseling***" as practical training on counseling caregivers is crucial for learning by doing.

Four out of five interviewees believed that physicians and nurses have the greatest need to understand nutrition education, communication, and counseling because they are in direct contact with the target groups for nutrition care (mothers and children). In Egypt, the public and patients usually seek nutritional advice and counseling from physicians, who often lack nutrition knowledge.

Regarding service delivery, there was a consensus that CSPM clinics needed to be strengthened by providing them with the required staffing for nutrition care services, nutrition training facilities (e.g., a working nutrition kitchen), and PEM to support both preventive and curative nutrition care. HCPs expressed a willingness to provide quality services if the necessary resources were made available and the issue of a large caseload was addressed. They also suggested increasing the availability of dieticians in childcare clinics, including malnutrition clinics.

Counseling was a challenging demand as counselors, on the one hand, try to simplify messages to make them easily understandable, and simultaneously provide mothers with sufficient information to make informed choices.

- Guidelines for efficient and effective nutrition care service

Guidelines must be developed on values that match the SES and culture of the clients. Disregarding those aspects have numerous and severe drawbacks, including infeasibility/inapplicability of the medical recommendations, confusion among both mothers and HCPs, and harmful feeding practices with diets that are inadequate for meeting the nutritional needs of the children.

Quantitative data analysis results

The PEM provided to the caregivers at the malnutrition clinic was assessed using the PEMAT-P scoring tool regarding the understandability and actionability of the material.

The PEM had an understandability score of 54% and an actionability score of 40%, respectively (Tables 1A, B).

Discussion

The current study explores the barriers to providing adequate nutrition care to children as perceived by the workforce (HCPs) at the CSPM malnutrition clinic which exists in a law-resource setting (i.e., has minimal budget allocations and serves a low-SES community). Although this clinic is logistically, financially, and legally affiliated with the MOH, it is located at the Children's Hospital of the Faculty of Medicine, Cairo University. It is considered a reference center to which cases diagnosed as malnutrition are referred from the hospital clinics. The CSPM malnutrition clinic is considered a model center for managing children's malnutrition using nutritional supplements and nutrition education to caregivers. Therefore, the conduction of the current study was crucial to help in decision-making for improving performance in the CSPM malnutrition clinic.

The study delineated that the most frequent malnutrition problems encountered in the studied clinic were nutritional deficiencies, namely rickets, underweight, kwashiorkor, and failure to thrive. This finding is consistent with the existing evidence in Egypt as per the Egypt Demographic and Health Survey (EDHS) and other local studies (12). The evidence also demonstrates that the significant factors, namely poverty, low maternal education level, and lack of health and nutrition awareness among parents, contributing to the high prevalence of such nutritional problems are related to the low SES of children caregivers (3, 17).

The study revealed the barriers to providing adequate nutrition care in three broad themes: physician-centered, health system-centered, and caregiver-centered.

The physician-centered barriers included limited education in clinical nutrition, mainly applied practical tactics, in medical school during both the undergraduate and postgraduate programs. HCPs perceived this barrier as the primary barrier. Many studies assessing the situation of nutrition education in medical schools have reported both undergraduate and postgraduate nutrition curricula as insufficient with a limited capacity of learners to identify cases of malnutrition or provide nutrition education for patients (18–20). However, other studies suggested that there is no need for more nutrition education in medical schools. The only requirement is to train future medical professionals to understand the role of nutrition in health and to encourage them to refer patients for nutrition counseling with a registered nutritionist or registered dietitian who is more qualified to provide dietary advice due to their greater education, training, and experience (21). Nevertheless, physicians who lack the necessary nutrition training could postpone making the initial diagnosis of malnutrition cases with the subsequent delay in the referral of cases to nutritionists or dieticians (7, 22).

The WHO defined the health system as all organizations, people, and actions whose primary purpose is to promote, restore, and maintain health (23). Therefore, as with any system, health system components are resources (workforce, finances, technology, and information, including updated standard of practice (SOP) and guidelines, process (the way of resource management), and output (range of provided services, e.g., how many of the clients are covered with services).[6] In our study, health system-centered barriers are related to the resources and process components of the health system.

There was a workforce shortage due to insufficient HCPs regarding the high caseload. Hence, it was not only the lack of or inadequate skills of HCPs that hindered the provision of adequate nutrition counseling but also the insufficient time available for each patient. Individual needs should be considered when developing and communicating nutrition advice (24). Accordingly, a full assessment and understanding of the patient's psychosocial needs require roughly 15 min longer than simply comprehending the patient's initial complaint (22, 25). With the limited time concerning the high caseload, it is impossible to set aside that time for a needs analysis or dietary counseling.

6 Available online at: https://healthmanager.ie/2011/03/the-differences-between-outputs-and-outcomes/ (accessed September 20, 2021).

Our findings also revealed the failure of the CSPM administration to recruit more HCPs, retain the competent HCPs, or upgrade the nutrition-related knowledge and service delivery skills of the existing HCPs, e.g., through providing updated SOP or guidelines and conducting periodic skill-based training. This situation led HCPs to try gaining updated information, infrequently and irregularly, from another healthcare institute, such as the National Nutrition Institute (NNI) at Cairo University.

In addition, HCPs complained of a lack of motivation due to the absence of appropriate incentives. Although some studies found that financial incentives did not cause long term behavior changes among physicians (26), yet, several other studies affirmed that the financial and otherwise incentives influence the behavior of HCPs in various ways, including adjustments to their output volume and effectiveness, as well as the type and standard of services they provide to clients (27, 28).

Nutritional supplementation with adequate nutrition education is an evidence-based essential package of nutrition interventions, particularly in low SES communities. To be effective, this package should be delivered during key life stages, such as during pregnancy and throughout childhood (29, 30). Hence, the lack of health technology and supplies such as nutritional supplements and PEM was viewed by the HCPs as a significant barrier to delivering adequate nutrition care. Moreover, the quality of the existing PEM was described by the HCPs as inadequate. This was also confirmed by the low PEM understandability and actionability scores (50 and 40%, respectively) which were far below the lowest recommended level (70%) necessary for patients to understand or act on the information they receive from the material (13). This is expected because the communication section of the MOH, which produces these PEMs, does not pre-test most of the health education materials or update the channels of conveying them. For instance, short educational videos that convey important health messages in a simple and practical form are not available at all at the CSPM.

Similar health system-centered barriers were stated by physicians in several studies, such as the pivotal study conducted by Kushner in 1995 and another study conducted 15 years later (31, 32). Those studies found that the most significant barriers to providing quality nutrition service were the lack of incentives and time followed by the lack of updated knowledge. However, in our study, HCPs first stated the lack of updated knowledge and refreshing training. This may be because Egypt's health sector workforce policy permits HCPs to work in both the public and private health sectors, allowing HCPs to operate their private clinics and increase their income.

Unfortunately, the insufficient resource component of the health system is a commonly encountered barrier in many countries (8, 31, 32) because healthcare funds are skewed mainly toward treatment, with little funds directed toward nutrition education programs or malnutrition prevention in general (33, 34). However, the insufficient resources barrier in child nutrition care is more encountered in low-and-middle-income countries and usually negatively impacts children under five the most. This is unlike in higher-income countries where children who are negatively impacted in nutrition care are those older than 5 years of age, usually hospitalized, with the barriers related mainly to the process component of the health system (35). Economic growth has been widely considered an effective tool for mitigating poverty and improving public health (4, 33, 36). In Egypt, even though the total health expenditure- as an absolute number- is increasing, the total health expenditure as a percentage of the gross domestic product is declining. Also, the Egyptian healthcare market is mainly based on out-of-pocket payments (the expenses for healthcare that are not reimbursed by insurance) (5, 8, 37). Thus, considering the progressively declining SES of the Egyptian population, the Egyptian healthcare system, specifically the preventive sector, whose budget is the primary source of funds allocated for child nutritional care in the public sector, is facing extreme financial challenges (5, 38). Cost-effectiveness (determining the expected gains and cost per gain) is central to the health system's success. Therefore, health system resources should be directed to health services after making cost-effective analyses to decide on proper resource allocation, e.g., allocating resources for nutrition care technology, such as nutritional supplements, and specific community groups (39, 40).

Implications

The study focused on a significant public health problem in Egypt and most developing and underdeveloped countries, childhood malnutrition. This study tackled a crucial issue related to the crucial role of pediatric clinical nutrition services in overcoming such a problem. As well, the study provided valuable insight into barriers to providing adequate nutrition care to children. The identified barriers are essential when considering quality improvement of nutrition care practices for malnourished children.

Strengths

First; the study was conducted in a model malnutrition clinic in a Children's Hospital, presenting a prototypical solution to overcome children's malnutrition problems and their impact on growth and development. Second; the study was of a qualitative research nature and thus provided an in-depth understanding of barriers hindering the provision of adequate clinical nutrition services and counseling. Third; using a specific approach for testing the PEM added another dimension to the study, as it raised the importance of capacity building in designing and testing the PEM. And fourthly; the clinical nutrition concept was raised in the study for specific pediatric clinics. The same concept could be applied to other medical clinics.

Limitations

From our view, limitations of the study include that the study was conducted in one center, the only reference center for managing malnourished children. Additionally, as with any exploratory operations research, information derived from the study could not be generalized. However, the methodology used in the study could be generalized to be used in different medical settings. Furthermore, the views of the clients (caregivers) were not examined as it was beyond the scope of this study. Those views may have led to more understating of nutrition services' quality and barriers to adequate service. However, surprisingly, previous studies, such as one conducted in Bangladesh, showed that caregivers' satisfaction was above average despite the low quality of child nutritional services (27). The low expectations of the caregivers in the low SES communities could explain this. Similarly, a relatively high level of satisfaction could have been shown in this study for the same reason and because there are not many pediatric nutrition care clinics serving this district, making this clinic a unique one-of-a-kind center.

Recommendations

To overcome barriers to providing adequate care in malnutrition clinics, there are multifaceted approaches directed to upgrading the resources and process components of the health system as follows: **Medical schools are encouraged to** integrate clinical nutrition in the pediatrics curriculum of undergraduate and postgraduate medical students and nursing students. Also, the specialty of clinical nutrition should be introduced into the masters and doctorate degrees and clinical nutrition training agenda should be included in the continuous medical education program to improve nutrition-related knowledge, counseling skills, and capacity building in designing and testing health education materials. Furthermore, marketing for the unique health and nutrition services provided to children in the nutrition clinics motivates HCPs to work in such clinics and encourages decision-makers to improve resources, especially regarding nutritional supplements, to such clinics. Regarding **MOH, we recommend the establishment of** pediatric clinical nutrition fellowship programs, introducing clinical nutrition clinics in the primary health care facilities and hospitals, increasing the production and availability of nutritional supplements, particularly for children's most common nutritional deficiency problems, and producing adequately designed and tested PEMs that suit the sociodemographic characteristics of the served communities.

Conclusion

There are different barriers to adequate nutrition care for child malnutrition in low-resource healthcare settings. Mainly nutritional deficiencies. Most of the barriers were health system-related in the form of insufficient resources (shortage of workforce; concerning the high caseload, nutritional supplements, and PEMs) and inadequate management of resources (lack of skill-based training, lack of updated SOP and guidelines, and lack of properly designed PEMs that facilitate communication with the target caregivers).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Faculty of Medicine, Cairo University (N-139-2022). The patients/participants provided their written informed consent to participate in this study.

Author contributions

GE has made substantial contributions to the conception and design, analysis and interpretation of data, and writing the manuscript. MS has made substantial contributions to the acquisition of data and writing the manuscript. AT, SH, EA, and SI were involved in drafting the manuscript (Sections Methods and Results) and revising it carefully for important intellectual content and statistical analysis. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1064837/full#supplementary-material

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Correlation of fundamental movement skills with health-related fitness elements in children and adolescents: A systematic review

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Objective: To examine the correlations between fundamental movement skills and health-related fitness elements (cardiopulmonary function, flexibility, body composition, muscle strength and endurance) in children and adolescents and investigate the evaluation methods and tools of fundamental movement skills and health-related fitness.

Methods: Six electronic databases (Web of Science, PubMed, ProQuest, Scopus, EBSCO and CNKI) were searched, and the research literature on the correlation between children's and adolescents' fundamental movement skills and health-related fitness published since 2002 was collected. The guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and the Consolidated Standards of Reporting Trials (CONSORT) statement were used to evaluate the quality of the literature, and the sources, samples, measurement methods, main results and statistical data of the study were analyzed, summarized and discussed.

Results: After applying the inclusion and exclusion criteria, 49 studies were included. There were 13 tools for evaluating fundamental movement skills and 4 tools for evaluating comprehensive health-related fitness in the included literature. Sufficient research evidence supports a significant positive correlation between fundamental movement skills and cardiopulmonary function (10, 100%) and muscle strength and endurance (12, 100%), and most studies support the positive correlation between fundamental movement skills and flexibility (4, 66.7%), and the significant negative correlation between fundamental movement skills and body composition (29, 67.4%). Studies used skinfold, AF%, BF%, FM, and FFMI as evaluation methods. They showed a consistently significant negative correlation between body composition and fundamental movement skills (9, 100%), while BMI or waist circumference as evaluation methods showed no consistent significant negative correlation result (20, 58.8%). Moreover, in the sub-item evaluation of fundamental movement skills, object manipulation, locomotor and balance skills were all significantly and positively correlated with cardiopulmonary function and muscle strength and endurance. In contrast, locomotor skills were more closely related to body composition than object manipulation skills.

Conclusion: A significant correlation exists between children's and adolescents' fundamental movement skills and health-related fitness elements.

KEYWORDS

fundamental movement skills, flexibility, body composition, muscle strength and endurance, cardiopulmonary function, health-related fitness

1. Introduction

Fundamental movement skills are the basis for more advanced and highly specific sports activities and are considered the "building blocks" of more advanced, complex movements required to participate in sports, games, or other context-specific physical activities (1, 2). Previous studies have confirmed that fundamental movement skills are associated with children's physical, cognitive, and social development and provide the basis for a positive and healthy lifestyle (3, 4). However, the relationship between fundamental movement skills and physical health in the current study has yet to be well documented, and whether fundamental movement skills improve the individual's physical health level needs a more detailed discussion.

Health-related fitness is closely related to health outcomes and health indicators (5), which has been defined by the President's Council on Physical Fitness as consisting of those specific elements of physical fitness that have a relationship with good health, including body composition, cardiopulmonary fitness (cardiopulmonary function), and musculoskeletal fitness (flexibility, muscle strength, and endurance) (6, 7). Evaluating health-related fitness elements can provide data that help formulate exercise prescriptions and establish reasonable and achievable fitness goals to motivate participants. Therefore, exploring the correlations between health-related fitness elements and fundamental movement skills will help us understand the role of fundamental movement skills in promoting physical health.

However, only a few studies have reviewed the association between fundamental movement skills and health-related fitness. In a review of fundamental movement skills and the health benefits of children and adolescents, Lubans et al. (8) found that fundamental movement skills were positively correlated with cardiopulmonary fitness (4 out of 4 studies) and negatively correlated with body weight (6 out of 9 studies). Nevertheless, the relationship between fundamental movement skills and musculoskeletal fitness has not been discussed due to the lack of relevant research at that time. In 2016, Cattuzzoa et al. (9) reviewed the association between motor competence and health-related fitness elements. They reported a positive association between motor competence and cardiorespiratory fitness and musculoskeletal fitness and an inverse association between body weight status. However, the motor competence mentioned in this review study cannot be equated with fundamental movement skills. Motor competence is a person's ability to execute different motor acts (10), including fundamental movement skills and motor coordination (11). Fundamental movement skills are often described more precisely as basic stability, object control and locomotor movements (2, 12, 13), while motor coordination is a general term that encompasses various aspects of movement competency (14), and needs the coordination of complex neural networks (15). Moreover, there are differences in the evaluation contents of motor competence and fundamental movement skills. Therefore, Cattuzzoa et al. (9) conclusion cannot be used to correlate fundamental movement skills and health-related fitness elements.

This review aims to systematically examine the correlations between fundamental movement skills and health-related fitness elements, investigate the evaluation methods and tools of fundamental movement skills and health-related fitness, and provide a scientific basis for theoretical and practical research on fundamental movement skills and health-related fitness.

2. Methods

2.1. Search of the literature

A structured electronic literature search was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (16). The search included six electronic databases (Web of Science, PubMed, ProQuest, Scopus, EBSCO, and CNKI). The retrieval was "[Title/Abstract] = ('Fundamental Movement Skills' OR 'Motor skill') AND [Title/Abstract] = ('health related fitness' OR 'health benefits' OR 'body composition' OR 'body mass index' OR 'weight' OR 'fat percentage' OR 'cardiorespiratory fitness' OR 'cardiopulmonary function' OR 'musculoskeletal fitness' OR 'muscle strength' OR 'muscle endurance' OR 'flexibility'). The search was conducted from January 1, 2000, to November 23, 2022, and only literature in English and Chinese published in peer-reviewed journals was considered.

Two researchers independently screened and reviewed the literature and jointly determined the final article list. If inconsistent screening results occurred, a third researcher was asked to decide.

2.2. Eligibility criteria

A PECO (population, exposure, comparison and outcome) approach (17) was used as inclusion criteria: (a) Population: participants were 3–16 years old and were in preschool education or school; (b) Exposure: fundamental movement skills, including comprehensive fundamental movement skills or subitems (locomotor, object manipulation, and balance skills); (c) Comparison: health-related fitness elements (cardiopulmonary function, muscle strength and endurance, flexibility, and body composition); (d) Outcome: report or data that makes it possible to estimate associations.

The exclusion criteria were as follows: (a) research articles on special groups, such as cardiovascular disease, developmental coordination disorders, mental disorders, etc.; (b) intervention study (literature on fundamental movement skills and health-related fitness association with an experimental intervention); (c) study sample of fewer than 50 people; (d) no cross-sectional data of fundamental movement skills and health-related fitness; (e) non-English or non-Chinese literature.

2.3. Data extraction and quality evaluation

The data extraction form retrieved the following information: first author and publication time, test method, health-related fitness elements, study design type, participant, and statistical method. Two researchers independently completed the data extraction, followed by discussion and cross-checking to ensure consistency and accuracy.

The literature quality was assessed using the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (18) and the Consolidated Standards of Reporting Trials (CONSORT) statement (19), based on Lubans et al. (8) and Cattuzzoa et al. (9). The quality score for each study was based on six questions: (1) Did the study describe the participant eligibility criteria? (2) Were the participants randomly selected (or for the experimental studies, was the randomization process clearly described and adequately carried out)? (3) Did the study report the sources and details of the FMS assessment, and did the instruments have acceptable reliability for the specific age group? (4) Did the study report the sources and details of the assessment of potential benefits, and did all the methods have acceptable reliability? (5) Did the study report a power calculation, and was the study adequately powered to detect the hypothesized relationships? (6) Did the study report the numbers of individuals who completed each of the different measures, and did participants complete at least 80% of the FMS and benefit measures? The above questions were scored as 0 (missing or underdescribed) or 1 (clear description and presence), and the scores for all questions were combined. Studies scoring 0–2 were considered low-quality studies, studies scoring 3–4 were classified as medium-quality, and 5–6 were classified as high-quality.

3. Results

3.1. Basic information about the literature

Figure 1 shows the study selection flow chart. A total of 49 articles met the eligibility criteria. These articles all had cross-sectional data, including 44 cross-sectional studies, four longitudinal studies, and one long-term trend study. These articles were published from January 2002 to November 2022. There were 42 English studies and 7 Chinese studies. Eight of the studies were conducted in the UK, eight in China, six in the US, five in Australia, five in Iran, four in Finland, four in Ireland, two in Croatia, and one each in Canada, Slovenia, Brazil, Italy, the Czech Republic, South Korea and South Africa. The study participants ranged from 50 (20) to 6,917 (21). Details are given in Table 1.

3.2. Quality evaluation of the research literature

The authors had a 94% consensus on the study assessment criteria and reached a complete consensus after discussion. Twenty-eight studies were identified as high-quality, 21 were rated as moderate-quality, and none were classified as low-quality. Most studies used valid and reliable measures of fundamental movement skills assessment. All studies reported reliable data on their potential benefits, methods for valid calculations, and whether the study had sufficient evidence to support the hypothesis relationship.

3.3. Fundamental movement skills assessment tools

The literature included 13 fundamental movement skill assessment tools, as shown in Table 2. Because the research topics were limited to fundamental movement skills, the literature using Koperkoordination-Test fur Kinder (KTK) (81) and Bruininks-Oseretsky Test of Motor Proficiency (BOTMP & BOT-2) (82), mainly used to test motor coordination and fine motor skills, was omitted.

The included studies have differences in the selection of fundamental movement skills evaluation tools. Thirty-five studies (71.5%) used process assessment, including 20 studies that used TGMD-2 as a single test, one used TGMD, 7 used POC, 3 used the Fundamental motor skills Assessment, two used OSU-SIGMA, 1 used PDMS-2, and one used Passport for Life and PLAYbasic. Eight (16.3%) studies used outcome assessments, 2 used the PE metric, 3 used the Move!, 1 study used POLYGON, and 2 used MABC-2. Six (12.2%) studies used a combination of process and outcome assessment, 5 of which used the TGMD-3 assessment tool, and 1 used the TGMD-2 and POLYGON.

3.4. Health-related fitness assessment tools

Among the included literature, there were 4 tools for comprehensive evaluation of health-related fitness, including the health-related fitness test battery for children and adolescents (ALPHA), FitnessGram assessment (FitnessGram), Monitoring system for physical functional capacity (Move!) and National Physical Fitness Test Standards Manual-Preschool part (NPFTSM-Preschool).

ALPHA was published by Ruiz et al. (83) based on assessment methodology for physical activity levels in the European Member States. Testing included a 20-meter shuttle run, grip strength, standing long jump, body mass index, skinfold thickness and waist circumference.

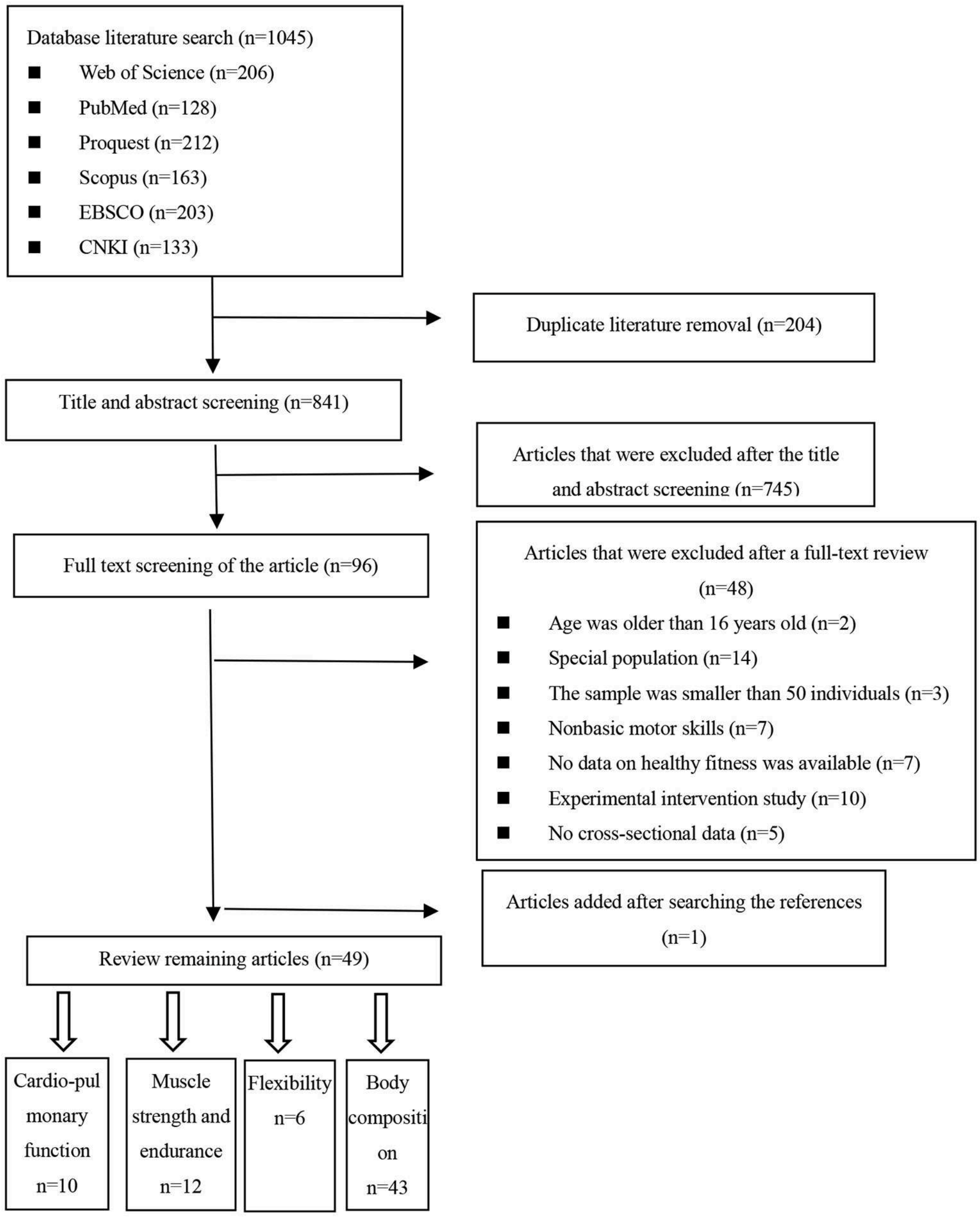

FIGURE 1
Flow chart of the literature review process.

FitnessGram is now the educational assessment of the Presidential Youth Fitness Program (84). The test items include pull-ups for boys/modified pull-ups for girls, straight leg sit-ups, shuttle run, standing broad (long) jump, 50-yd dash, and softball throw for distance, 600-yd run/walk, and three aquatic tests that are rarely used.

Move! is a national physical functional capacity monitoring and feedback system for Finnish 5th and 8th-grade pupils (80). Move! consists of eight sections of measurements that provide information about the state of physical functional capacity. The sections measure pupils' endurance, strength, speed, mobility, balance, and fundamental movement skills. The specific items are the 20-meter line run, five continuous jumps, upper body lift, push-up, body mobility, squat, lower back extension, right and left shoulders, and a throw-catch combination.

NPFTSM-Preschool (85) was promulgated by the Ministry of Education of the People's Republic of China in 2003. The test content included morphometric measures, a 10-meter return run, standing long jump, tennis throwing, continuous jump, sit and reach, and walking on the balance beam.

In addition to the above tools, some studies selected different evaluation tools for comprehensive utilization; for example, Behan et al. (23) adopted BMI and waist circumference, sit and reach, grip strength (86), plank (87), a 20 m sprint run (88) as health-related fitness assessment content.

TABLE 1 Summary of the included literature.

Order	References	Date	FMS test method	Health-related fitness test method	Health-related fitness elements	Type of study	Sample	Statistical methods
1	Aalizadeh et al. (22)	2013	TGMD-2	BMI	BC	C	241 (age 7–10)	Pearson correlation, multiple linear regressions
2	Behan et al. (23)	2022	TGMD-3, vertical jump, balance	BMI, WC, grip strength, plank, sit and reach, PACER,	BC, CVE, MF, Flex	C	2,098 (age 5–12)	MANCOVA
3	Bolger et al. (24)	2019	TGMD-2	BMI, WC, 550-meter walk/run	BC, CVE	C	296 (mean age 7.9 ± 2.0)	Pearson correlation
4	Bryant et al. (25)	2014	POC	BMI	BC	C	281 (age 6–11)	MANOVA
5	Bryant et al. (26)	2014	POC	BMI, BF%	BC	L	T1: 281 (mean age 8.9 ± 1.4); T2: 252 (mean age 9.8 ± 1.4)	Multiple linear regression
6	Butterfield et al. (27)	2002	TGMD	BMI	BC	C	65 (age 5–8)	Multiple linear regressions
7	Chen et al. (28)	2016	PE metrics	FitnessGram assessment	CVE, MF, Flex	C	565 (age 9–10)	Multiple linear regressions
8	Comeau et al. (29)	2017	Passport for Life, PLAYbasic	BMI, grip strength, PACER, BF%	BC, CVE, MF	C	145 (age 9–12)	Pearson correlation, Multiple linear regressions
9	Duncan et al. (30)	2017	POC	BMI, BF%	BC	C	248 (age 6–11)	MANCOVA
10	Duncan et al. (31)	2021	TGMD-2	BMI	BC	L	T1: 177 (mean age 4.0 ± 0.7); T2: 91 (mean age 5.0 ± 0.7)	Multiple linear regressions
11	Foulkes et al. (32)	2021	TGMD-2	BMI	BC	L	T1: 240 (mean age 4.5 ± 0.6); T2: 181 (mean age 10 ± 0.6)	Linear regression
12	Franjko et al. (33)	2012	TGMD-2, POLYGON	BMI, BF%	BC	C	73 (Grade 2)	Pearson's correlation
13	Gu et al. (34)	2021	PE Metrics	FitnessGram assessment, BMI	BC, CVE, MF	C	342 (mean age 8.4 ± 0.50)	Pearson correlation
14	Hardy et al. (21)	2012	POC	PACER, BMI	BC, CVE	C	6,917 (age 7–14)	Odds ratios (ORs)
15	Hua et al. (35)	2017	TGMD-2	BMI	BC	C	240 (age 7–10)	One-way ANOVA
16	Huan et al. (36)	2019	TGMD-3	NPFTSM-Preschool	MF, Flex	C	646 (age 3–6)	Canonical correlation coefficient
17	Hume et al. (37)	2008	Fundamental motor skills Assessment	BMI	BC	C	248 (age 9–12)	Pearson correlation
18	Huotari et al. (38)	2018	Move!	BMI	BC	S	T1: 2,390 (grade 9); T2: 1,346 (grade 9)	General linear model
19	Jaakkola et al. (39)	2019	Move!	PACER, curl-up test, push-up	CVE, MF	L	491; T1: mean age 11.26; T2: mean age 12.26	The standardized parameter estimates of the multigroup model

(Continued)

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TABLE 1 (Continued)

Order	References	Date	FMS test method	Health-related fitness test method	Health-related fitness elements	Type of study	Sample	Statistical methods
20	Jarvis et al. (40)	2018	POC	ALPHA, 20-meter sprint	BC, CVE, MF	C	$n = 553$ (age 9–12)	Zero order correlations
21	Jing et al. (41)	2019	TGMD-2	NPFTSM-Preschool	MF	C	498 (age 3–5)	Partial correlation and multiple regressions
22	Joensuu et al. (42)	2018	Move!	FMI, FFMI	BC	C	$n = 594$ (mean age 12.4 ± 1.3)	Unstandardized regression coefficients
23	Jones et al. (43)	2010	POC	BMI	BC	C	1,414 (age 9–11)	One-way ANOVA
24	Kelly et al. (44)	2019	TGMD-3	BMI	BC	C	$n = 414$ (age 6–12)	Independent samples t-tests
25	Kemp et al. (45)	2013	TGMD-2	Skinfolds, WC, BMI	BC	C	816 (mean age 6.87 ± 0.39)	One-way ANOVA
26	Khalaj and Amri (46)	2013	TGMD-2	BMI	BC	C	160 (age 4–8)	One-way ANOVA
27	Kim and Lee (47)	2016	TGMD-2	BMI	BC	C	216 (age 5–6)	Pearson correlation
28	Marinsek et al. (48)	2019	Eight FMS	BMI	BC	C	$n = 322$ (age 5–10)	MANCOVA
29	Morano et al. (49)	2011	TGMD-2	BMI	BC	C	80 (mean age 4.5 ± 0.5)	One-way ANOVA
30	Musalek et al. (50)	2017	MABC-2	Skinfolds, BMI	BC	C	152 (age 3–6)	Variance ANOVA
31	Nervik et al. (19)	2011	PDMS-2	BMI	BC	C	50 (age 3–5)	Pearson correlation, multiple regressions
32	Okely et al. (51)	2004	Fundamental motor skills Assessment	BMI, WC	BC	C	4,363 (grades 2, 4, 6, 8, 10)	Multiple linear regressions
33	Poulsen et al. (52)	2011	TGMD-2	BMI	BC	C	116 (mean age 8.6 ± 1.4)	Multiple linear regressions
34	Rainer and Jarvis (53)	2019	POC	ALPHA	BC, CVE, MF	C	307 (age 10–11)	Pearson product-moment correlation
35	Roberts et al. (54)	2012	MABC-2	BMI	BC	C	4,650 (age 4–6)	One-way ANOVA
36	Roscoe et al. (55)	2019	TGMD-2	BMI	BC	C	185 (age 3–4)	Univariate ANOVA
37	Shengkou et al. (56)	2015	TGMD-2	NPFTSM-Preschool, BMI	BC	C	289 (age 3–6)	Correlation analysis
38	Siahkouhian et al. (57)	2011	TGMD-2	BMI	BC	C	200 (age 7–8)	Pearson correlation
39	Slotte et al. (58)	2015	TGMD-2	BF%, AF%, WC, BMI	BC	C	304 (age 8)	Spearman's correlations
40	Spessato et al. (59)	2012	TGMD-2	BMI	BC	C	178 (age 4–7)	Multiple regression
41	Vameghi et al. (60)	2013	OSU-SIGMA	BMI	BC	C	400 (age 4–6)	Multiple regression
42	Vameghi et al. (61)	2013	OSU-SIGMA	BMI	BC	C	600 (age 3–6)	Kendall's tau-b test
43	Webster et al. (62)	2021	TGMD-2	BMI, BF%, FMI, FFMI	BC	C	244 (mean age 6.05 ± 2.01)	Multiple linear regressions
44	Wesley et al. (63)	2016	TGMD-2	BMI	BC	C	85 (mean age 12.7 ± 0.4)	Multiple linear regressions
45	Yameng et al. (64)	2019	TGMD-3	NPFTSM-Preschool, BMI	MF, Flex, BC	C	201 (age 3–5)	One-way ANOVA

(Continued)

TABLE 1 (Continued)

Order	References	Date	FMS test method	Health-related fitness test method	Health-related fitness elements	Type of study	Sample	Statistical methods
46	Yang et al. (65)	2015	TGMD-2	BMI	BC	C	1,200 (age 3–7)	One-way ANOVA
47	Yanmin et al. (66)	2021	TGMD-3	NPFTSM-Preschool	MF, Flex	C	304 (age 3–6)	Partial and bivariate correlation, multiple regressions
48	Yuanchun et al. (67)	2013	TGMD-2	BMI	BC	C	852 (age 6–9)	One-way ANOVA, Kendall's tau-b test
49	Zuvela and Kezic Krstulovic (68)	2016	POLYGON	standing long jump, sit and reach, 1/4-Mile	MF, CVE, Flex	C	90 (age 8)	Multiple linear regressions

FMS, fundamental movement skills; TGMD, test of gross motor development; POC, get-skilled get-active process-oriented checklists; POLYGON, a new fundamental movement skills test for 8-year-old children; PE metrics, physical education metrics elementary assessments; Move!, monitoring system for physical functional capacity; MABC, movement assessment battery for children-second edition; PDMS, peabody developmental motor scales; OSU-SIGMA, the Ohio State University scale of intra gross motor assessment; BMI, body mass index; WC, waist circumference; PACER, progressive aerobic cardiovascular endurance run; BF%, body fat percentage; FitnessGram Assessment, Presidential Youth Fitness Program assessment; ALPHA, the health-related fitness test battery for children and adolescents; NPFTSM-Preschool, National Physical Fitness Test Standards Manual-Preschool part; AF%, abdominal fat percentage; FMI, fat mass index; FFMI, fat-free mass index; BC, body composition; CVE, cardiopulmonary function; MF, muscle strength and endurance; Flex, flexibility; C, cross-sectional study; L, longitudinal study; S, secular trend study;T1, the first measurement; T2, the second measurement; MANCOVA, multivariate analysis of covariance; ANOVA, analysis of variance.

Moreover, health-related fitness assessment can be an overall assessment of all elements, and it can also be an assessment of only one element. In evaluating sub-elements of health-related fitness, various tools have been used in the included studies.

The cardiopulmonary function was assessed by the PACER (Progressive Aerobic Cardiovascular Endurance Run), 550 m walking and running test (89) or long-distance running (68, 89, 90).

The musculoskeletal function was evaluated by two groups, muscle strength and endurance, and flexibility. Methods to assess muscle strength and endurance included grip strength, curl-ups, push-ups, plank, and standing long jump. Furthermore, methods to assess flexibility included sit and reach and trunk lifting.

Body composition assessment methods were body mass index (BMI), waist circumference (WC), skinfold thickness, body fat percentage (BF%), abdominal fat percentage (AF%), fat mass index (FMI), and fat-free mass index (FFMI).

3.5. Correlation between fundamental movement skills and cardiopulmonary function

A total of 10 articles (19, 23, 24, 28, 29, 34, 39, 40, 53, 68) have studied the correlation between fundamental movement skills and cardiopulmonary function, and all the findings showed a significant positive association between fundamental movement skills and cardiopulmonary function.

Among the subitems of fundamental movement skills, five studies (19, 23, 29, 34, 39) showed a significant correlation between locomotor skills and cardiopulmonary function, six studies (19, 23, 28, 29, 34, 39) showed a significant correlation between object manipulation skills and cardiopulmonary function, and three studies (19, 29, 39) showed a significant association between balance skills and cardiopulmonary function. Thus, there is strong evidence for a positive association between the total and subitems of fundamental movement skills and cardiopulmonary function.

3.6. Correlation between fundamental movement skills and muscle strength and endurance

A total of 12 studies (23, 28, 29, 34, 36, 39–41, 53, 64, 66, 68) were included that evaluated the correlation between fundamental movement skills and muscle strength and endurance. These studies found a significant positive correlation between total fundamental movement skills and muscle strength and endurance.

Regarding the subitems of fundamental movement skills, seven studies (23, 29, 34, 36, 39, 64, 66) showed a positive correlation between locomotor skills and muscle strength and endurance, eight studies (23, 28, 29, 34, 36, 39, 64, 66) showed a significant correlation of object manipulation skills with muscle strength and endurance, and three studies (34, 40, 68) showed a significant correlation between balance skills and muscle strength and endurance. All studies supported the conclusion that the total and subitems of fundamental movement skills were significantly positively correlated with muscle strength and endurance.

TABLE 2 List of fundamental movement skill evaluation tools.

Evaluation tools	Full name	Publisher, date	Applicable age
TGMD	Test of gross motor development	Ulrich (69)	3–10
TGMD-2	Test of Gross Motor Development-2	Ulrich (70)	3–10
TGMD-3	Test of Gross Motor Development-3	Ulrich (71)	3–10
POC	Get-skilled Get-active process-oriented checklists	Bibby (72)	3–12
Fundamental motor skills assessment	Fundamental motor skills assessment: A manual for classroom teachers	Walkley et al. (73)	3–10
POLYGON	A new fundamental movement skills test for 8-year-old children	Zuvela et al. (74)	8
OSU-SIGMA	The Ohio State University scale of intra gross motor assessment	Loovis and Ersing (75)	2.5–14
MABC-2	Movement assessment battery for children-2	Henderson and Sugden (10)	3–16
PE metrics	Physical education metrics elementary assessments	Dyson et al. (76)	3–18
PLAYbasic	The physical literacy assessment for youth	Kriellaars (77)	7–12
Passport for life	Passport for life assessment	Physical & Health Education Canada (78)	8–12
PDMS-2	Peabody developmental motor scales 2nd edition	Folio and Fewell (79)	0–6
Move!	Monitoring system for physical functional capacity	The Finnish National Ministry of Education and Culture (80)	7–18

3.7. Correlation between fundamental movement skills and flexibility

Six studies examined the correlation between fundamental movement skills and flexibility. Four studies (23, 28, 36, 66) showed a significant correlation between fundamental movement skills and flexibility, and 2 showed no significant correlation (29, 64).

Moreover, as to the subitems of fundamental movement skills, one study showed that locomotor skills were significantly associated with flexibility, but the correlations between object manipulation skills and flexibility were not significant (66). Another study (23) found that three subitem skills in the 9–10 age group and the flexibility association were significant; however, in the 11–12 age group, locomotor, and balance skills were still significant, while object manipulation skills were no longer significant. These results indicate that the evidence of the relationship between the total and subitems of fundamental movement skills and flexibility is uncertain.

3.8. Correlation between fundamental movement skills and body composition

Forty-three studies examined the correlation between fundamental movement skills and body composition. Twenty-nine studies showed a significant association of overall fundamental movement skills with body composition, and 14 showed no significant association with body composition. Of the 29 significantly related studies, 18 studies used BMI alone as an assessment, four studies (26, 29, 31, 33) used BMI and BF, two studies (24, 53) used BMI and waist circumference, one study (50) used BMI and skinfold thickness, one study (45) used BMI, waist circumference and skinfold thickness, 1 used BF%, AF%, BMI, and waist circumference (58), 1 used FMI and FFM (42), and 1 used BF%, BMI, FMI, and FFMI (62). Of the 14 studies showing no significant association with body composition, 13 studies (19, 22, 27, 35, 37, 40, 47, 53, 55, 56, 59, 64, 67) used BMI as a single body composition assessment method, and one article (24) used both waist circumference and BMI. Overall, studies that used skinfold, AF%, BF%, FM, and FFMI as evaluation methods obtained consistently significant negative correlation results, while in studies that used BMI or waist circumference as evaluation criteria, there was no consistent significant correlation result.

Furthermore, as to the subitems of fundamental movement skills, three studies (23, 29, 39) showed a consistent inverse correlation of balance skills with body composition. Meanwhile, locomotor skills and body composition reflected a more significant correlation than object manipulation skills. Six studies (34, 35, 45, 54, 57, 62) showed that object manipulation skills were not associated with body composition, while locomotor skills were significantly associated with body composition. Therefore, there is evidence that the relationship between locomotor skills and body composition is closer than that of object manipulation skills.

4. Discussion

The main objective of this review was to explore the correlation between fundamental movement skills and health-related fitness elements in children and adolescents. We found strong evidence from cross-sectional study results that the children's and adolescents' fundamental movement skills and cardiopulmonary function, muscle strength and endurance had a significant positive correlation. These results complement the need for correlation analysis between fundamental movement skills and musculoskeletal function by Lubans et al. (8) and also make up for the lack of specific correlation analysis between fundamental movement skills and health-related fitness in Cattuzzoa et al. (9).

The positive correlation between fundamental movement skills and cardiopulmonary function may be related to the role of fundamental movement skills in promoting physical activity. Previous studies have proven that fundamental movement skills are associated with moderate- to high-intensity physical activity (4, 24, 25, 29). Bolger et al. (24) believed that people with higher fundamental movement skills are more likely to participate in organized physical activities, which will allow them to obtain more guidance on basic athletic skills from coaches and promote the improvement of their physical activity intensity.

As for the positive correlation between fundamental movement skills and muscle strength and endurance, this may be because fundamental movement skills contribute to the maturation of skeletal and neuromuscular. Freitas et al. (91) believed that individual differences in fundamental movement skills interact with the habits of play and physical activities, as well as with the maturation of children's bones and neuromuscular. Stodden et al. (92) also noted that fundamental movement skills require the generation and decay of physical strength, which is related to the strength of the muscle itself and the neural function related to muscle movement.

The negative correlation of fundamental movement skills with body composition has been confirmed in most studies but has yet to obtain consistent results, which may be related to how body composition is assessed. Using BMI and waist circumference as evaluation criteria did not obtain consistent correlation results, while studies with skinfold, BF%, AF%, FM, FM, and FFMI as evaluation results showed consistent negative correlation results. Previous studies have also found that BMI and waist circumference are proxy measures and should not be considered accurate measures of total body or abdominal fat (26, 93, 94). In assessing body composition, it is crucial to assess weight status using more accurate methods than BMI alone to obtain more precise evidence.

A possible reason for the negative correlation of fundamental movement skills with body composition is that an increased amount of body fat hinders the performance of fundamental movement skills (9), which may affect the control of posture. Marinsek et al. (50) found that overweight boys did not lean slightly forwards during running compared with non-overweight boys, did not bend their hips and knees during dribbling, and did not side to the target during single-handed hitting. From the perspective of postural control, strengthening the proficiency of motor skills or increasing the muscle strength of body control can reduce the adverse effects of body weight. Based on this, when teaching exercises to obese students, more attention should be given to the exercise of movement and posture control, such as strengthening the muscles and training fundamental movements.

Most studies support a significant positive correlation between fundamental movement skills and flexibility, but the association of fundamental movement skills with flexibility still needs further study. Indeed, developing flexibility is very important for adolescent health, but there is insufficient evidence that flexibility is directly related to individual health status (90), which could be related to the limitations of flexibility assessment. Flexibility mainly reflects the stretching and elasticity of the joints, ligaments and muscles. Excessive tension or relaxation can affect the performance of movement skills (95). Studies have found that children with low exercise ability have heterogeneous fitness characteristics, and an extreme range of flexibility and inflexibility can be observed in these children (9). However, the current commonly used flexibility assessment method (sit and reach) cannot detect a lack of function due to muscle relaxation. Of the studies on flexibility assessment included in this review, one used trunk lifting to assess flexibility (28), which showed that fundamental movement skills were significantly associated with flexibility. However, the use of trunk lifting has a specific need for trunk muscle strength and endurance, and there is a lack of validated methods for evaluating the flexibility of children and the elderly (90). Overall, an appropriate level of flexibility has positive implications for motor skill development and physical health, but exploring scientific and reasonable methods of flexibility assessment should receive more attention.

In addition, this study found some similarities and differences in the correlations between the fundamental movement skills sub-item (locomotor, object manipulation and balance skills) and health-related fitness elements. Locomotor, object manipulation and balance skills with cardiopulmonary function, muscle strength and endurance presented consistent positive correlations, while locomotor and object manipulation skills were associated differently with body composition. Six studies showed that object manipulation skills were not associated with body composition, while locomotor skills were significantly associated with body composition; this is quite different from the conclusions of some previous studies, in which object manipulation skills were given great attention. Barnett et al. (96) noted that the relationship between object manipulation skills and physical activity is seen as a "positive feedback loop" and that those with better object manipulation skills may be more willing to participate in activities involving these skills. Vlahov et al. (97) also found that object manipulation skills in a prospective study of preschool children were better predictors of health-related fitness. However, the health-promoting effect of object manipulation skills on health-related fitness is more of a concern for the individual's "willingness to participate." There may be great obstacles between "willingness to participate" in physical activities and health-related fitness, such as the impact of the sports environment and atmosphere, the shift of physical entertainment to internet entertainment, and the compromise between students' physical health goals and the goals of school knowledge acquisition.

Conversely, developing individual locomotor skills is often associated with greater body calorie expenditure, which may contribute to maintaining a healthy body weight. Okely et al. (98) noted that locomotor skills in overweight children tend to be more difficult to show because they need more support and have a greater obstacle to exercise than object manipulation skills. Locomotor skills can better promote the maintenance of healthy body weight in the early stage of individual movement development, which has the same positive significance as promoting object manipulation skills to encourage participation in physical activity.

4.1. Limitations and suggestions for future research

Our study has limitations. Due to the lack of longitudinal research literature, this study only analyzed cross-sectional outcomes. Due to the various evaluation tools and large differences in the outcome data types of the reviewed articles, this review does not offer a quantitative summary (i.e., meta-analysis). With the increase in the research literature, future reviews can analyze the impact of fundamental movement skills on health-related fitness from a longitudinal perspective, explore scientific teaching strategies of fundamental movement skills, and conduct quantitative research data analysis to obtain more accurate correlations.

5. Conclusion

This systematic review found strong evidence that fundamental movement skills correlated with health-related fitness elements (cardiopulmonary function, muscle strength and endurance, and body composition) in children and adolescents. Most of the studies supported the conclusion that fundamental movement skills were also positively correlated with flexibility. In the fundamental movement skills subitems, object manipulation, locomotor, and balance skills were significantly and positively correlated with cardiopulmonary function and muscle strength and endurance, while locomotor skills were more closely related to body composition than object manipulation skills.

Author contributions

CL and RG participated in the study design and protocol and wrote the manuscript. GQ sorted out the research process and retrieved literature. YC and ZZ screened the literature and drafted the manuscript. All authors reviewed the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association of elevated plasma CCL5 levels with high risk for tic disorders in children

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Abnormal levels of some peripheral cytokines have been reported in children patients with tic disorders (TDs), but none of these cytokines can be a biomarker for this disease. Our aim was to systemically profile differentially expressed cytokines (DECs) in the blood of TD patients, examine their associations with TD development, and identify from them potential biomarkers for the prediction and management of the risk for TDs. In this study, a cytokine array capable of measuring 105 cytokines was used to screen for DECs in the plasma from 53 comorbidity-free and drug-naïve TD patients and 37 age-matched healthy controls. DECs were verified by ELISA and their associations with TD development were evaluated by binary logistic regression analysis. Elevation of a set of cytokines was observed in TD patients compared with controls, including previously uncharacterized cytokines in tic disorders, CCL5, Serpin E1, Thrombospondin-1, MIF, PDGF-AA, and PDGF-AB/BB. Further analysis of DECs revealed a significant association of elevated CCL5 with TD development ($p = 0.005$) and a significant ROC curve for CCL5 as a risk factor [AUC, 0.801 (95% CI: 0.707–0.895), $p < 0.0001$].

Conclusion: This study identifies associations of a set of circulating cytokines, particularly CCL5 with TD development, and provides evidence that high blood CCL5 has potential to be a risk factor for TD development.

Clinical Trial Registration: identifier ChiCTR-2000029616.

KEYWORDS

tic disorders, cytokine, biomarker, risk factor, inflammation

Introduction

Tic disorders (TDs) are childhood-onset neurodevelopmental conditions characterized by sudden, rapid, recurrent, and nonrhythmic motor movements or vocalizations (1), and based on the type of tics and duration of tic symptoms, they can be classified into 3 major groups: Tourette syndrome (TS), chronic tic disorder (CTD) and provisional tic disorder (PTD). As the most common movement disorders in the pediatric population, TDs affect up to 5% children worldwide (2). Previous literature have supported that this disease can cause physical and mental impairments in multiple domains, such as educational attainment, peer relationships, quality of life, and even premature mortality (2, 3). Tics tend to be refractory to medical treatments and non-medical interventions, and most patients experience relapses that often persist into adulthood. Prediction and management of the risk for TD onset and relapse rely largely on biomarkers which, however, are severely lacking (4).

The etiology of TDs appears to be complex and multifactorial. Growing evidence reveals associations between TDs and various immune disorders, including streptococcal infection-included autoimmunity and many other autoimmune diseases, common allergies, asthma, and maternal immune activation (2, 5, 6). A recent large-scale genome-wide pathway analysis indicates an implication of immune-related pathways in TS (7). These findings link dysregulation of immune responses to TD development. As critical effectors and modulators of immune responses, hundreds of cytokines, consisting of interleukins, chemokines and growth factors, have the potential to be involved in TD development, which is favored by the fact that abnormal levels of a few cytokines in the peripheral blood, like TNF-α, IL-12 and IL-1β have been reported in TD patients (8–10), and the knowledge that TS-associated streptococcal infections are certainly able to induce production of various cytokines. Previous studies, however, were limited to a small number of cytokines, leaving many more cytokines uncharacterized. The goal of this study was to use a cytokine array to simultaneously profile plasma levels of over a hundred cytokines in TD patients and controls, characterize differentially expressed cytokines (DECs), and examine their potential associations with TDs.

Methods

Study design and participants

53 patients (median age 8, range 3–16 years) with CTD (11), TS (12) or PTD (13) and 37 age-matched healthy children (median age 9, 3–16 years) who passed outpatient physical examination were recruited for this study. The patients were diagnosed in accordance with the DSM-V criteria and evaluated carefully to exclude those who had any known comorbidities, including mental retardation, autism, attention deficit hyperactivity disorder, and those who received medication within 1 year before admission. The tic severity of each patient was evaluated using the Yale Global Tic Severity Scale (YGTSS), a gold-standard, clinician-administered, semi-structured interview (14). A clinician rates motor and vocal tics in terms of number, frequency, intensity, complexity and interference over the preceding week as well as overall related impairment. Items are rated on a scale from 0 to 5, with higher scores indicative of higher tic severity. YGTSS shows moderate to excellent test–retest reliability, good to excellent internal consistency, inter-rater reliability, convergence validity and moderate to excellent discriminant validity (12, 14, 15). The peripheral blood samples were collected within 4 h of admission, and plasma was immediately prepared, aliquoted, and stored at −80°C for analysis.

The study was approved by the Ethics Committee of Shanghai Children's Medical Center (SCMCIRB-K2019080-3), registered at www.chictr.org.cn (ChiCTR-2000029616), and conducted between July 2020 and November 2021. Informed consent and verbal assent (as appropriate) were provided by parents or legal guardians of all subjects. The study was carried out in accordance with the Helsinki Declaration.

Detection of cytokines in the plasma

Plasma cytokine profiling was performed with a commercial human cytokine array (R&D Systems, Cat. No.: ARY022B) to measure the relative levels of 105 cytokines according to the manufacturer's instructions. Briefly, equal volume of individual plasmas had been mixed evenly for each group of patients and controls, and the resultant 4 sets of mixed plasma samples were subjected to the array analysis simultaneously. DECs detected in TD patients were individually confirmed by using Quantikine enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems [CCL5(DY478), PDGF-AA(DY221), PDGF-BB(DY220)] as described previously (11).

Statistical analysis

Data regarding subject characteristics are collected at first visit. Summary statistics for continuous variables are assessed by Kolmogorov–Smirnov test and presented by mean ± standard deviation. Unpaired *t*-test were used for normal distribution data, while Wilcoxon test was used for skewed distribution data. Correlations of DECs levels with tic severity that was scored by following the YGTSS were tested by Pearson's correlation test or Spearman's rank correlation test (depending on the distribution of the variables). Due to the significant differences in gender between healthy control group and TD group, a binary logistic regression analysis was performed to predict TD occurrence from gender, CCL5, PDGF-AA in data collection section and results were expressed by estimating odds ratios (OR) with their 95% confidence intervals. The predictive values of the binary logistic regression analysis were determined using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated accordingly.

All the data were exported to Excel and SPSS statistics version 26.0. Statistical analyses were performed using the SPSS, and GraphPad Prism 7 was used for mapping. Two-tailed tests were conducted to test statistical significance, and the significance level was set at $p < 0.05$.

Results

Since comorbidities and prior medications are reported to affect the blood levels of cytokines (10, 16), we excluded comorbid patients and those recently medicated when enrolling tic disorder patients. To systemically compare the relative expression levels of cytokines in TD patients and controls, we employed a cytokine array to profile 105 cytokines (**Supplementary Table S1**) in the plasma from 3 groups of TD patients and 1 group of control (**Table 1**). Cytokine signals were developed as spots on film (**Figure 1B**), and pixel intensity of each spot was quantified for an accurate comparison (**Supplementary Table S2**). Consistent with previous studies that reported elevation of proinflammatory cytokines, such as TNF-α, IL-12 and IL-1β (8–10), these cytokines were also increased to varying degrees in TD patients in our array assay (**Supplementary Table S2**). A heatmap analysis of relative levels of all tested cytokines indicated the overall similarities and differences between control subjects and these groups of TD patients (**Figure 2**). Obviously, the major alterations in the 3 groups of TD patients were elevations of a set of cytokines, including the chemokine RANTES (also known as CCL5), Serpin E1, Thrombospondin-1, MIF, PDGF-AA, and PDGF-AB/BB (a mixture of the B subunit containing PDGF factors detected by antibody to the B subunit that was incapable of distinguishing between AB and BB) (**Figure 2**), that appeared to be the major DECs.

Among the major DECs, CCL5 that ranked in top 3 in all 3 groups of TD patients (**Supplementary Table S2**) and the two related growth factors, PDGF-AA and PDGF-AB/BB, were selected for further ELISA analysis which confirmed that both CCL5 and PDGF-AA were significantly increased in all 3 groups of TD patients ($p < 0.02$), and PDGF-BB was significantly augmented in TS and PTD patients ($p < 0.05$) but not in CTD patients (**Figure 3**).

Correlation analysis of these 3 cytokines and tic severity of all TD patients assessed with the YGTSS were revealed by Pearson's correlation test, no significant correlation was found for any of these cytokines (**Figure 4**). The predictive power of these three cytokines and the gender of the subjects that also had a significant difference between patients and controls (**Table 1**) were evaluated by using binary logistic regression analysis, and the result revealed that both gender ($p = 0.02$) and CCL5 ($p = 0.005$) significantly contributed to TD development (**Table 2**).

In the case of gender, TD incidence for boys was found to be 3.78 times higher than that for girls in this study (**Table 2**), which is in line with the reported range of gender preference for TD (17–19). Regarding CCL5, this analysis indicated that an increase of CCL5 concentration by 100 pg/ml caused 50% increase of risk for TD development (OR = 1.005, 95% CI: 1.001–1.008, $p = 0.005$) (**Table 2**), suggesting a potential for CCL5 to be a TD risk factor. Finally, we combined all TD patients and control subjects for ROC analysis and found that CCL5 had a significant ROC curve [AUC: 0.801 (95% CI: 0.707–0.895), $p <$ 0.0001] (**Figure 3D**). These results suggest CCL5 as a promising predictor for the risk of developing TD.

TABLE 1 General clinical data of healthy control and TD patients.

	Control ($n = 37$)	TD ($n = 53$)	p
Age (year)	8.89 ± 3.13 (4–15)	7.91 ± 2.71 (3–16)	0.12
Sex male (%)	17 (45.9%)	41 (77.36%)	0.001*
YGTSS		21.45 ± 7.60	
Motor tics		9.19 ± 2.97	
Vocal tics		4.53 ± 4.79	
Impairment		7.74 ± 4.66	

Values are shown as mean ± standard deviation (SD).
*Statistically significant at $p < 0.05$.

Discussion

Aberrant levels of multiple cytokines have been observed in TD patients in previous studies (8–10). However, to our knowledge,

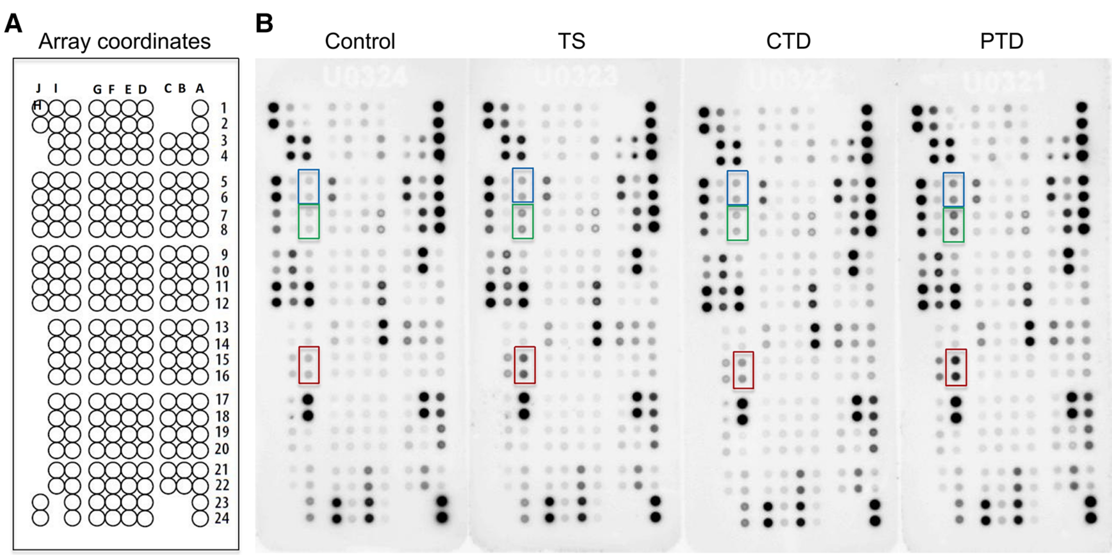

FIGURE 1
Cytokine array analysis of plasma from patients with tic disorders and healthy controls. (A) Schematic diagram of cytokine array coordinates representing 105 different capture antibodies printed in duplicate. (B) Array results for control subjects, and TS, CTD, and PTD patients. Dots representing CCL5, PDGF-AA, and PDGF-AB/BB are highlighted in red, blue and green, respectively.

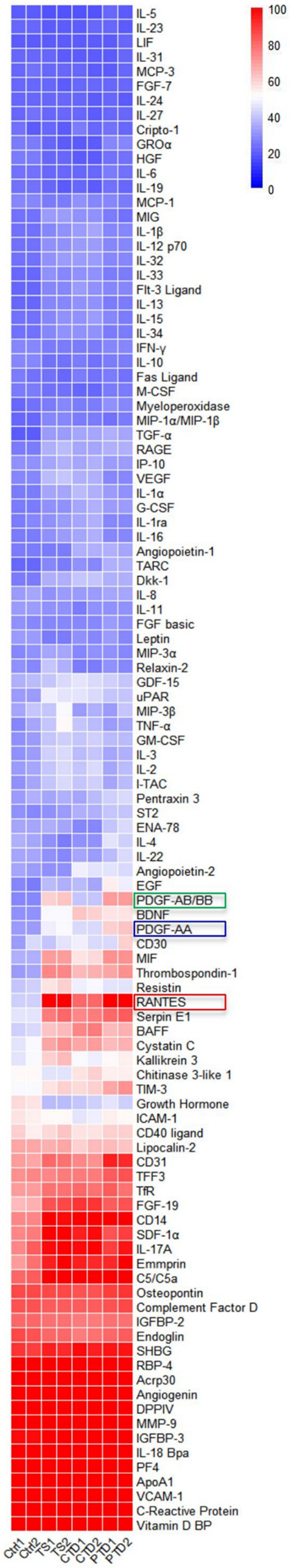

FIGURE 2
Heat map of original derivation sample, comparisons calculated *via* 1-normal, 2-TS, 3-CTD, 4-PTD. The red, blue, and green boxes are marked with cytokines that differ significantly.

none of these cytokines have been characterized as a risk factor of TDs. In this study we used a commercial cytokine array capable of measuring 105 cytokines to unbiasedly profile differentially expressed cytokines in the plasma from comorbidity-free and drug-naïve TD patients and healthy controls and evaluated their associations with TD development. This assay provides the first set of large-scale cytokine profiling data that can be used as a resource for future studies of TDs from the perspective of cytokines. For the first time, we discover CCL5 and PDGF-AA in TDs as two major elevated cytokines in all 3 groups of TD patients and demonstrate their association with TDs. More importantly, we show that while having no correlation with tic severity, peripheral CCL5 has the potential to be a risk factor for evaluating the predisposition to TD development.

Elevation of CCL5 in the blood have been documented in multiple central nervous system (CNS) diseases, such as Parkinson's disease (20), Alzheimer's disease (21), Multiple sclerosis (22, 23), stroke (24), and Traumatic brain injury (25). Interestingly, up-regulated blood CCL5 has also been identified as a risk factor of ischemic stroke that could predict future stroke events (24). These studies, together with ours, reveal a broad association of blood CCL5 with CNS diseases and start to unravel the emerging role of this chemokine in raising the risk for these diseases.

CCL5 is a CC type of chemokine that is widely expressed by many immune cells such as T lymphocytes, macrophages, and platelets. The best known function of CCL5 is to control activation and chemotaxis of many types of immune cells by engaging its cognate receptors expressing on these cells, primarily CCR5, thereby modulating immune responses (26). In the brain, CCL5 and CCR5 are constitutively expressed in astrocytes and microglia and regulate not only chemotaxis of immune cells but also non-immune cell functions (13, 27, 28). It has long been known that chemokines and their cognate receptors are involved in regulation of glial and neuronal cell functions, and that the interactions between glial cells and neurons and through CCR5 and its ligands, e.g., CCL5, are crucial for maintaining neuronal activities, such as neurotransmitter release, ion channel gating and long-term potentiation (27, 29). For instance, after motor neuron injury CCL5 attenuated excessive production of neurotoxic inflammatory mediators in microglia *via* CCR5, and CCR5 deficiency accelerated demise of motor neurons in mice, suggesting that the CCL5/CCR5 pathway plays a neuroprotective role in a manner independent of chemotaxis (30, 31). A later study with a mouse model of Parkinson's disease further demonstrated that CCR5 deficiency resulted in lower numbers of dopamine neurons, reduced levels of striatal dopamine, and decreased locomotor activity (29), indicating that the CCL5/CCR5 pathway plays an important role in maintaining striatal dopamine levels by promoting neuron survival.

The CCL5/CCR5 pathway involved in tic disorders remains unclear so far. Pathologically, tic disorders are considered as a disturbed interplay within and between different brain regions, particularly the basal ganglia-cerebellar-thalamo-cortical network

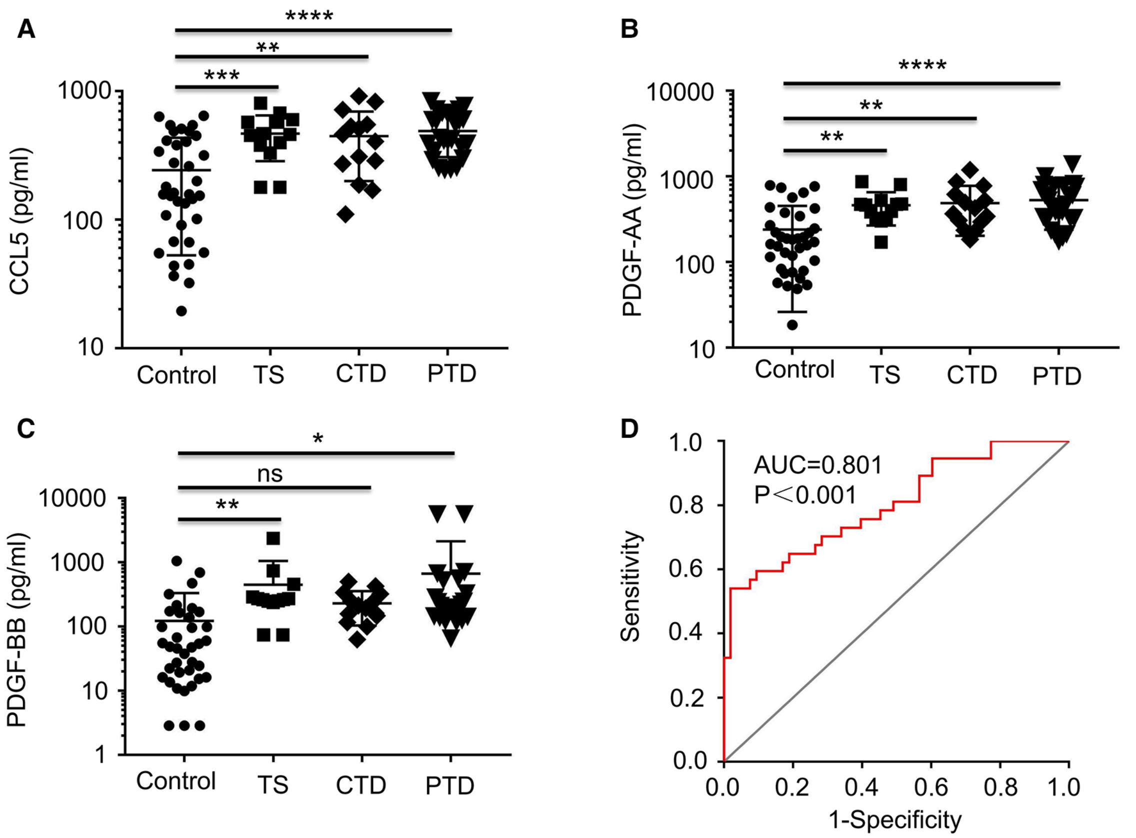

FIGURE 3
Plots showing the levels of plasma CCL5, PDGF-AA, and PDGF-BB. Plots showing the levels of plasma CCL5 (A), PDGF-AA (B), and PDGF-BB (C) from healthy controls and TD patients (TS, CTD, PTD. (D) ROC curve analysis combining CCL5 in the differential diagnosis between TD and normal. ROC, receiver operating characteristic; AUC, area under the curve.

(BGCTC) that functions to inhibit undesired actions. It has been shown that the dysfunction of BGCTC plays a critical role in the pathophysiology of tics (32). Moreover, excessive release of striatal dopamine appears to be the reason for the dysfunction of BGCTC in tic patients (33), and dopamine receptor D2 antagonists that can inhibit dopamine-induced effects represent the most efficacious pharmacotherapy of tics in clinic (34). Thus, it is reasonable to speculate that the CCL5/CCR5 pathway may control tic occurrence by modulating the dopamine neuron-striatal dopamine-BGCTC axis.

Nevertheless, the origin of the elevated blood CCL5 levels is unknown. There are at least two possibilities. One is that blood CCL5 comes from the brain where an inflammatory response is going on and a high level of CCL5 is produced to directly disturb the dopamine neuron-striatal dopamine-BGCTC axis, leading to tic symptoms. Meanwhile, the brain-generated CCL5 can somehow leak into the peripheral blood causing elevation of blood CCL5. The other possibility is that the elevation of blood CCL5 is due to diffusion from other inflamed organs/tissues. It remains to be further studied how the increase of blood CCL5 leads to the risk of functional impairment of brain.

Given that chemokines in the peripheral blood by themselves can hardly cross the blood–brain barrier (BBB) that mainly consists of specialized brain microvascular endothelial cells to control the entry of cells and damaging agents from the blood to brain (35), it is unlikely that low-grade elevation of CCL5 in the blood can directly cause significant detrimental effect to the CNS. Interestingly, CCL5 and its cognate receptors, including CCR5, have been shown to involve in the regulation of BBB permeability and immune cells' entry into the brain. By binding to proteoglycans attached to endothelial cells, CCL5 can be immobilized on endothelial surfaces to enable a high local concentration that facilitates its interaction with the receptors expressed by incoming immune cells in the blood (36). Adhesion of the immune cells to EC-immobilized CCL5 leads to signaling events triggering increase of BBB permeability (35). Increase of BBB permeability presumably exacerbates the access of insults that otherwise cannot penetrate the BBB and enter the brain. In support of the importance of CCL5 and its receptors for BBB regulation, animal studies of epilepsy demonstrated that antagonist-based inhibition of CCR5 on blood cells or blocking CCL5 can reduce BBB permeability and mitigate disease severity (35). A very recent *in vivo* study using highly sensitive radiochemical-based assays showed that circulating CCL5 can be transported across BBB in mice by binding to heparan sulfates at the endothelial surface in a manner independent of CCR2 and CCR5 (37). This finding raises another possibility that

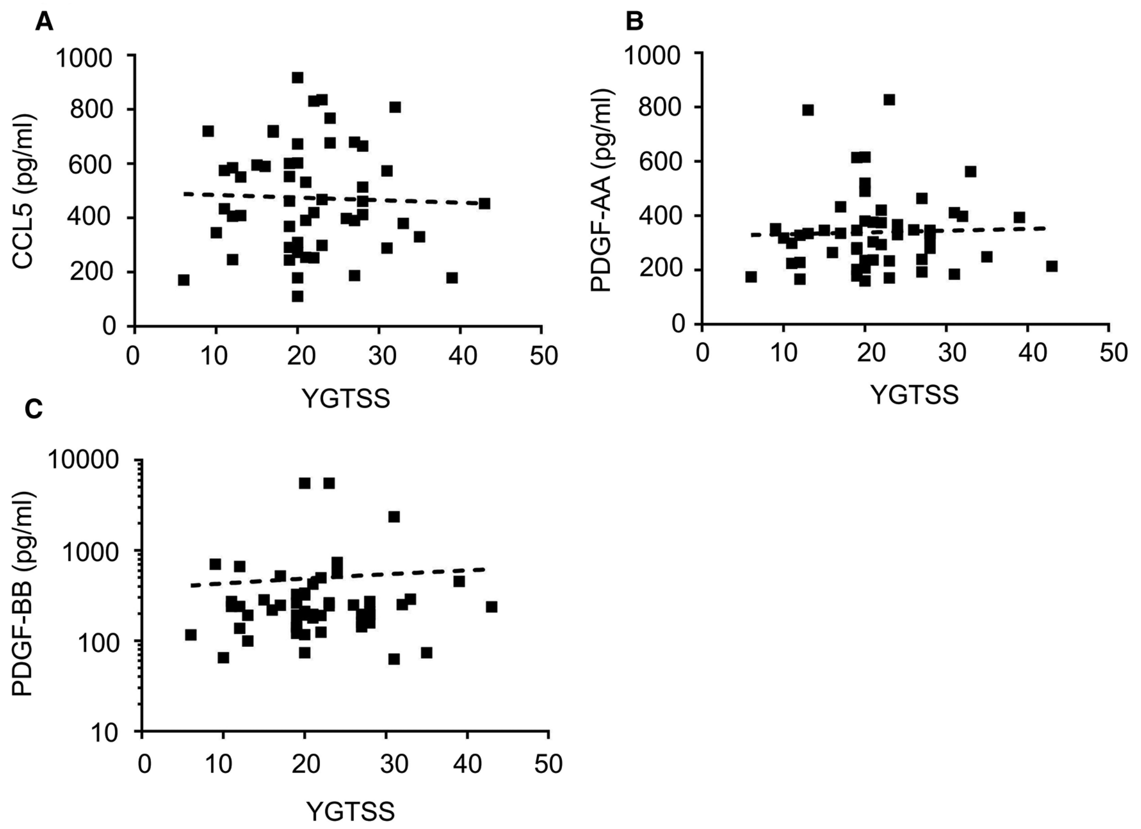

FIGURE 4
The correlations of the levels of plasma CCL5, PDGF-AA, PDGF-BB with tic severity of all TD patients. The correlations of the levels of plasma CCL5 (**A**), PDGF-AA (**B**), PDGF-BB (**C**) with tic severity of all TD patients assessed with the YGTSS.

TABLE 2 Analysis of influencing factors in children with TDs.

	OR (95% CI)	*p*
Gender		**0.02***
female	1.00	
male	3.79 (1.21–11.88)	
CCL5 (pg/ml)	1.005 (1.001–1.008)	**0.005***
PDGF-AA (pg/ml)	1.004 (0.99–1.01)	0.12

*Statistically significant at $p < 0.05$.

circulating CCL5 may exert its regulatory role inside the brain. It is interesting to explore if elevated circulating CCL5 plays a role in reducing BBB permeability or contributing the brain level of CCL5 in the pathogenesis of TDs.

There is evidence that in the brain increased CCL5 can cause pathologic consequences by engaging its cognate receptors CCR5 and CCR1 both of which are expressed on multiple types of cells, such as microglia, astrocytes and neurons (38–41). For example, in a mouse model of intracerebral hemorrhage, CCR5 activation by intracerebroventricularly administrated CCL5 promoted neuronal cell death in the form of inflammatory proptosis, thereby leading to neurological deficits (38). Additionally, CCL5-CCR1-mediated microglial activation in the brain resulted in neurologic deficits and neuroinflammation (42). These animal studies imply that targeting the CCL5-CCR1/5 cascades in the brain could be a promising therapeutic option for neurological diseases associated with CNS.

Based on our findings, we propose that CCL5, and its cognate receptors CCR1/5, could be potential therapeutic targets for TDs. Given the nature of recurring of TDs, pharmaceutical lowering of the level of blood CCL5, attenuation of expression or function of CCR1/5, or inhibition of CCL5-CCR1/5 or CCL5-heparan sulfates interactions, such as by CCL5 antagonist, monoclonal antibodies to CCR1/5, or heparan sulfates competitive inhibitor heparin (37), would hold promise for better risk management of TD relapse.

Due to the limitations to this study that were caused by relatively small numbers and a single cohort of patients, the potential of CCL5 as a risk factor for TD development needs to be validated in multicenter studies of larger cohorts in the future.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by IRB of Shanghai Children's Medical Center Afflicted to Shanghai Jiao Tong University School of Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XY and KS conceived and supervised the project; HY and JZ performed most of experiments; YD, PY, LL, and JS contributed to the performance of the experiments; HY, YM, ZH and XY analyzed data; HY, XY and KS wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1126839/full#supplementary-material.

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Relationships of the gut microbiome with cognitive development among healthy school-age children

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Background: The gut microbiome might play a role in neurodevelopment, however, evidence remains elusive. We aimed to examine the relationship between the intestinal microbiome and cognitive development of school-age children.
Methods: This cross-sectional study included healthy Israeli Arab children from different socioeconomic status (SES). The microbiome was characterized in fecal samples by implementing 16S rRNA gene sequencing. Cognitive function was measured using Stanford-Binet test, yielding full-scale Intelligence Quotient (FSIQ) score. Sociodemographics and anthropometric and hemoglobin measurements were obtained. Multivariate models were implemented to assess adjusted associations between the gut microbiome and FSIQ score, while controlling for age, sex, SES, physical growth, and hemoglobin levels.
Results: Overall, 165 children (41.2% females) aged 6–9 years were enrolled. SES score was strongly related to both FSIQ score and the gut microbiome. Measures of α-diversity were significantly associated with FSIQ score, demonstrating a more diverse, even, and rich microbiome with increased FSIQ score. Significant differences in fecal bacterial composition were found; FSIQ score explained the highest variance in bacterial β-diversity, followed by SES score. Several taxonomic differences were significantly associated with FSIQ score, including *Prevotella*, *Dialister*, *Sutterella*, *Ruminococcus callidus,* and *Bacteroides uniformis*.
Conclusions: We demonstrated significant independent associations between the gut microbiome and cognitive development in school-age children.

KEYWORDS

gut microbiome, children, healthy, school age, cognitive development, socioeconomic status

1. Introduction

The gut microbiome is important in health and disease (1, 2). The microbiota is increasingly recognized for its ability to influence the nervous system and several complex behaviors of the host, by modulation of neurodevelopment through the microbiome-gut-brain axis (3, 4).

The gut-brain axis is characterized by a bidirectional communication between the gut and the brain, that might modify both gastrointestinal and nervous systems function, influencing emotion and cognition (4). Preclinical and clinical studies showed that variations in microbiota composition contribute to various cognitive states, including functional brain connectivity, depression, stress, anxiety, and autism spectrum disorder (5–12). The mechanisms underlying these relationships are not fully understood, but a compelling hypothesis is that gut microbiota variation during childhood with vulnerable neurodevelopmental window, might influence both mental and cognitive outcomes (13).

The first years of life are characterized by intense structural and functional changes in the brain and thus are critical for neurodevelopmental plasticity (14). Intriguingly, these changes occur simultaneously with dynamic intestinal microbiome alterations, thus raising the possibility of dialogue between the microbes that inhabit the gastrointestinal tract and the brain in early life (15, 16). Animal models demonstrated that early life gut microbiome influences later neurodevelopment (17). However, evidence from human populations remains limited and focused merely on infancy, demonstrating the association between the intestinal microbiome with both temperament (18, 19) and cognitive performance (12, 20). Evidence suggests substantial functional and taxonomic differences in the gut microbiota of healthy children compared to those of adults, suggesting that the development of gut microbiome may continue into school age and more slowly than previously thought and that the gut microbiota of children may be more malleable to environmental factors than that of adults (21, 22). Moreover, neurodevelopment remains an ongoing critical process during the early to middle childhood years (23), nevertheless the association between the microbiome and cognitive development during school age remains elusive.

Environmental exposures, including socioeconomic status (SES) play a critical role in both intestinal microbiome (24, 25) and neurologic development (26, 27). Moreover, iron deficiency anemia, a main risk factor for diminished neurodevelopmental and cognitive abilities in children (28–30), was linked with the gut microbiome, in both animal models and human studies (31–33). However, the interconnection between the microbiome, environmental exposures, and cognitive function in childhood is not fully clear. To address these gaps, we examined the association between the intestinal microbiome and cognitive development of school-age children, with the possible intermediating effect of environmental exposures, including sociodemographics, physical growth, and nutritional status. Our working hypothesis was that the gut microbiome might be related to cognitive development of healthy school-age children, independent of potential confounders.

2. Materials and methods

2.1. Study population and design

This cross-sectional study focused on a population under transition, the Israeli Arab population, the main ethnic minority in Israel. This population comprises 20% of the Israeli population (34, 35), while 75% are Jews and 5% belong to other population groups. The Arab population has lower educational levels and SES compared to the Jewish population (35, 36), but there is an ongoing improvement in the educational level and health indicators among Arabs. Access to care is universal in Israel, due to the universal health insurance law (37).

This study was conducted in 2007–2009, in three Arab villages in Hadera sub-district. In 2007, there were about 153,000 Muslim Arab residents living in this region, with 3,921 live births (34). One village had approximately 14,000 residents during the study period and the other two villages had about 10,000 residents each. According to the Central Bureau of Statistics, one village belonged to cluster 2 SES, one belonged to cluster 3 SES, and the third village belonged to cluster 4 SES. The clusters are on a scale of 1–10, the lower the index, the lower the SES (36). At the national level, these villages are of low and intermediate SES levels (36). Given the SES differences across the villages, they were referred herein as village A = high SES, village B = intermediate SES, and village C = low SES. The drinking water supply in these villages is piped, and all households are connected to the national electricity company similar to the rest of the country. Connection to the internet and cable television is also available.

In this cross-sectional study, we examined the gut microbiome in archived stool samples obtained from healthy children who participated in a study on gastrointestinal tract infections. Briefly, in 2003–2004, a cohort of 289 healthy children aged 3–5 years from three villages of different SES were recruited. In 2007–2009, a follow-up was performed among 196 children at age 6–9 years (38, 39). Overall, 176 children who provided stool samples had sufficient material for 16S rRNA sequencing. Eight children were excluded due to medical conditions that might affect cognitive function directly (thalassemia minor, type-1 diabetes, Glucose-6-phosphate dehydrogenase deficiency with anemia, major heart defect, panhypopituitarism, hemophilia, and significant developmental delay). Three additional children with missing IQ scores were omitted from the analysis, thus leaving 165 participants in the analysis.

2.2. Data collection

Information on household and socioeconomic characteristics was obtained via personal interviews with the mothers, by trained Arabic-speakers interviewers. The questionnaire included information on age, sex, the village of residence, maternal education, maternal age, paternal education, monthly family income, number of persons living in the household, and number of rooms in the household. Crowding index was calculated by dividing the number of people living in a household by the number of rooms in a household. Data were collected on early life determinants e.g., birth weight, breastfeeding, and daycare center attendance.

2.3. Current hemoglobin levels

Blood collected by finger lancing was used for hemoglobin measurement using a portable hemoglobinometer (Hemocue Hb

201+, Sweden). Hemoglobin was assessed as an indicator of nutritional status.

2.4. Anthropometric measurements

Anthropometric measurements were performed by trained registered nurses. Body weight was measured to the nearest 0.1 kilogram using an analog scale (calibrated before use), and height (to the nearest 0.1 centimeter) with a stadiometer. Information on anthropometric measurements in early childhood (ages 18–30 months) was obtained from medical records. *Z* scores of height for age (HAZ), weight for height (WAZ), and body mass index for age (BMIZ) were calculated using Epi/Info software [Center for Disease Control and Prevention, Atlanta, Georgia (CDC)] based on the 2,000 CDC growth reference curves. BMI was calculated as weight (kg)/height $(m)^2$.

2.5 . Socioeconomic status (SES)

Multiple SES indicators were examined: (1) community SES rank as classified by the Israel Central Bureau of Statistics, (2) household socioeconomic characteristics: (a) maternal education, (b) paternal education, (c) crowding index, and (d) reported family income. We used these variables to generate a composite SES score, based on confirmatory factor analysis. The analysis was implemented using "Principal Axis" method, including rotation with "varimax" (*r* package psych). Since maternal education was significantly correlated with parental education (Pearson's $r = 0.46$), we included only maternal education level in the analysis. The selected variables were tested with Bartlett's test of homogeneity of variances (p-value <0.0001) and Kaiser–Meyer–Olkin factor adequacy resulting in adequate scores for all selected variables: village of residence = 0.7, crowding index = 0.7, maternal education = 0.7, reported family income = 0.68. The newly generated SES score was composed of a combination of the standardized loadings, based on the correlation matrix of the selected variables (**Supplementary Figure S1**).

2.6. Assessment of cognitive function

Cognitive function was measured by Intelligence Quotient (IQ) score using Stanford-Binet-5th edition (*SB5*) test, performed by a trained Arabic speaking psychologist (39). The following parameters were assessed: full-scale IQ (FSIQ), non-verbal IQ and verbal IQ. The test was performed at standard conditions, lasting 45–60 min. The *SB5* was scored with the *SB5 Scoring Pro*, a Windows®-based software program. Since FSIQ is highly correlated with non-verbal and verbal IQ (Pearson's correlation $r = 0.95$ and $r = 0.94$ respectively), FSIQ score was selected as the main outcome variable in this study. The psychologist was masked to background information of the participants.

2.7. Samples collection, DNA extraction and bacterial DNA amplification

Fresh stool samples were obtained from the children using collection plastic cups and transferred on ice to the laboratory at Tel Aviv University. Samples were divided stored at −80°C until testing. All samples underwent a single thaw prior to DNA extraction. DNA was extracted from 180 to 220 mg of fecal material from each sample using the QIAamp® Fast DNA Stool Mini Kit (Qiagen, Valencia, CA) following the manufacturer's instructions (40) and stored at −20°C until shipment to the Sequencing Core at the University of Illinois. Genomic DNA was prepared for sequencing using a two-stage amplicon sequencing workflow (41). Initially, genomic DNA was amplified via PCR using primers targeting the V4 region of microbial 16S ribosomal RNA (rRNA) genes. The primers, 515F modified and 806R modified (42), contained 5' linker sequences compatible with Access Array primers for Illumina sequencers (Fluidigm, South San Francisco, CA). The PCR assays were performed in a total volume of 10 µl using MyTaq™ HS 2X Mix (Bioline) with primer concentrations at 500 nM. Thermocycling conditions were as follows: 95°C for 5 min (initial denaturation), followed by 28 cycles of 95°C for 30 s, 55°C for 45 s, and 72°C for 30 s. One microliter of the PCR product from each reaction was transferred to the second-stage PCR assay. Each second-stage reaction was conducted in a final volume of 10 µl using MyTaq HS 2X mix, and each well contained a unique pair of Access Array primers containing Illumina sequencing adapters, single index sample-specific barcode, and linker sequences. Thermocycling conditions were as follows: 95°C for 5 min (initial denaturation), followed by 8 cycles of 95°C for 30 s, 60°C for 30 s, and 72°C for 30 s. Libraries were pooled and purified using 0.6× concentration of AMPure XP beads to remove short fragments below 300 bp. Pooled libraries were loaded onto a MiniSeq sequencer (Illumina, San Diego, CA) with 15% phiX spike-in and paired-end 2 × 153 base sequencing reads.

2.8. Statistical analyses

Quality control analysis of demultiplexed sequences was performed using the Deblur (43) workflow, following the construction of a phylogenetic tree (mafft-fasttree) and taxonomy assignment with QIIME2 (44). The quality process with Deblur uses sequence error profiles to obtain putative error-free sequences, referred to as "sub" operational taxonomic units (s-OTU). Taxonomic composition was assigned to the s-OTUs using a pre-trained Naive Bayes classifier, trained on the Greengenes (45) 13_8 99% OTUs. Downstream analysis was conducted using R version 4.0.3. Diversity analysis was calculated at rarefaction depth of 11,158. Bacterial α-diversity, which quantifies the intra-sample diversity, i.e., the distribution of species abundances in a given sample, was estimated using Shannon's diversity and Pielou's evenness indexes (46) and compared across independent variables using multivariate analysis of variance (ANOVA) tests. β-diversity, which measures dis-similarities between samples (46), was calculated using the Bray-Curtis dissimilarity index, the Jensen-Shannon divergence (JSD), and the phylogenetic weighted and unweighted Unifrac distances. Permutational multivariate analysis of variance (PERMANOVA) was used to test differences in overall microbiome composition [vegan; Adonis (47)], implementing a multivariate model with the covariates: age, sex, SES score, hemoglobin levels, HAZ at age 18–30 months and current BMIZ scores. The Analysis of Composition of Microbiomes (48) (ANCOM) was applied for the identification of differentially abundant features in association with FSIQ scores, with the false discovery rate (FDR) level set to 0.05. ANCOM uses a linear framework to statistically detect features whose composition varies across FSIQ scores, while controlling for other covariates of interest (a linear model comprised of the abovementioned covariates). A feature was considered significantly varying in composition across an independent variable of interest at a detection level of ≥0.6, meaning that the feature composition varied across the independent variable with respect to 60% of reference features. Non-parametric Spearman's correlation coefficient was used to evaluate the association between α-diversity indices and FSIQ scores.

Differences in demographic characteristics across the study villages were examined using one-way ANOVA for continuous variables, the Kruskal–Wallis *H* test for rank-based variables and the χ^2 test for categorical variables. Post-hoc pairwise comparisons were conducted using Games–Howell test, including multiple comparisons correction with FDR.

2.9. Ethical Approval

The Institution Review Board of Hillel Yaffe Medical Center (approval number 6/2005, year of approval 2005) and the Ethics Committee of Tel Aviv University approved the study (approval year 2018). Written informed consent was obtained from the parents of the participants.

3. Results

3.1. Demographic characteristics of the study participants

Data from 165 children (41.2% females) who provided stool specimens and underwent a cognitive assessment were included in the analysis. The participants' mean age was 7.8 years, [SD = 0.9], with significant differences between the villages ($p = 0.019$). The composite SES score ranged from −2.1 to 4.6 [mean 2.1 (SD = 1.4); **Supplementary Figure S1B**] and was profoundly different between the villages ($p < 0.0001$; **Supplementary Figure S2A**). Children from village C (low SES) had significantly worse SES indicators than children from villages A/B, but there were no significant differences between the villages in early life determinants, e.g., birth weight, breastfeeding, and attending a daycare. HAZ scores in infancy were significantly lower ($p = 0.026$) in children from village C (low SES) than children from villages A/B (high/intermediate SES). The mean BMIZ score at school age was higher among children from village C compared to villages A/B ($p < 0.001$) (**Table 1**). The mean FSIQ of

TABLE 1 Characteristics of the participants by the village of residence (*N* = 165).

	Villages A/B (intermediate/high SES)	Village C (low SES)	*p* value
Number of participants, (%)	100 (60.6%)	65 (39.4%)	–
Age, years, mean (SD)	7.9 (0.9)	7.6 (0.8)	0.019
Sex, females, *N* (%)	40 (40.0%)	28 (43.1%)	0.818
Household crowding index[a], mean (SD)	1.4 (0.6)	2.6 (1.3)	<0.001
Household monthly income[b]			<0.001
Above average	16 (16.0%)	3 (4.6%)	
Average	34 (34.0%)	8 (12.3%)	
Below average	50 (50.0%)	54 (83.1%)	
Father education, years, mean (SD)	11.3 (3.4)	8.3 (3.5)	<0.001
Maternal education, years, mean (SD)	11.2 (3.5)	6.5 (3.7)	<0.001
SES score[c], mean (SD)	3.0 (0.9)	0.8 (1.0)	<0.001
Birth weight (kg), mean (SD)	3.2 (0.5)	3.4 (0.5)	0.225
Breastfeeding, yes, *N* (%)	98 (98.0%)	57 (87.7%)	0.09
Age of introducing solid foods, months, mean (SD)	6.0 (2.9)	5.9 (2.6)	0.741
Daycare center attendance in early life, *N* (%)	20 (20.0%)	12 (18.8%)	0.697
Current hemoglobin level (g/dl), mean (SD)	12.6 (0.9)	12.5 (1)	0.567
Height for age *z*-score (age 18–30 months), mean (SD)	0.10 (0.80)	−0.20 (0.80)	0.026
Weight for age *z*-score, (age 18–30 months), mean (SD)	0.00 (0.9)	0.20 (1.0)	0.275
BMIZ score[c], mean (SD)	0.20 (1.0)	0.82 (0.9)	<0.001
Full scale IQ score	105.0 (9.2)	89.2 (12.3)	<0.001

BMIZ, body mass index *z* score; SD, standard deviation; SES, socioeconomic status.
[a]Household crowding: Number of people living in the household/Number of rooms in the household.
[b]Household income: Household income as compared to the national average.
[c]Individual level socioeconomic status score—a composite score based on confirmatory factor analysis including village of residence, maternal education, household crowding, and household income.

this cohort was 98.8 [SD = 13.1] points. FSIQ score was lower among children from village C compared to villages A/B (**Supplementary Figure S2B**).

A significant positive association was found between the composite SES score and FSIQ scores ($p < 0.0001$ by ANOVA; **Supplementary Figure S3A** and Spearman's $r = 0.61$, $p < 0.0001$; **Supplementary Figure S3B**). FSIQ score was not correlated with hemoglobin level, nor with WAZ score at age 18–30 months (**Supplementary Figures S4A,B**). Significant associations were found between HAZ at age 18–30 months with FSIQ (Spearman's $r = 0.22$, $p = 0.004$) and between current BMIZ scores and with FSIQ (Spearman's $r = -0.17$, $p = 0.025$), **Supplementary Figures S4C,D**).

Based on these results and existing knowledge regarding the environmental effects of SES on both the microbiome (2, 49–51) and FSIQ (16, 52, 53), we examined the association between FSIQ score and fecal microbiome alterations, while adjusting for covariates that were associated with microbial alterations and FSIQ score.

3.2. The association between FSIQ score and bacterial α-diversity

Bacterial α-diversity as estimated by the Shannon's diversity index followed a normal distribution (**Supplementary Figure S5**). We found a significant positive association between Shannon's diversity and FSIQ score (**Figure 1A**). A multivariate analysis of variance model that adjusted for sex, age, SES score, hemoglobin level, HAZ at age 18–30 months and current BMIZ scores on bacterial diversity (**Figure 1B**), showed that FSIQ and sex were significantly associated with Shannon's diversity index ($F = 6.16$, $p = 0.014$ and $F = 4.89$ $p = 0.029$, respectively). A multivariate analysis that included FSIQ score as the dependent variable, showed a strong positive association between fecal α-diversity and FSIQ ($F = 9.73$, $p = 0.002$; **Figure 1C**). In this model, SES scores had the strongest association with FSIQ score ($F = 97.91$, $p < 0.0001$). Hemoglobin level was significantly associated with FSIQ score ($F = 3.94$, $p = 0.049$; **Figure 1D**). Bacterial α-diversity and FSIQ score were positively linearly correlated (Person's $r = 0.20$, $p = 0.015$; **Figure 1E**).

These associations were further strengthened by an estimation of bacterial α-diversity with Pielou's evenness index. There was a strong association between FSIQ score and increased species evenness (**Supplementary Figure S6A**), with FSIQ being the strongest and the only significant variable associated with altered species evenness ($F = 11.32$, $p < 0.0001$; **Supplementary Table S1A**). This model showed a borderline significant association between hemoglobin level and Pielou's evenness index ($F = 2.91$, $p = 0.089$). A multivariate model showed a significant relationship between FSIQ score and species evenness ($F = 17.41$, $p < 0.0001$), but the effect of SES ($F = 91.13$, $p < 0.0001$) on FSIQ score was stronger (**Supplementary Table S1B**). Significant positive linear correlation between FSIQ score and species evenness (Spearman's $r = 0.24$, $p = 0.002$; **Supplementary Figure S6C**).

3.3. The association of gut microbiome composition and FSIQ score

We found significant differences in fecal bacterial composition, as measured by the Bray–Curtis dissimilarity index ($F = 10.79$, $R^2 = 0.06$, $p = 0.001$; **Figure 2A**, **Supplementary Table S2A**), the phylogenetic unweighted and weighted UniFrac distance matrixes ($F = 5.04$, $R^2 = 0.03$, $p = 0.001$, and $F = 8.59$, $R^2 = 0.05$, $p = 0.001$ relatively; **Figure 2B**, **Supplementary Tables S2B, S2C**), and by the JSD ($F = 7.40$, $R^2 = 0.04$, $p = 0.001$; **Figure 2C**, **Supplementary Table S2D**). All multivariate models included the covariates age, sex, SES score, hemoglobin, HAZ and BMIZ scores.

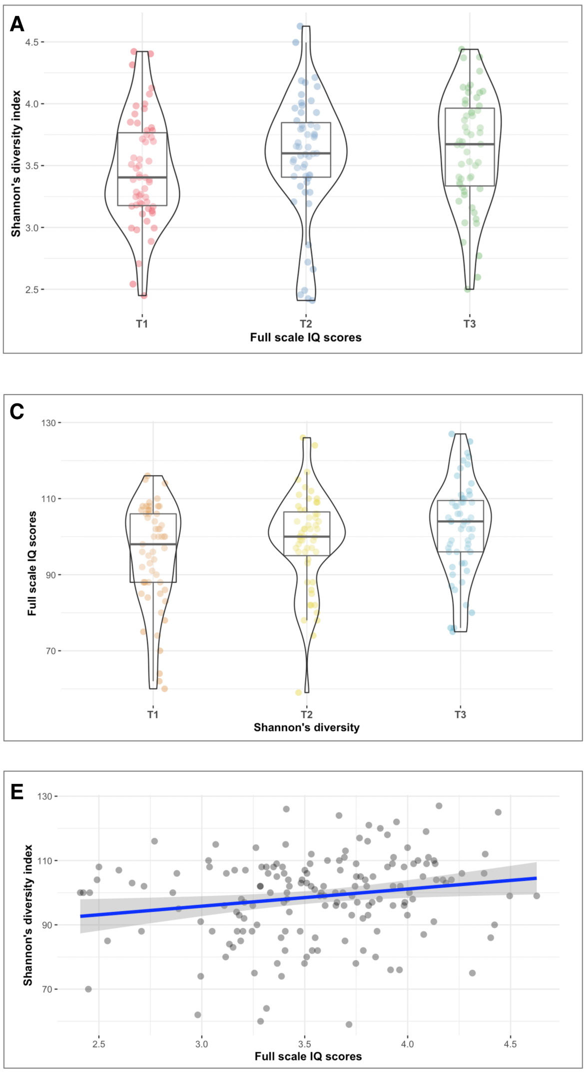
FSIQ score explained the highest variance in bacterial β-diversity as measured by the Bray-Curtis dissimilarity index, followed by the SES score ($F = 10.79$, $R^2 = 0.06$, $p = 0.001$, and $F = 5.17$, $R^2 = 0.03$, $p = 0.001$, respectively), the phylogenetic unweighted UniFrac distance matrix ($F = 5.04$, $R^2 = 0.029$, $p = 0.001$, and $F = 3.33$, $R^2 = 0.019$, $p = 0.001$, respectively), the weighted UniFrac distance matrix ($F = 8.59$, $R^2 = 0.048$, $p = 0.001$, and $F = 4.35$, $R^2 = 0.024$, $p = 0.001$, respectively) and the JSD ($F = 15.99$, $R^2 = 0.085$, $p = 0.001$, and $F = 7.4$, $R^2 = 0.039$, $p = 0.001$, respectively).

We found a significant association of weaker magnitude, between the participant's age, sex, and BMIZ score, and bacterial composition, in some β-diversity measurements. Age was significantly associated with the Bray-Curtis dissimilarity index ($F = 2.13$, $R^2 = 0.012$, $p = 0.014$), the weighted UniFrac ($F = 2.82$, $R^2 = 0.016$, $p = 0.003$) and the JSD ($F = 2.64$, $R^2 = 0.014$, $p = 0.011$). BMIZ was significantly associated with bacterial composition when measured by the Bray-Curtis dissimilarity method ($F = 1.72$, $R^2 = 0.010$, $p = 0.03$) and the JSD ($F = 1.94$, $R^2 = 0.010$, $p = 0.046$), while sex was significantly associated the weighted UniFrac index ($F = 1.88$, $R^2 = 0.011$, $p = 0.043$).

The multivariate model using the JSD method explained the overall highest amount of variance 16.6% of the variation in bacterial composition (**Figure 2D**). The remaining models explained a smaller amount of β-diversity variation: 12.8%, 11.8% and 8.3% for the Bray-Curtis dissimilarity, the weighted UniFrac and the unweighted UniFrac, respectively.

3.4. Taxonomic alterations associated with FSIQ score

In agreement with the profound differences of bacterial composition, we found significant associations between the relative abundance of several bacterial genera, with adjustment for age, sex, SES score, hemoglobin, HAZ and BMIZ scores (**Figure 3A**). Genus *Prevotella* was detected at the highest detection level ($W_{stat} = 706$), followed by *Dialister* ($W_{stat} = 675$), *Sutterella* ($W_{stat} = 637$), *Ruminococcus callidus* ($W_{stat} = 609$), *Bacteroides uniformis* ($W_{stat} = 605$) and Lachnospiraceae ($W_{stat} = 553$). At a lower detection level, there was an association with *Bacteroides*, *Prevotella copri*, *Oscillospira* and *Clostridium* (**Supplementary Table S3**). FSIQ scores were inversely associated



B	Df	Sum Sq	Mean Sq	F value	Pr(>F)
FSIQ	1	1.25	1.246	6.159	0.014
Sex	1	0.99	0.988	4.886	0.029
Age	1	0.02	0.022	0.109	0.741
SES score	1	0.06	0.06	0.295	0.588
Hemoglobin (g/dL)	1	0.58	0.582	2.879	0.092
HAZ score	1	0.06	0.057	0.280	0.592
BMIZ score	1	0.24	0.238	1.174	0.280
Residuals	157	31.76	0.202		

D	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Shannon's diversity	1	996	996	9.732	0.002
Sex	1	150	150	1.466	0.228
Age	1	6	6	0.054	0.816
SES score	1	10024	10024	97.905	< 2e-16
Hemoglobin (g/dL)	1	404	404	3.943	0.049
HAZ score	1	263	263	2.567	0.111
BMIZ score	1	36	36	0.355	0.552
Residuals	157	16074	102		

FIGURE 1
The association between full-scale IQ scores and bacterial α-diversity. (A) Box-violin plots of microbial diversity, measured by Shannon's diversity index, across tertiles of FSIQ scores, showing a significant increase in microbial α-diversity with increased FSIQ ($p = 0.014$). (B) Results of a multivariate analysis of variance displaying the association between FSIQ score and covariates of interest with bacterial diversity. FSIQ score and sex were significantly associated Shannon's bacterial α-diversity index ($F = 6.16$, $p = 0.014$ and $F = 4.89$ $p = 0.029$, respectively). (C) Box-violin plots of FSIQ scores across tertiles of Shannon's diversity index, show a significant increase in FSIQ scores with increased bacterial diversity ($p = 0.002$). (D) Results of a multivariate analysis of variance displaying the association between the individuals' gut Shannon's diversity and covariates of interest with FSIQ scores. Bacterial α-diversity and SES scores were strongly associated with FSIQ score ($F = 9.73$, $p = 0.014$ and $F = 97.91$, $p = 0.029$, respectively), while hemoglobin levels had a more delicate albeit significant association ($F = 3.94$, $p = 0.049$). (E) The correlation between Shannon's α-diversity index and FSIQ score; Pearson's $r = 0.20$, $p = 0.015$. SES, socioeconomic status; FSIQ, full-scale IQ; HAZ, height for age z-score at age 18–30 months; BMIZ, body mass index z-score at age 6–9 years. *The x axis in figures (A,C) represents tertiles, T1 = lowest tertile, and T3 = highest tertile. **The mid line in the box plots [figures (A,C)] represents the median, the lower bound of the box represents the 25th percentile, the upper bound of the box represents the 75th percentile, the lowest point of the lower whisker represents the minimum and the highest point of the upper whisker represents the maximum. The violin plot implements a rotated kernel density plot on each side, adding information regarding the full distribution of the measured data; the width of the violin indicates the frequency.

with the relative abundance of *Prevotella* (including species *Prevotella copri*), *Dialister* and *Sutterella*, while *Ruminococcus callidus, Bacteroides uniformis and* Lachnospiraceae were characterized by a positive association with FSIQ levels (**Figures 3B–I**).

An unadjusted analysis revealed significant correlations between FSIQ scores and *Prevotella* (Spearman's $r = -0.42$, $p < 0.0001$), *Dialisted* (Spearman's $r = -0.19$, $p = 0.012$), *Sutterella* (Spearman's $r = -0.2$, $p = 0.01$), the species *Ruminococcus callidus* (Spearman's $r = 0.27$, $p = 0.001$), and *Bacteroides uniformis* (Spearman's $r = 0.41$, $p < 0.0001$; **Supplementary Figures S7A–E**).

Since a significant percentage of bacterial variance was explained by SES scores, we performed a stratified analysis by village of residence. We found a consistent bacterial variation associated with FSIQ score in all villages, thus independent from SES and adjusted for the aforementioned covariates (**Figures 4A, B**). Among children from village C (low SES), *Bacteroides uniformis* was the most strongly associated species with FSIQ

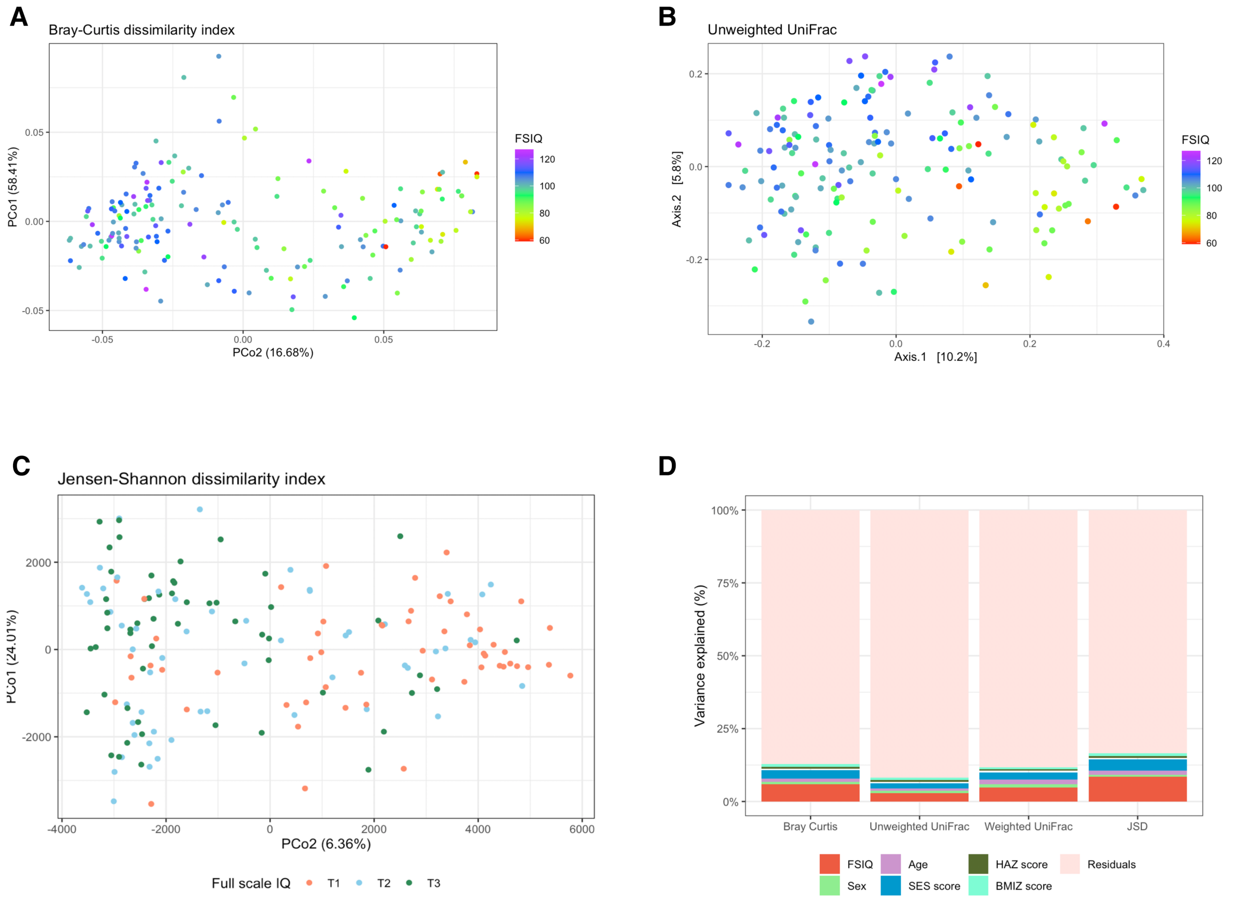


FIGURE 2
The association between full-scale IQ scores and bacterial β-diversity. (A) Principal coordinate analysis (PCoA) of the Bray-Curtis dissimilarity index, notably altered with changing FSIQ scores ($F = 10.79$, $p = 0.001$). (B) PCoA of the phylogenetic unweighted uniFrac distance matrix, significantly separated with altered FSIQ score ($F = 5.04$, $p = 0.001$). (C) PCoA of the Jensen-Shannon divergence (JSD), clearly separated according to FSIQ tertiles ($F = 15.90$, $p = 0.001$). (D) Stacked (100%) bar-plots of the explained variance in microbial beta diversity by the multivariate models. The FSIQ score explained most of the variance in all β-diversity measurements, followed by SES score. The JSD method explained the highest percentage of variance in microbial β-diversity (16.6%). FSIQ, full-scale IQ; PCoA, principal coordinate analysis; JSD, Jensen-Shannon divergence. *FSIQ scores in Figures (C,D) are represented as tertiles, T1 being the lowest tertile (FSIQ scores between 59 and 96), T2 the middle tertile (FSIQ scores between 97 and105), and T3 the highest tertile (FSIQ scores between 106 and 127). **The midline in the box plots [figure (D)] represents the median, the lower bound of the box represents the 25th percentile, the upper bound of the box represents the 75th percentile, the lowest point of the lower whisker represents the minimum and the highest point of the upper whisker represents the maximum. The violin plot implements a rotated kernel density plot on each side, adding information regarding the full distribution of the measured data; the width of the violin indicates the frequency.

score ($W_{stat} = 700$), followed by *Prevotella* ($W_{stat} = 635$), the species *Clostridioforme* ($W_{stat} = 607$), including the lower taxonomic levels Clostridiales ($W_{stat} = 581$) and *Clostridium* ($W_{stat} = 567$), *Veillonella dispar* ($W_{stat} = 567$), *Bacteroides* ($W_{stat} = 557$) and *Ruminococcus torques* ($W_{stat} = 539$). Importantly, FSIQ score was positively associated with the relative abundance of Bacteroides, including *Bacteroides uniformis*, Clostridium, including species *Clostridioforme*, Ruminococcaceae including *Ruminococcus torques* and *Veillonella dispar*, while Prevotella was inversely associated with FSIQ score (Figure 4C).

FSIQ score of children from the higher SES villages (A/B), was associated with altered relative abundance of *Faecalibacterium prausnitzii* ($W_{stat} = 643$), *Oscillospira* ($W_{stat} = 587$), *Coprococcus* ($W_{stat} = 562$) and *Catenibacterium* ($W_{stat} = 520$). The full results of the stratified ANCOM analysis are presented in Supplementary Table S4. Notably, *Coprococcus*, *Ruminococcaceae*, including genus *Oscillospira* were positively associated with increased FSIQ score, while *Coriobacteriaceae*, *Faecalibacterium prausnitzii* and *Catenibacterium* levels were depleted with increasing FSIQ score (Figure 4D).

4. Discussion

We characterized the cognitive development of school-age children, in association with intestinal microbiome diversity and composition and environmental exposures, including SES, a major factor that influences both cognitive development and the gut microbiome.

We found a significant association between microbial α-diversity, measured by both Shannon's diversity and Pielou's evenness indices and FSIQ scores. There was a progressive

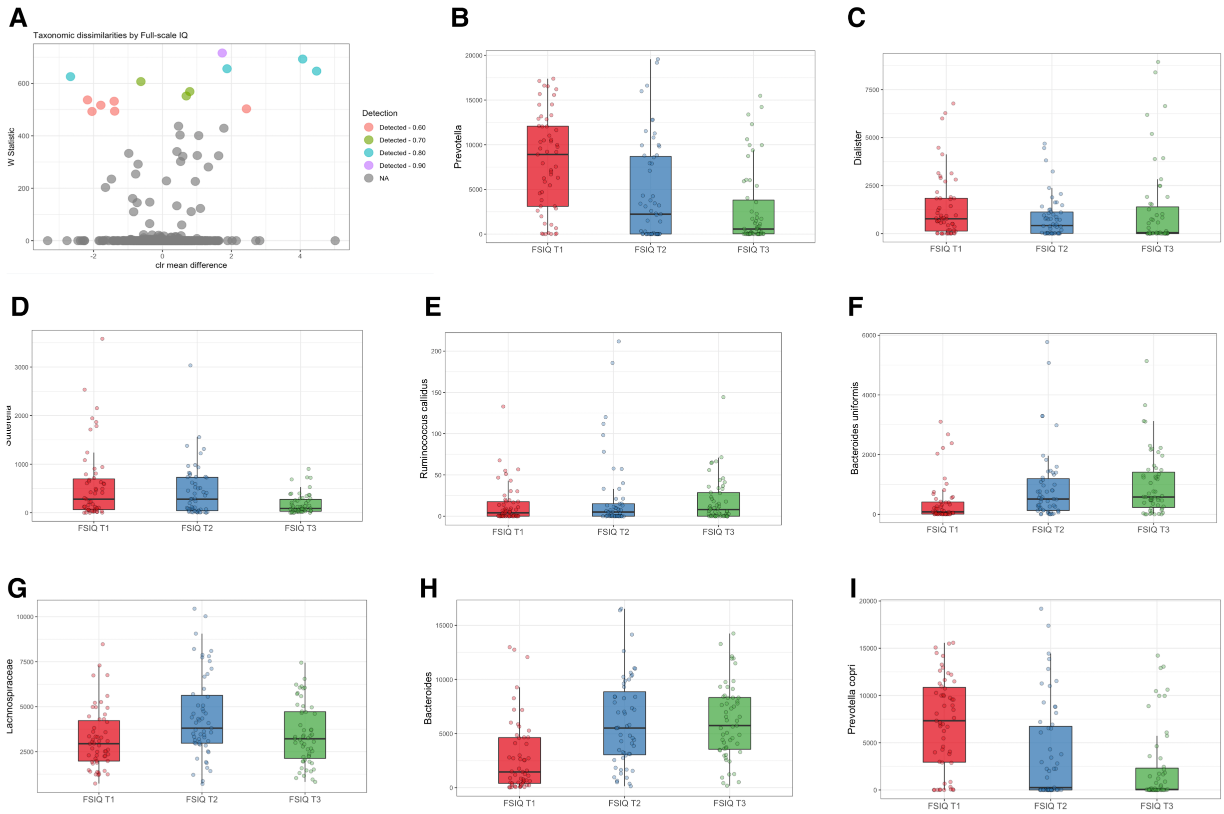


FIGURE 3
Differentially abundant taxa associated with full-scale IQ scores. (A) Volcano plot showing differentially abundant s-OTUs associated with FSIQ scores in the whole cohort, as detected by ANCOM. The *x*-axis represents the difference in mean centered log ratio (clr)-transformed abundance between groups, and the *y*-axis represents the ANCOM W Statistic. s-OTU points are colored by the level of ANCOM significance, with 0.9 being the highest level; s-OTUs in gray were not significant. (B–I) Boxplots of clr-transformed abundance of s-OTUs significantly associated with FSIQ scores, adjusted for sex, age, SES score, hemoglobin level, HAZ and BMIZ scores. Tertiles of FSIQ were categorized as low, middle and high FSIQ score tertiles, T1 being the lowest tertile (FSIQ scores between 59 and 96), T2 the middle tertile (FSIQ scores between 97 and105), and T3 the highest tertile (FSIQ scores between 106 and 127). The midline in the box plots represents the median, the lower bound of the box represents the 25th percentile, the upper bound of the box represents the 75th percentile, the lowest point of the lower whisker represents the minimum and the highest point of the upper whisker represents the maximum. FSIQ, full-scale IQ; s-OTUs, sub-operational taxonomic units; ANCOM, analysis of composition of microbiomes; SES, socioeconomic status; HAZ, height for age *z*-score at infancy (18–30 months); BMIZ, body mass index *z*-score at age 6–9 years.

increase in both diversity indices with increased FSIQ score. The Shannon diversity index accounts for both richness and evenness of s-OTUs and largely mirrors the evenness findings of this cohort. In general, lower values of Shannon diversity index indicate less diversity, thus the intestinal microbiome of children with lower FSIQ scores was less diverse, less even, and less rich compared to children with higher scores. Correspondingly, Pielou's evenness considers the number of species and the relative abundance of species in a sample. We found a positive relationship between evenness and FSIQ score. Lower values of Pielou's index represent less even distributions of species, thus implying potential dominance of some species in the gut. Therefore, in our study, lower FSIQ scores were associated with less evenness of species inhabiting the human gut. We also found significant differences in the intestinal microbiome composition according to FSIQ score. These associations were observed even after adjustment for SES and nutritional status, measured by hemoglobin levels, BMIZ and HAZ scores.

A limited number of studies examined the associations of the gut microbiome diversity and composition with children's developments, mainly between ages 2 of 3 years, (20, 54, 55). These ages are usually characterized by profound changes in the gut microbiome until it stabilizes. Unlike our study, Carlson et al. (20) in their study of 89 children aged 1–2 years demonstrated that greater α-diversity was associated with poorer cognitive performance. Streit et al. studied 323 children aged 45 months and showed weak negative correlations between alpha diversity, as measured by Faith phylogenetic diversity index and FSIQ (correlation coefficient ranged between −0.10 and −0.14), but such differences were not observed for other indices of alpha diversity when adjusting for confounders and multiple comparisons (54). Rorthenberg and colleagues studied 46 children from rural China, and reported no significant association between alpha diversity and cognitive development at age 3 years (55). The negative associations between alpha diversity and cognitive development in prior studies (20, 54), might be unexpected, since higher α-diversity usually indicates a more mature, adult-like community, while reduced α-diversity is commonly associated with poor health outcomes, including metabolic and inflammatory bowel diseases (1, 56). The

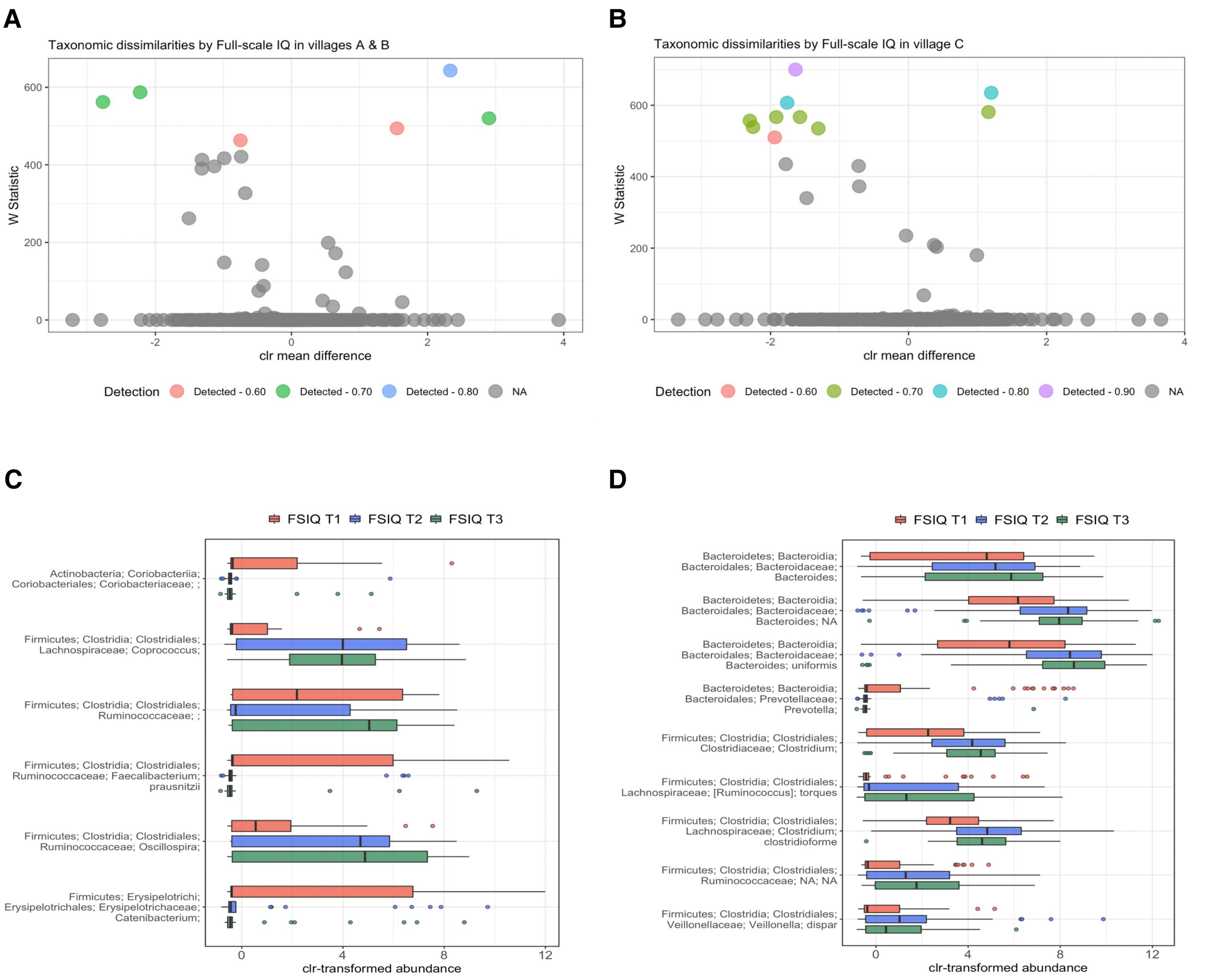


FIGURE 4
Differentially abundant taxa by village of residence and socioeconomic status. (**A,B**) Volcano plots showing differentially abundant s-OTUs as detected by ANCOM, stratified by village; A/B [high/intermediate SES] (**A**), and C [low SES] (**B**). The *x*-axis represents the difference in mean centered log ratio (clr)-transformed abundance between groups, and the *y*-axis represents the ANCOM W Statistic. s-OTU points are colored by level of ANCOM significance, with 0.9 being the highest level; s-OTUs in gray were not significant. (**B,C**) Boxplots of clr-transformed abundance of s-OTUs significantly associated with FSIQ scores in villages A/B [high/intermediate SES] (**C**) and in village C [low SES] (**D**), adjusted for sex, age, SES score, hemoglobin level (g/dl), HAZ and BMIZ scores. Tertiles of FSIQ were categorized as low, middle and high FSIQ score tertiles, T1 being the lowest tertile (FSIQ scores between 59 and 96), T2 the middle tertile (FSIQ score between 97 and 105), and T3 the highest tertile (FSIQ scores between 106 and 127). The mid line in the box plots represents the median, the lower bound of the box represents the 25th percentile, the upper bound of the box represents the 75th percentile, the lowest point of the lower whisker represents the minimum and the highest point of the upper whisker represents the maximum. FSIQ, full-scale IQ; s-OTUs, sub-operational taxonomic units; ANCOM, analysis of composition of microbiomes; SES- socioeconomic status; HAZ, height for age *z*-score at infancy (18–30 months); BMIZ, body mass index *z*-score at age 6–9 years.

differences between our finding of a positive relationship between alpha diversity and others (20, 54) showing inverse associations might be related to discrepancies in the study population, specifically, our study included school-age children that likely have adult-like stable microbiomes, while other studies mainly included infants and pre-school children, characterized by a microbiome that is still evolving.

Our model was adjusted for SES and we observed a strong and significant association between SES and cognitive performance. These results are in line with existing evidence, demonstrating the profound influence of SES on cognitive development, and behavioral outcomes (57), and on the gut microbiome at school age (25). This complex interplay between environmental exposures, the intestinal microbiome, and individual neurodevelopment emphasizes the need for tailored developmental programs and policies that are designed to alleviate SES-related disparities in cognitive performance in children.

We found significant associations between the intestinal microbiome composition and FSIQ score, which were consistent in four distance measures for quantifying β-diversity: the binary Bray-Curtis, the JSD, and the phylogenetic weighted and unweighted UniFrac. Cognitive performance explained the highest percentage of variance in all methods, followed by the SES score. Age was significantly, yet more finely associated with microbial composition. Overall, JSD was the most sensitive method capturing 16.6% of the variance. While the FSIQ score explained the most variance, SES score was an important determinant of β-diversity, suggesting that these factors independently influence both the intestinal microbiome and cognitive performance. The composition of the gut microbiome is a complex trait, with the quantitative variation in the microbiome affected by a large number of host and environmental factors, each of which may have only a small additive effect, making it difficult to identify the association for each separate item (58, 59). Falony et al. reported significant relationships between previously unidentified factors such as red blood cell count and hemoglobin levels and fecal bacterial composition (58), while in our study the association between hemoglobin level and beta diversity was not statistically significant, possibly due to the smaller sample size. Our model explained 16% of the variance in microbial composition, a relatively high percentage, nonetheless indicating the need to explore additional contributions for example from dietary habits, stochastic effects, and/or biotic interactions.

While alpha and beta diversity capture complex variation across the community, we observed significant differences in the relative abundance of specific genera and species in association with FSIQ score. High relative abundance of the genera *Prevotella, Dialister* and *Sutterella* was associated with the lower cognitive performance tertiles, while Bacteroides were positively correlated with elevated FSIQ score. Interestingly, Carlson et al. (20) described a strong association between high levels of *Bacteroides* with the highest level of cognitive performance at 2 years old. Similarly, Tamana et al. (60) showed that *Bacteroidetes*-dominant gut microbiome and higher relative abundance of genus *Bacteroides* in late infancy were associated with enhanced neurodevelopment by the age of 2 years among Canadian children, mainly among males (60). It was also found that *Bacteroidetes*-dominant microbiome was enriched with numerous metabolic functions including sphingolipid metabolism and glycosphingolipid biosynthesis. Furthermore, genes involved in metabolism of folate, biotin, pyruvate, vitamin B6, lipoic acid and fatty acid biosynthesis were enriched in *Bacteroidetes*-dominant microbial composition (60). The intestinal microbiome at 6–9 years is substantially different and more diverse compared to age two years, thus our study adds new knowledge regarding potential involvement of the gut microbiome with cognitive function at school age and not only in early life, when the gut microbiome is less mature, and still affected by early life factors, such as delivery mode (61). Collectively these findings support the idea of microbiota gut-brain-axis during childhood.

Nutrition and dietary patterns are considered major determinants of cognitive performance in children and adolescents (62, 63). For example, iron deficiency anemia is linked to lower neurodevelopmental achievements (28). We measured hemoglobin levels as a proxy for iron deficiency anemia, and included this parameter in all multivariable models, suggesting that the gut microbiome was associated with cognitive function regardless of hemoglobin levels. Additional nutritional factors might influence cognitive performance and academic achievements, including B vitamins, e.g., folate, vitamin B12 (64–66), and overall dietary patterns (63). Diet in turn affects the development of the intestinal microbiome in early life (67). We also found altered composition of the gut microbiome in relation to dietary intake of polyunsaturated fatty acids in a different cohort of Arab children aged 10–12 years (68). Our study lacks information on dietary intake of this cohort. Therefore, the associations between intestinal microbiome and cognitive function in children should be further explored in large-scale prospective studies, while deciphering potential mechanistic role of dietary intake and nutritional status in such associations and possibly intervention studies including probiotic or prebiotic supplementation to assess the association with the microbiome and cognitive performance.

Our study has some limitations. First, this is a cross-sectional study design, thus the directionality of the observed association between the gut microbiome and cognitive development remains to be determined in prospective studies. Second, diet is one of the main determinants of the gut microbiome and affects the (development) of cognitive (dys)function (24), and we did not obtain detailed dietary questionnaires for the participants. In the current cohort, early life dietary exposures were relatively similar and characterized by a high prevalence of breastfeeding, a similar age of first exposure to solid foods, and a late entrance to a daycare. Moreover, since all participants belong to the same ethnic group, they share common dietary practices, mainly a high prevalence of home-cooked, traditional meals and a diet rich in fruit, vegetables, and legumes. Nevertheless, at school-age, there are uncontrolled dietary exposures, that might have an important association with the child's microbiome and cognitive function.

We used archived stool samples that were collected during 2007–2009. There might have been changes over time, that might affect both cognitive development and the gut microbiome. The SES rank of the study villages remained stable during over one decade (69). Conversely, changes in diet and nutritional status were documented (70, 71), which might influence both the gut microbiome and cognitive development. Although, these changes should not affect the observed association between the gut microbiome and cognitive development in our study, future studies using specimens reflecting an up-to-date host-microbiome-environment interaction are needed.

The strengths of the current study include a relatively large cohort of healthy school-age children, with a defined geographic, ethnic, and cultural background, yet divergent SES. Geographic residency and ethnicity are strong modulators of the intestinal microbiome (72), thus the associations demonstrated in the current study are independent from these important confounders. Moreover, our results were adjusted for potential confounders that affect both the microbiome and FSIQ score.

5. Conclusions

We demonstrated significant associations between the gut microbiome and cognitive development in healthy school age children, independent of SES. Future longitudinal studies are needed to understand the directionality of the associations and mechanisms that might explain these relationships.

Data availability statement

Data generated in the framework of the study cannot be made publicly available due to legal and ethical restrictions. Aggregate anonymized data might be available upon request from the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institution Review Board of Hillel Yaffe Medical Center and the ethics committee of Tel Aviv University. Written informed consent was obtained from the parents of the participants.

Author contributions

The authors contributed to the study as follows: YL, study concept, analysis and interpretation of data, drafting of the manuscript, and statistical analysis. LR study design, laboratory methods, data analysis, critical revision of the manuscript for important intellectual content. MM study concept, acquisition of data and data management. DC study design, supervision, acquisition of data and samples, critical revision of the manuscript for important intellectual content. UG study design, critical revision of the manuscript for important intellectual content. AO study design, critical revision of the manuscript for important intellectual content and acquisition of funding. KM study concept and design, acquisition of data and samples, study supervision, contributed to writing of the manuscript, and acquisition of funding. All authors had access to the study data, reviewed, and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1198792/full#supplementary-material.

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How understanding and strengthening brain networks can contribute to elementary education

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Imaging the human brain during the last 35 years offers potential for improving education. What is needed is knowledge on the part of educators of all types of how this potential can be realized in practical terms. This paper briefly reviews the current level of understanding of brain networks that underlie aspects of elementary education and its preparation for later learning. This includes the acquisition of reading, writing and number processing, improving attention and increasing the motivation to learn. This knowledge can enhance assessment devices, improve child behavior and motivation and lead to immediate and lasting improvements in educational systems.

KEYWORDS

attention, memory, elementary education, number, reading, mindset

1. Introduction

In the late 20th century, it became possible to examine the living human brain during the performance of cognitive tasks, including those normally taught in school [see (1) for a review]. The main method of doing this is to place the person in a magnetic resonance imager. The signal detected in functional magnetic resonance imaging (fMRI) reflects changes driven by localized brain blood flow and blood oxygenation, which are coupled to the level of neuronal activity. This allows construction of an image of the brain marked with the areas of increased neural activity.

From the earliest studies of brain imaging it was clear that even very simple tasks, like retrieving the use of a "hammer", activated neurons in several widely separated cortical and subcortical brain areas related to different aspects of language. During the last 35 years new methods of imaging the brain have also been developed. One of these, Diffusion Tensor Imaging (DTI) allows connections between active areas of the brain to be imaged.

Many of the brain networks imaged in adults performing tasks like reading are also active when the person is not performing a task, but is in a resting state (2). The ability to image networks in the resting brain allows them to be studied even in infancy, when the baby is not able to perform a task. Language networks have been imaged from birth using this resting state method (3). Thus, during the early years of this century a tool kit of methods to study brain networks related to cognitive tasks and the resting state has been developed.

While books (4), scholarly articles and even podcasts have attempted to inform teachers and others involved in education about the relevance of brain developments, recent articles have noted widespread failure of current methods to reflect the relevance of brain imaging findings to education (5, 6). The implication of brain research for teaching in elementary schools has either not been understood or failed to be applied for other reasons.

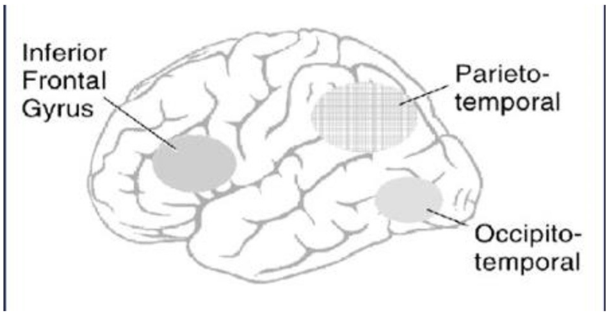

FIGURE 1
Application of imaging to reading acquisition reveals two posterior brain areas (phonological and visual word form areas), both of which can access word meaning via the ventral frontal lobe. The phonological pathway is related to word sound and the visual word form area is related to the rules for visual words (orthography). The left frontal lobe serves as a means to access semantic information stored in various brain areas.

The goal of this paper is to make clear findings in the human brain that could influence elementary school education, improving learning by students and increasing their understanding of why the effort required of them is worthwhile. We attempt to outline in a non-technical way the specific brain networks related to instruction in reading and number that are critical for elementary school subjects. In addition we discuss attention and motivation as important tools for learning. Finally, we discuss concrete steps that teachers may consider taking to assist brain changes that occur while students carry out the tasks of elementary school.

2. Reading and writing

Reading curricula in elementary school either involve phonics instruction, the whole word method or more recently a "balanced" curriculum that places emphasis on reading for meaning and is based to a large degree on whole words. Brain research has been helpful in resolving the dispute between the phonics and whole word forms of training. In literate adults two different networks connect areas in the posterior part of the brain to attention and brain areas related to meaning (see Figure 1).

One pathway involves obtaining the word name (phonological code) through blending letter sounds into words. For most readers phonics training allows them to handle either unfamiliar or familiar words by blending letter sounds to pronounce them. Words that are familiar from speaking can then be connected to the word meaning. This pathway is based on phonics training and the child's vocabulary from exposure to spoken words (7).

This form of reading is not fluent and does not by itself produce a child likely to read on their own or to enjoy reading (8). The extreme difficulty of reading without a visual word form area is illustrated by adult patients with disconnection of the visual word form area from the primary visual cortex of one hemisphere or both hemispheres. Words presented to the disconnected hemisphere are painfully sounded out letter by letter (9) rather than read fluently (9). Practice in reading induced by assignments and/or reading for pleasure builds the visual word form area. This visual word form area chunks letters into a unit and connects to word meaning (semantics). There is some evidence that the visual word form area is also developed by early reading in the first year of schooling. Thus, phonics reading instruction not only provides a basis for decoding but also helps to develop the visual word form area (10). Reading instruction encroaches on parts of the brain that are initially weakly specialized for tools and close to but distinct from those responsive to faces (10).

The visual word form area may also involve subareas of increasing sensitivity to whole words as one moves from the more early visual with area to later (more anterior) parts of the visual word form area (11). There is also evidence that the development of the visual word form area and its connections to other parts of the brain (connectivity) continues long after decoding has been developed. The time course of connectivity and function of these subareas is under active investigation (12). Exercises that expose children to materials of interest to them help to ensure that they become fluent readers as adults. Individual differences in the reliance on phonology vs. visual word form can be achieved by measuring the accuracy of sounding out nonwords in comparison to the skill of pronouncing exception words, that do not follow the common rules of orthography (13, 14). These measures could be useful to teachers to adapt their methods to ensure that each child reaches reading fluency, but may not be useful in some languages.

Children who are diagnosed as dyslexic, that is who fail to learn to read despite having the apparent ability to do so, show reduced activation of both phonological and visual word form areas (15). As expected, a computerized program to teach phonics improved the ability of the dyslexic children to sound out words and increased activation in phonological brain areas (16). In addition, emphasis on letters by spacing of the visual text can also provide help for some dyslexic children (17).

It is likely that writing may also help to develop the visual word form area. Cursive writing requires the child to develop specific movements for each letter. The emphasis on the letter as a constituent of the word may help develop both the phonological and the teaching visual word form area. In addition, there is some evidence that teach cursive writing may provide better overall memory for the material than would be the case with typing (18). This may support the idea of teaching cursive to foster development of reading skill as well as improved memory.

3. Number

The number sense allows animals and human infants to come into the world with a primitive understanding of small numbers. Babies can even perform simple calculation. For example, infants look longer when adding a puppet to the display of one puppet produces a single puppet than when it correctly reveals two puppets (19). Thus babies, like adults, can be puzzled by an error in the visual display of small quantities and this detection activates part of the executive attention network [(20) described in the attention section of this paper].

When adults are asked to determine which of two digits is larger they are faster the larger the distance between the two. We believe this result arises from representation of quantity within the brain's parietal cortex that is called the number line. It is a

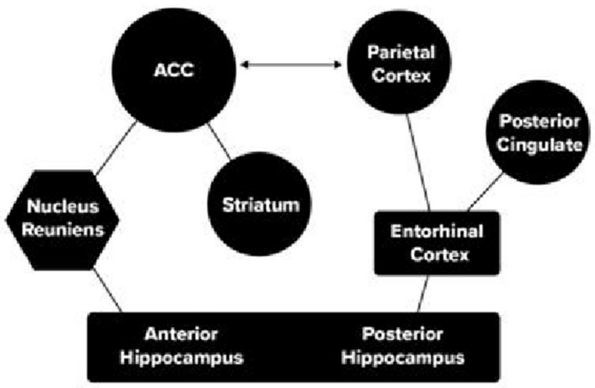

FIGURE 2
Two pathways between attention nodes (circles) and memory (rectangles), anterior pathway between attention and memory (hexagon). Reprinted with permission from Frontier Neuroscience (24).

goal of specific training to develop and expand this representation of quantity. Wilson et al. (21) used a race game which required number comparison. Performance on number comparison did improve, but a subsequent study showed that it did not improve more than a control condition and did not generalize to other math skills (22).

A four-week training program using several games, including the race game used in the Wilson et al. study, produced improved appreciation of quantity and strengthened connections in a brain pathway between the parietal lobe and hippocampus (23). This pathway also plays a role in retrieval of newly learned associations (see Figure 2).

Although much research remains it does seem possible to aid in the development of the number line that forms a basic understanding of quantity and serves as a framework for early arithmetic. Another important step for the teacher is to ensure that the concept of quantity is connected to the language network to allow exact calculation (25). This effort could involve discussion of sample problems designed to have the student articulate their concept of quantity in their own language and thus help in the development of the connections between the number line and language that is needed for exact calculation (25).

4. Attention and learning

Most of school learning depends on paying attention. Viewing attention as having a single unified function creates confusion in applying it to classroom learning. There is no single brain network of attention, and so far, three mainly different brain networks are related to (1) obtaining and maintaining the alert state, (2) orienting to sensory information, and (3) executive control of voluntary behavior, thoughts and feelings. Each of these functions involves largely separate networks of attention (26, 27).

Both the orienting and the executive attention networks have connections with memory formation and retrieval involving the hippocampus, a central node in consolidating and retrieving long term memories. Figure 2 indicates two somewhat separate pathways between attention and memory networks.

The executive attention network connects the Anterior Cingulate Cortex (ACC) through the thalamus to exert control of the anterior hippocampus during storage of information (28). A posterior route between the parietal orienting network and the hippocampus is largely involved in navigation in rodents and more general retrieval from long-term memory in humans (24).

Two forms of training have been found to improve attention networks. One involves young children and is a 5-day adaptation of training used to send chimpanzees to perform work in space (29). It began by teaching 4–6-year-olds to use a joystick and ended with practice in resolving conflict (30, 31). It has been shown to improve the network underlying self regulation and control of cognition and to allow more behavioral control over delay of gratification. A second method involves training the control of attention through forms of mindfulness meditation. Five days of meditation training improved executive attention (32) and two weeks of training produced a strong 4–8 Hz (theta) rhythm over the frontal cortex even when the person is at rest (33). In mice, 4 weeks of near theta stimulation in the ACC changes connectivity near to the site of stimulation (34).

The ability to train attention in childhood through network training and meditation shows promise as a way of helping children to learn. Attention training was used in central Europe to reduce the gap between high-and-low income families and increase school success (1). Training attention either directly through cognitive exercises or through meditation could be used for the same purpose in the US schools where inequality in pre-school education remains high.

5. Training mindset and improving function

There is substantial evidence that the beliefs students have about their brain can greatly influence their behavior (35, 36). For example, those with a growth mindset, who believe that intelligence can be changed by effort, show greater ability to attend and learn new material than those with a fixed mindset, who believe intelligence is fixed and effort has little influence (37). In one study, children with fixed mindset show larger frontal activity to negative feedback but sustained their attention less and learned less than those with a growth mindset, who use negative information to sustain learning. In a national sample of 6,320 American adolescents a one-hour mindset intervention delivered on-line in two sessions not only improved their growth mindset but also improved school achievement for low and medium level students. High level achievers showed reduced variability in their already strong grades (38).

A four-week growth mindset training program was designed to enhance foundational, school related, cognitive skills in 7–10-year-old children (39). The training included a one-on-one tutoring program in number skills and on-line games related to the number sense. In comparison with a non-contact control group the trained children not only improved in growth mindset but the improvement in mindset predicted the improvement in later math skills. Prior to and after training an fMRI was given while children performed a math problem solving (addition) task. The gains in growth mindset were strongly associated with increased activation of the dorsal ACC and to a lesser extent the hippocampus. There were also significant connectivity increases between the ACC and the hippocampus.

Thus, change in mindset from a strong intervention strengthened the pathways between attention and memory during mathematics problem solving. These results show that growth mindset not only provides information on the child's attitude but also serves as a possible proxy for the strength of pathways between attention and memory and provides evidence that intervention can be effective in improving their strength.

6. Lessons for elementary teachers

Neuroscience does not dictate the correct curriculum for teaching reading, writing or arithmetic.

What it does do is equip the designers of these curricula and those responsible for their execution with a view of the underlying brain structures and changes that are involved when learning this material. These principles can be associated with assessments that reveal how the affected brain structures are working. These assessments do not require the use of brain scans or other neuroscience methods that are critical for knowledge about the brain.

What might teachers do to achieve the needed background for applying neuroscience findings to their work? Jolles and Jolles (5) argue that four themes in neuroscience are critical for obtaining such knowledge. These are:

Theme 1. The nervous system controls and responds to body functions and directs behavior.

Theme 2. Nervous system structure and function are determined throughout life by genes and environment, including the person's own actions.

Theme 3 The brain is the foundation of the mind.

Theme 4: Research leads to understanding that is essential for development of therapies for nervous system dysfunction and helps improve the circumstances under which people learn.

For more general principles of classroom mangement based on psychological research the reader could turn to https://www.apa.org/ed/schools/teaching-learning.

It may be necessary that every school granting credentials to teachers make sure that at least this level of knowledge is available, and every school board might seek to hire and reward teachers with this relevant knowledge.

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Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Positive or negative environmental modulations on human brain development: the morpho-functional outcomes of music training or stress

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In the last couple of decades, the study of human living brain has benefitted of neuroimaging and non-invasive electrophysiological techniques, which are particularly valuable during development. A number of studies allowed to trace the usual stages leading from pregnancy to adult age, and relate them to functional and behavioral measurements. It was also possible to explore the effects of some interventions, behavioral or not, showing that the commonly followed pathway to adulthood may be steered by external interventions. These events may result in behavioral modifications but also in structural changes, in some cases limiting plasticity or extending/modifying critical periods. In this review, we outline the healthy human brain development in the absence of major issues or diseases. Then, the effects of negative (different stressors) and positive (music training) environmental stimuli on brain and behavioral development is depicted. Hence, it may be concluded that the typical development follows a course strictly dependent from environmental inputs, and that external intervention can be designed to positively counteract negative influences, particularly at young ages. We also focus on the social aspect of development, which starts *in utero* and continues after birth by building social relationships. This poses a great responsibility in handling children education and healthcare politics, pointing to social accountability for the responsible development of each child.

KEYWORDS

development, brain, behavior, childhood, environment, music, stress

1. Introduction

The study of brain development from pregnancy to adult age has been devoted for years to establishing a fix sequence of events in the morpho-functional development. This vision was the consequence of two concurrent causes, in different fields of knowledge. First, the development of theories of cognitive development in the field of child psychology, during the last century, that described a rather fixed sequence of functional acquisitions from birth onwards, during typical development. This brought forward the underlying idea that both the sequence and timing of acquisition were rather stable and culture-independent, at least in the first phases of development. A revision of the literature on these topics is outside the scope of this review: the readers can refer to the seminal works of leaders in the field, like Jean Piaget and Lev Semënovič Vygotskij. Second, in the emerging field of neuroscience, most data on brain development were from histology, while physiological recordings were limited to certain ages and were mostly not intended to detect lifelong changes. This had the consequence of transmitting the idea that fixed steps of structural and functional development are reached at precise times, with an invariant sequence and limited variability in timing. Some notable exceptions included the studies on plasticity of the visual cortex, that led David Hubel and Torsten Wiesel to share the Nobel prize in 1991. However, technical advances like functional neuroimaging and powerful electrophysiological registration, coupled to the enhanced information processing and miniaturization of devices, led in the last three decades to a paradigm shift in neurosciences. This happened for the inspiring works of Penfield on cortical registrations (Penfield and Boldrey, 1937; Penfield and Jasper, 1954), leading to the definition of brain functional maps (the so-called 'homunculus'), that now appear more and more plastic even in adults. It is becoming increasingly clear that any function of the brain emerges from a complex network of interactions between gene expression and environmental inputs, at the micro- and macro-scale. Under usual circumstances, moving from one step to the other occurs along a phylogenetically defined best-fit pathway, common to most mammals, that goes from sensory-motor to social and cognitive development, linked to the maturation of specific brain areas and networks. As such, any anomaly may hamper the typical developmental scheme (see Figure 1) and triggers a wealth of downstream effects aimed at fixing the path, with outcomes that may be fitting or not.

However, during the developmental path (summarized in Table 1) some critical periods of particular sensitivity and plasticity may be delimited, which span through infancy (for example: language acquisition) and extend to adolescence, in particular for some functions like memory and social stress management (Fuhrmann et al., 2015). Actually, time is a critical factor in development, since the susceptibility to some influences may dramatically vary, as well as the consequences at different time frames, including biochemical, electrical, genomic and epigenetic mechanisms, up to the effects at the level of development of the organism, which may be lifelong (Boyce et al., 2020).

Here we review the recent literature on the development of the human brain and its susceptibility to both negative and positive environmental influences. A search on PubMed was done on March 24, 2023 with the following terms: BRAIN and PLASTICITY and CHILD and DEVELOPMENT, in any field, with no filters for language or year of publication: 1705 papers were retrieved. By applying the filters: Meta-Analysis, Review and Systematic Review 573 papers were excluded to give 1,132 papers. The goal was to focus on healthy brain development, hence abstracts were read and evaluated to exclude papers exclusively or mainly related to Autism ($n = 75$), other diseases ($n = 376$) or out of focus, including studies done on cells or animals, or retracted studies ($n = 311$). The resulting 370 articles were evaluated, sorting out those describing studies on the morphological and functional normal development of the brain, stress effects on the brain and music training effects on the brain. Articles related to second language learning or other manipulations were excluded, as well as comment articles or introduction to issues, or duplicate publications (same authors, title or content, also in different languages). The 125 resulting relevant articles are reviewed here.

2. Morphological and functional development of the brain

2.1. Structural changes across development

A large longitudinal study addressed the question of whether cognitive improvement preceded, accompanied or followed the changes in the thickness and surface area of the cortex from infancy to adulthood, when an association between cortical measurements and cognitive performance is apparent: being the rate of change at each measurement predictive of subsequent changes, it was concluded that structural changes in the cortex are related to cognitive performance and *vice-versa*, without a clear sequence in any measure (Estrada et al., 2019). Cortical thickness has been also specifically

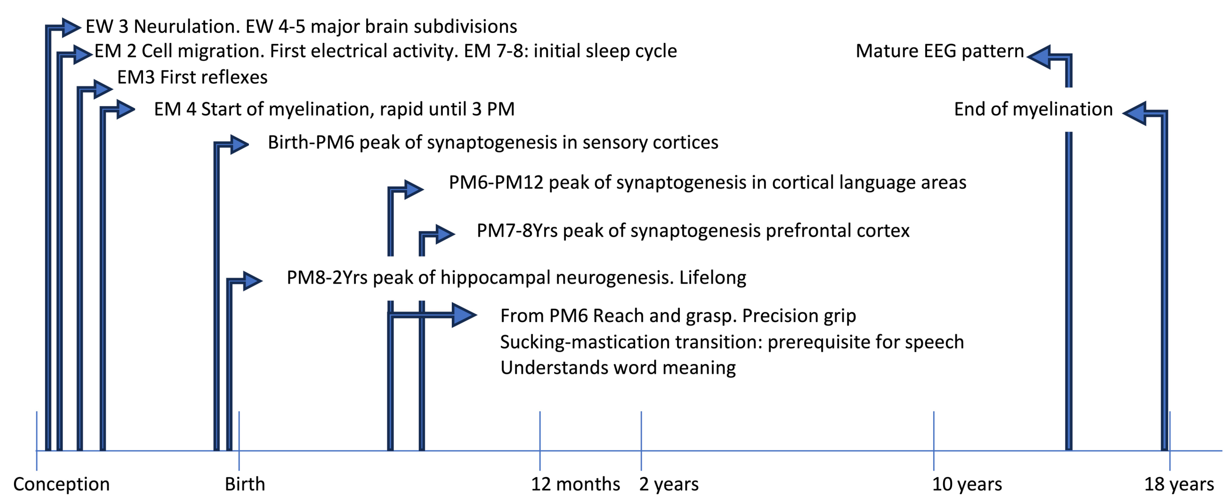

FIGURE 1
The timeline shows some acquisitions during typical development. EEG, electroencephalographic; EM, embryonic month; EW, embryonic week; PM, postnatal month; Yrs, years.

TABLE 1 Summary of the main developmental steps during infancy.

Age	Stage of development	Main changes	Developmental abilities
Prenatal period	Fetal development	Structural features of the brain Neurons and synapses start to mature from the spinal cord Gyri and sulci formation First synapses and myelination	- First movement of the fetus - Sensory development of the fetus
First two years	Sensory-motor stage	Gradual development of prefrontal cortex and cerebellum Fusiform gyrus (visual attention) Myelination increase Visual/auditory cortex Increased brain connectivity Experience dependent synapse formation	0–3 months - Development of visual and sound perception: turns head toward speakers and follows face - Emerging head control - More controlled movements (hands in the middle line) - Looks at adult face/Respond to facial expression - Smile at response
		Continue development of motor cortex Visual/auditory cortex Experience-dependent synapse formation	3–6 months - When pulled to sitting, holds head in line with body - Reaches side position - Mouths toys - Reaches and grasps toys - Looks toward noises - Smiles in response to speakers
		Connectivity between the amygdala and bilateral anterior insula (fear expression); experience dependent synapse formation	6–9 months - Sits alone and extends arm if falling to the side - Crawls forward on belly - Picks up object easily and transfers them from hand to hand - Expresses emotional states - Responds differently to caregivers and strangers - Looks at objects and family members when named - Imitates facial expressions, actions and sounds
		- Angular Gyrus/Broca area maturation	9–12 months - Cruises holding on the furniture - Stands alone momentarily - Imitates actions (claps hands and waves on command) - Turns when called by name - Gives objects by request - Expresses emotions and affections - Articulates most speech sounds
		- Angular Gyrus/Broca area refinement (receptive language and speech production)	12–24 months - Walks forward and backwards - Walks up and down stairs with assistance - Demonstrates use of everyday items - Language fast development - Plays alone and with peers
2–7 years	Pre-operational stage	- Synaptic density in the prefrontal cortex reaches its peak - Frontal and temporal lobes (executive function and emotional regulation)	- Language improvement - Increased cognitive abilities - Uses symbols in play and pretending - Executive functions (attention control, memory self-regulation, emotional regulation)

linked to different neurodevelopmental and psychiatric disorders (Patel et al., 2021).

Normative structural data in the first 6 years of life highlight a generalized thinning of cortex, with the exception of the occipital areas, which first decrease and then become thicker (Remer et al., 2017). Cortical thinning is mostly related to pyramidal neurons, astrocyte and microglia marker genes (Shin et al., 2018). Also, during the first 5 years of life, genes in cortical neurons change dramatically their methylation status, while later changes are much reduced (Price et al., 2019).

Structural maturation of the frontal cortex, crucial for executive functions, requires a prolonged postnatal development, which involves also the migration and integration of newly formed inhibitory interneurons (Paredes et al., 2016). Interestingly, inhibitory control training in children shows larger effects that in adolescent, both on the efficiency of behavioral control and in the structure of some subdivisions of the inferior frontal gyrus in the prefrontal cortex (Delalande et al., 2020). Maturation of cortical circuits are also echoed by biochemical fingerprinting in specific cell types. Neural cell adhesion molecule (NCAM) isoforms are implicated in cell migration, axonal growth and synaptic plasticity, besides schizophrenia. As determined in post-mortem samples, they peak at different times during development in the various areas, from fetal/early infancy to late adolescence, supporting specific roles in neural circuitry formation, emerging at precise developmental timepoints (Cox et al., 2009). Also, connections between areas mature with time: for example, at 9 months the connections over longer distance are emerging, while local network connectivity decreases (Damaraju et al., 2014). Throughout development, structural and functional connectivity develop with non-linear trajectories, which also differ for the various areas, starting *in utero* and extending to late adolescence (Vandewouw et al., 2021). Increased connectivity boosts the emergence of executive and cognitive functions, with a differential contribution of the striatum, which improves cognitive functions in childhood through increase in the cortico-cortical connections, while its effects on the executive functions appear less age-related (Darki et al., 2020). During adolescence, myelin microstructure refines to increase the speed of electrical signal transmission, at the expenses of diminished plasticity, and mature first in sensorimotor areas and then in associative areas (Baum et al., 2022).

2.2. Development of sensory-motor functions

In the striate cortex, functional plasticity mirrors the number of synapses that peaks in the first year of age and is rapidly refined and reduced in the subsequent pre-school years (Huttenlocher and de Courten, 1987). Early imaging studies reported a decrease in grey matter of frontal and parietal cortices during adolescence (Jernigan et al., 1991), while enzymes related to cholinergic and glutamatergic neurotransmission vary across the entire lifespan, in specific areas (Court et al., 1993). Notably GABA-ergic neurotransmission show a protracted period of postnatal refinement, spanning the first years of life and possibly accounting for the protracted plasticity of visual areas, which allows therapeutic interventions (Murphy et al., 2005).

Also, in the primary motor cortex GABAergic interneurons mature after childhood, fostering plasticity and motor learning (Walther et al., 2009). Contrary to findings in monkeys, in humans the corticospinal projections start connecting with spinal cord at 24 post-conception weeks, between 2 and 4 postnatal months the spontaneous activity becomes more coordinated between limbs, yet functional control of distal effectors is reached much later, between 6 and 12 months of age, to support goal-directed movements (Eyre et al., 2000; Kanemaru et al., 2012).

Movement of the hand requires the identification of targets, which is usually based on vision: already 2 days after birth, newborns may be trained to discriminate kinematic patterns of biological movement, characterized by subsequent acceleration/deceleration, even if they spontaneously do not (Craighero et al., 2020). Already at 5–6 months, the movement of the hand is typically directed to a person or to an object: this specificity is missing in children not sharing typical developmental paths (Ouss et al., 2018). Sensorimotor coordination accuracy improves in primary school children while sensorimotor integration relies on subcortical circuits maturing at a later stage, towards adulthood (Savion-Lemieux et al., 2009). On the other hand, in children and adults, observation of an action activates the same mirror-neurons system (premotor cortex-inferior frontal gyrus and posterior parietal lobe), but with a more widespread and more bilateral activation in children than in adults (Biagi et al., 2016). Human movement develops through the progressive control of tools use, which requires a complex dynamic between body size representation and sensory inputs, so that only in late puberty the body representation acquires adult features and may rely on proprioception instead of visual perception (Martel et al., 2021). Of note, children do not adapt as adults to tactile stimuli, until 8–10 years of age, suggesting a different sensory experience in addition to a different stimulus processing (Domenici et al., 2022).

Expert visual processing of face is lateralized to the right hemisphere and requires visual input during infancy to become fully operational, suggesting protracted need for stimulation (Le Grand et al., 2003), yet face specialization starts before reading acquisition an impinges on the decreased cortical responses to the other stimuli (Cantlon et al., 2011), as well as on higher glutamate relative to GABA levels in the inferior frontal gyrus (Cohen Kadosh et al., 2015). Similarly, movement-directed visual attentional shifts for actions appears already at 7 months, suggesting concomitant maturation of visual and attentional systems (Daum et al., 2016). Later on, during school-age period, the increase in activity of the adrenal gland with dehydroepiandrosterone (DHEA) surge, promotes the concomitant maturation of amygdala with occipital lobe, related to visual awareness, parietal lobe, related to visuomotor abilities, and frontal lobe, related to attention (Nguyen et al., 2016). Apparently, DHEA in childhood helps optimization of attentional and working memory functions but may impair the processing of spatial cues by reducing the connections from hippocampus to cortex (Nguyen et al., 2017).

Functional lateralization requires the maturation of corpus callosum, which has a critical refinement period after 6 years of age, thus affecting language transfer between the two hemispheres (Westerhausen et al., 2011). Myelinization is indeed critical for full functional maturation, but while myelin turnover is fast, the number of oligodendrocytes in the corpus callosum is stable from childhood, with a yearly exchange rate of only 1 out of 300 (Yeung et al., 2014). Prolonged maturation and myelin plasticity appear related also to increased functional cognitive ability already by 3 years of age (Deoni et al., 2016). In the first 2 years of life myelination and microstructural properties of glia appear related to cognitive abilities, with protracted development associated to better performance in cognitive and language tasks (Girault et al., 2019). Also, cortical thickness in the first 2 years appears related to cognitive abilities, yet the contribution of gestational age and maternal education may overcome structural differences (Girault et al., 2020).

More complex sensory functions, including multisensory integration, appear subsequently after middle childhood (Ernst, 2008), and their fine-tuning appears complete by 14 years (Brandwein et al., 2011). Cognitive mathematical abilities may be related to white matter in the left parietal lobe (Matejko et al., 2013) and better outcomes of intense math training rely on left perisylvian tracts plasticity (Jolles et al., 2016a), with a specific effect on connectivity of the intraparietal sulcus, but not of the angular gyrus, with hippocampus, lateral prefrontal and ventral temporo-occipital cortex (Jolles et al., 2016b). The intraparietal sulcus content in glutamate and GABA appears developmentally linked to math abilities (Zacharopoulos et al., 2021). Similarly, abacus training in primary school children improves performance and executive functions by modulating frontoparietal activation (Wang et al., 2017), and appears linked to the volume of fusiform gray matter (Zhou et al., 2022). In the first 2 years of primary school, better outcomes in mathematical abilities are associated with specific changes in some cortical areas, in detail: arithmetic abilities are linked to folding change in the right intraparietal sulcus, and thickness changes in right temporal lobe and left middle occipital gyrus, while visuospatial abilities are linked to right superior parietal thickness, and other frontal areas in the right hemisphere (Kuhl et al., 2020). However, complex visuospatial tasks elicit strong bilateral parietal activation in both adults and children from age 5 onwards (Ferrara et al., 2021).

Quantitative differences in cognitive abilities, operationally defined as a higher IQ, appear linked to a prolonged sensitivity to environmental influences (Brant et al., 2013) while its relationships to cortical thinning and surface area in late childhood appears controversial (Burgaleta et al., 2014; Schnack et al., 2015). Functional control for cognitive functions emerges at a later time, for example executive attention is linked to planning and inhibitory control, and allows the development of self-regulation (Rueda et al., 2005). Functional plasticity appears high in late childhood also for memory function (Brehmer et al., 2007). Emotional regulation steers impulsivity in the context of prospective thinking: it appears in late childhood and is related to insula thickness (Churchwell and Yurgelun-Todd, 2013). As outlined above, amygdala development is crucial in managing the emotional reactivity: it is noteworthy that the paralaminar nuclei of amygdala host a population of immature cells that slowly develops through childhood and adolescence into excitatory neurons but still persists even in old age, suggesting a protracted plasticity in this area (Sorrells et al., 2019).

The developmental trajectory goes through a reduction in modularity and local efficiency of brain processing, while increasing global efficiency. This increase in the efficiency of global processing, linked to functional maturation, initially affects sensorimotor areas. At variance, associative and paralimbic areas show a protracted plasticity during late childhood, which may account for peripubertal behavioral modulation (Khundrakpam et al., 2013). In school-age children, enhanced brain modularity may also prepare for disclosing effects of physical activity on cognitive and executive functions (Chaddock-Heyman et al., 2020).

2.3. Sleep to grow

Already during the first year of life, the pattern of night sleep and awakening may predict typical and atypical cognitive trajectories (Pisch et al., 2019), while slow waves propagation during the night, which depends on brain connectivity, is reduced in toddlers compared to older children (Schoch et al., 2018). Also, the decline in slow-wave non-REM sleep activity is steeper during adolescence, in caudal-rostral direction, suggesting late functional reorganization following structural synaptic pruning (Feinberg et al., 2011). At variance, local increase in slow-wave activity over the right parietal areas, related to visuomotor-dependent plasticity, is higher in children (Wilhelm et al., 2014), as it is the slow-wave increase in left frontoparietal areas after working memory training (Pugin et al., 2015). Around 1 year of age, sleep spindles appear to be related to semantic generalization of words (Friedrich et al., 2015), while in school-age children the learning-dependent hippocampal activity and sleep-related frontal activity do change at a faster rate than in adults (Urbain et al., 2016). Children also show the largest overnight slope change in slow waves, which may be related to the increased plasticity of children brain (Jaramillo et al., 2020). Slow waves are generated by corticocortical connections while spindles results from thalamocortical activity and in adolescents appear modulated by genetic background in posterior areas, while spindles in anterior areas are more sensitive to environmental factors (Rusterholz et al., 2018). Interestingly, the larger modulation of slow-wave activity during night in children is not accompanied by the change in glutamate/glutamine which is apparent in adults, pointing to different biochemical pathways in children (Volk et al., 2019). Another feature of human EEG activity is the alpha oscillation, which shows a maturation during childhood, most apparent for the aperiodic component: this is related to increased thalamocortical connections and attentional performance (Tröndle et al., 2022).

3. How environment may interact with developmental trajectories

The effect of environment on development can be positive or negative from the very beginning of pregnancy throughout postnatal life. Among negative environmental regulations with a heavy societal impact, the effect of pre-natal alcohol exposure has long been studied in both animals and humans. Several studies have documented the long-lasting effects of maternal alcohol consumption on both the structure and functions of the developing brain and ultimately child fitness. Despite the detailed discussion of this topic is outside the scope of this Review, we highlight that early longitudinal studies proved the adverse effects of heavy drinking during pregnancy on the morpho-functional development, in particular in the parietal cortex (Lebel et al., 2012) and in the development of white matter in relation to executive functions (Gautam et al., 2014).

Also, other environmental stimuli or their absence may interfere with the development of structural features and functional acquisitions during postnatal development. In order to develop harmonic abilities, the interaction with environment may foster or hinder functions after their appearance. As an example, children with blind parents normally show the eye contact from birth, which usually is a common means of communication, but by age 6 months onwards they display progressively less attention to gaze processing, even if this is not related to impairments in social or cognitive abilities, suggesting that even 'obvious' abilities require a strong social/environmental input and practice to be fully operational (Senju et al., 2015). Hence, the neuroscientific literature provides several lines of evidence that support the steering role of environmental stimuli in early development, with durable effects in different areas, both anatomical and functional, including cognitive, emotional, and social abilities.

3.1. Case studies

Here we briefly introduce two examples, one of negative (stress) and one of positive (music training) environmental influences on the development of the brain and its functions, to highlight how much we as adults are responsible for the life paths of future generations. In order to include articles from different countries, socioeconomical status and cultures, we focused on two modulators that were less likely linked to these factors. Stressful environmental conditions like low socioeconomical status, trauma or neglect share similar characteristics among different cultures. Also, music and music training are widespread in all cultures, and include learning sensory-motor abilities which makes them less dependent on overall cognitive abilities or higher socioeconomical status than, for example second language training. Thus, music training appears a robust example to explore in this review.

3.2. The role of stress

Stress may profoundly impact on neurodevelopmental trajectories, at different ages, by means of the different neural, endocrine, neuroendocrine, metabolic and immune responses. Notably, the brain itself is the target of stress hormones, that shape the brain stress response, tuned to plasticity, a double-edged sword that may either blunt or enhance adaptive responses, modifying the vulnerability to early life stressors. Under this respect, the concept of resilience includes the processes leading to positive adaptation to relevant traumas or adverse challenges. Early rehabilitation and care, including proprioceptive stimulation as sensory-tonic stimulation and kangaroo care, coupled to parenting support may influence the development of very preterm infants (Guittard et al., 2023), while severe maltreatment or abuse impairs functional and structural brain development, thus representing a relevant threat for the single person and a significant cost for society. Hence, boosting resilient responses in high-risk persons may promote neural and neuroendocrine plasticity to decrease maladaptive or even psychopathological responses (Cicchetti, 2010). In the first 2 years of life, elicited imitation task as a tool to investigate declarative memory, reveals that neglected children do not receive maternal feedback while abused children do, leading to a loss of plasticity in neglected children, while increased imitation in abused infants possibly leads them to increased cognitive but decreased social competence (Cheatham et al., 2010). The brain-derived neurotrophic factor (BDNF) is involved in synaptic plasticity and is differentially expressed in childhood (Sterner et al., 2012). Interestingly, the exposure to unfavorable environment leads to depression in persons carrying the Val66Met BDNF polymorphism (Comasco et al., 2013), with Val carriers of the same polymorphism more prone to self-injurious behavior (Bresin et al., 2013), while childhood abuse in Met carriers results in poorer cognitive performance and brain anomalies, including larger lateral ventricles and reduced right hippocampus (Aas et al., 2013). The same polymorphism appears to impact stress experience more at late stages (Lehto et al., 2016). BDNF methylation in adolescent brain is related to neighborhood disadvantage and thinner lateral orbitofrontal cortex (Wrigglesworth et al., 2019). Children outcome on different measures was linked to parenting quality, but also to BDNF status and genes involved in dopamine and serotonin neurotransmission, that appear to convey some vulnerability to environmental stress, fostering the vision of a continuum of general traits to describe the responses to stress, instead of two susceptibility traits (e.g., the orchid/dandelion duality) leading to different responses (Zhang et al., 2021). By widening the analysis to the BDNF gene network, it appeared that this network interacted with adverse prenatal conditions to affect later cognitive development, so that a high BDNF network score coupled to high prenatal adversity resulted in slower cognitive development and grey matter density in associative cortical areas (de Mendonça Filho et al., 2021).

Material hardship linked to poverty may lead to different amygdala-prefrontal cortex connectivity in late infancy, and leads to reduced amygdala-orbitofrontal cortex connections in adolescents, also related to anxiety and depression, indicating some preferential windows of plasticity for targeted supporting interventions (Hardi et al., 2022).

Low socioeconomic resources may impair visual working memory, as a proxy for cognitive abilities, and related brain activity in the left frontal cortex of children up to 4 years old (Wijeakumar et al., 2019). The socioeconomical status may result in differential exposure to language or stress, which may be the bases for the differences in hippocampus and amygdala seen in socioeconomically disadvantaged children, with an additional contribution of age, inducing additional differences in the left superior temporal and inferior frontal gyri (Noble et al., 2012). Similar reductions in amygdala and hippocampus were detected in children experiencing early life stress in the form of physical abuse, early neglect or low socioeconomic status (Hanson et al., 2015). Child abuse appears also to affect the morphological complexity of the prefrontal cortex and to increase recruitment of perineuronal networks, mediated by oligodendrocyte precursors, that lead to decreased plasticity (Tanti et al., 2022).

A large study confirmed that trauma exposure resulted in adolescent thinner superior frontal gyri and right amygdala and larger cingulate cortices (Jeong et al., 2021). Child maltreatment results in increased Cornu Ammonis (CA) 4 subfield of hippocampus, most apparent in males, while larger CA1 is associated with late-onset psychopathology, suggesting that maltreatment differentially affects hippocampal subfields, which may precede the appearance of psychopathology (Whittle et al., 2016). The level of self-perceived stress is also associated with smaller hippocampal volume in adolescents (Piccolo et al., 2018), and in a longitudinal study, attachment dimensions like anxiety and avoidance were linked to larger decreases in prefrontal and anterior temporal cortices in adolescent brain (Puhlmann et al., 2023).

In adolescents, post-traumatic stress disorder, as a result of altered fear regulation, is linked to decreased grey matter volume in the centromedial and basolateral amygdala, whose connectivity with left orbitofrontal and subcallosal cortices is increased, while connections to the right cingulate and prefrontal cortices appear less strong (Aghajani et al., 2016).

Volumetric correlations among different areas indicate that prenatal stress but not childhood trauma may de-couple amygdala growth from the development of other regions involved in emotional processing (Mareckova et al., 2022). Early childhood deprivation induces long-term modifications, apparent in adult white matter tracts, in particular of the limbic circuits and long-ranging association fibers, while the microstructural organization appears not altered (Mackes et al., 2022). Also, epigenetic changes in some genes associated to child abuse may enhance the risk of child depression

(Weder et al., 2014), and regions of low methylation differentiated children receiving less tactile contact (Moore et al., 2017). Lastly, genome-wide mapping fished out some loci linked to postnatal stress and subcortical structures like caudate and accumbens nuclei, which have a role in neuronal plasticity and neurodevelopmental disorders, however causality remains to be ascertained (Bolhuis et al., 2022).

3.3. Music training – positively steering development

Highlights for positive experience-related brain plasticity stem from the effects of music training in infancy, because of the worldwide diffusion of music across all human cultures, paralleled by a widespread training at young age, which is however not diffuse to all persons. Because of the multimodal nature and prolonged practice of instrument or voice, music training appears well suited to exploit plastic capabilities of the brain.

Adult musicians show increased sound discrimination, as a result of training. Early music training enhances children performance in specific musical skills like melody discrimination (Ireland et al., 2019). After 2 years of training in school age children, an improvement in tonal discrimination and increased maturity of auditory processing are apparent (Habibi et al., 2016). In 9 to 15 years old trained or untrained subjects, cognitive flexibility was linked to sound discrimination performance, which was more apparent in music-trained group (Saarikivi et al., 2016).

Instrument practice allows a regional-specific increase in the organization of the pyramidal tract already in childhood (Bengtsson et al., 2005) and extend to cognitive abilities underlying musical training, initially on more closely related fields (Schlaug et al., 2005). Long lasting effects on motor performance appear stronger if the music practice starts before age seven, even if the amount of training was similar, pointing to the existence of a sensitive period in infancy (Penhune et al., 2005).

Interestingly, even relatively a short period (9 months) of music training may produce benefits for pitch processing in music but also in language, showing that cognitive benefits extend over different cognitive domains, by modifying their neural substrates and related pattern of brain activity (Moreno et al., 2009). Musical and linguistic syntactic abilities may be learned through similar processes in early infancy and about age 4–5, music training affects timbre identification and improve language abilities, like morphologic rule formation and memory for words, showing that training effects extend beyond the music domain (Marin, 2009). Notably, increased right brain activity due to human voice processing is related to intelligence in toddlers and school-age children (An et al., 2020).

Preschool children benefit even from short (20 days) music training, whose effects spill over to verbal intelligence and executive function tasks (Moreno et al., 2011). Over 2 years of training around 8 years old, speech segmentation skills improve more than in untrained children suggesting therapeutic strategies for children with language impairments and related learning difficulties (François et al., 2013).

In preschool children, music or second language training induce long-lasting improvement in processing of the trained sounds and increase suppression of untrained, non-relevant sounds, as shown by event-related potentials (Moreno et al., 2015).

By exploring the brain structure, aptitude to music in school-age children is related to pre-training structural organization of the right corticospinal tract while the corpus callosum structure appears more linked to tonal ability (Zuk et al., 2022).

Increased pitch discrimination is related to larger auditory regions in both untrained and music-trained adults and children, while in musicians it is also associated to larger inferior frontal gyrus (Palomar-García et al., 2020).

After only 15 months of practice, music training may induce structural changes in the brain, directly related to improvements in auditory and motor skills (Hyde et al., 2009). Apparently, starting musical training before age 7 changes white matter connectivity, more robustly in the isthmus of corpus callosum: therein, fractional anisotropy, related to myelinization, is linked to both age of starting the training and sensorimotor synchronization performance (Steele et al., 2013). On the other hand, the benefits of music appear to extend also to prenatal age, since in preterm infants exposed to musicotherapy, the maturation of white matter improved in acoustic radiations, claustrum and uncinate fasciculum, and also amygdala volumes increased, suggesting improved acoustic and emotional processing, compared to non-exposed preterm and full-term babies (Sa de Almeida et al., 2020). The age of onset is critical for structural changes to appear: focusing on exposure to a second language and music, it emerged that the arcuate fasciculus, which participates in both music and language activities by linking areas of the dorsal auditory pathway, is sensitive to second language in the left hemisphere, while in the right one it changes according to music exposure (Vaquero et al., 2020). Hence, the structure of different areas is selectively modified according to the type of experience mostly in early infancy.

4. Development is socially modulated

A relevant, yet underappreciated, issue in developmental neuroscience is the social nature of our species. In a study involving both parents and children, focused on the intergenerational transmission of sociality, the parents' limbic, embodied simulation and mentalizing networks appeared linked to the use of strategies for children's emotion regulation, suggesting a strong link between parent–child interactions and later child social life (Abraham et al., 2016). However maternal influence starts prenatally, since maternal stress (e.g., pandemic-related) affects 3 months infants' regulatory capacity (Provenzi et al., 2021), and also extends to calibration of growth rate and timing of sexual development, by affecting postnatal testosterone levels in infants (Corpuz, 2021). Maternal depression during pregnancy appears to influence the development of amygdala, by interacting with the canonical transforming growth factor-beta (TGF-β) signaling pathway (Qiu et al., 2021).

In school-age children, parental praise as a positive parenting style may result in increased openness to experiences and carefulness, together with increase in gray matter in the posterior insula, which is involved in empathy modulation due to the connections with amygdala (Matsudaira et al., 2016). By using fMRI-based neurofeedback, it was possible to demonstrate that both children and adolescents can learn to upregulate amygdala function, suggesting a possible tool to act on regulation of emotional reactivity (Cohen Kadosh et al., 2016).

5. Conclusion

The possibility of non-invasive exploration of the living brain also in children, emerged in the last years, led to a dramatic increase in our understanding of development of the brain and its functions, in the context of the growing body. The development of cognitive, emotional, and social behaviors appears more along a continuum than limited to narrow developmental windows, while certain attainments may be specific to some developmental periods (Guyer et al., 2018). Out of the laboratory, the increasing knowledge of the developmental processes led to a paradigm shift in the approach to children, in the context of parental relationships and pedagogical approaches, up to inform the political processes. Actually, sharing knowledge accumulating through dedicated studies on brain development and the increasing evidence about the long-lasting functional outcome of environmental modifications, may serve to raise consciousness about the actions to undertake to provide support and care to fragile children. While awareness of environmental risks for development and overall health is increasing (Chesney and Duderstadt, 2022), a widespread knowledge of the risks and possibilities for external actions to drive children development is still on the way. The possibility of early detection of child needs even with primary pediatric care and support to the family increases the chances of steering cognitive, emotional and social development towards positive outcomes (Williams and Lerner, 2019). Addressing adverse childhood experiences requires fostering health and educational services to promote the foundation of lifelong health, with the necessary inclusion of family (Bethell et al., 2017). Assistance for families, starting from maternal health, and for communities will provide supporting relationships to lay the foundation of resilience throughout life (Traub and Boynton-Jarrett, 2017). This should be declined across different cultures and is particularly relevant for children with additional requirements, like neurodevelopmental disorders (Bannink Mbazzi and Kawesa, 2022). Including constructs like 'neuroplasticity' in the educational trajectories led to an empowerment of the main actors, children, parents and teachers by fostering executive functions (Choudhury and Wannyn, 2022). The contribution of widespread schooling on the social construction of cognition and neurocognitive development has long been appreciated (Baker et al., 2012). In these last years, programs have been designed to support selective attention in children from low socioeconomic status with some genotypes which may represent a risk factor (Isbell et al., 2017). However, cognitive development is only one side of the coin: the role of social regulation of development, starting from parents to the group of peers needs to be recognized and actively included in political long-sighted plans. More can be done on the bases of the recent data on the involvement of social processes in the development of self-regulatory processes, to improve both personal development and society.

Author contributions

CM-C: Conceptualization, Data curation, Funding acquisition, Investigation, Writing – original draft. GS: Writing – review & editing.

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Conflict of interest

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Econeurobiology and brain development in children: key factors affecting development, behavioral outcomes, and school interventions

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The Econeurobiology of the brain describes the environment in which an individual's brain develops. This paper explores the complex neural mechanisms that support and evaluate enrichment at various stages of development, providing an overview of how they contribute to plasticity and enhancement of both achievement and health. It explores the deep benefits of enrichment and contrasts them with the negative effects of trauma and stress on brain development. In addition, the paper strongly emphasizes the integration of Gardner's intelligence types into the school curriculum environment. It emphasizes the importance of linking various intelligence traits to educational strategies to ensure a holistic approach to cognitive development. In the field of Econeurobiology, this work explains the central role of the environment in shaping the development of the brain. It examines brain connections and plasticity and reveals the impact of certain environmental factors on brain development in early and mid-childhood. In particular, the six key factors highlighted are an environment of support, nutrition, physical activity, music, sleep, and cognitive strategies, highlighting their potential to improve cognitive abilities, memory, learning, self-regulation, and social and emotional development. This paper also investigates the social determinants of health and education in the context of Econeurobiology. It emphasizes the transformative power of education in society, especially in vulnerable communities facing global challenges in accessing quality education.

KEYWORDS

public health, brain development, brain connectivity, plasticity, learning, education, self-regulation, social determinants of health

1 Introduction

The human mind is capable of astonishing function. We are still understanding how the brain develops and adapts to life experiences and the environment in which a child grows. A glance at the United Nations Sustainable Development Goals (1), shows the importance of a child's environment in maximizing educational opportunity and attainment. The first 3 years of life are when the brain is most plastic (capable to change and adapt through life experiences). Research has shown that early environmental influences significantly shape brain architecture. For example, studies have demonstrated how socioeconomic factors can affect brain development, linking poverty to alterations in brain structure and function (2, 3).

This article focuses on brain research related to child development and learning in early and middle childhood (2–5 years and 6–11 years, respectively), examining how environmental and epigenetic factors – collectively referred to as the econeurobiology of the brain – interact to influence brain development. We present an econeurobiological model that integrates these factors and offers educational and policy proposals inspired by Gardner's model of intelligence. This model is first introduced here to provide a framework for understanding the subsequent sections of the manuscript. Additionally, a detailed outline of the manuscript is provided to help readers grasp the overall picture and navigate the complex interactions discussed in the following sections.

Econeurobiology is defined as the study of how environmental and epigenetic factors influence neurobiological developmental processes in the brain, particularly during early childhood. This multidisciplinary field examines the intricate interactions between the environment, genetic predispositions, and brain development.

In order to understand how to optimize learning inside and outside the classroom, an appreciation of how the human brain develops and functions, and how cognition, concentration, learning and memory are enhanced through brain connectivity and plasticity is important. The context in which a child grows is crucial, especially when environmental exposure can affect – positively or negatively – the dynamics behind neural functional connectivity throughout development. The context can enhance learning, well-being, and resilience when environmental conditions are optimized, but can substantially disadvantage a child who is subjected to environments of continuous stress and privation (2–4). These factors exert their effects into adulthood, with implications for individuals, families, communities, and societies. These factors are both the social determinants of learning and the social determinants of health. Their interaction is at multiple levels and is cumulative. Thus, positive interventions that affect health and education in early childhood have potentially profound and far-reaching impacts on individuals, families, and their communities (5–8).

Drawing on a wide range of literature from neurodevelopmental biology to pedagogy, this paper introduces the econeurobiological model, which examines how environmental and epigenetic factors influence neurodevelopmental processes in the brain. Our model integrates these factors to understand their impact on brain development, especially in children. In addition to detailing the neurobiological mechanisms involved, the paper presents educational and policy proposals inspired by Gardner's model of intelligence, aiming to enhance cognitive development through tailored educational strategies.

1.1 Evolution of the human brain

Research into the evolution of primates has revealed that the uniqueness of the human brain is not determined by its volume but by the number of neurons within the brain and the network of connections between them (9). Human brain volume as a ratio to body mass is larger than that of other mammals. For example, the adult elephant brain weighs 4–5 kg, while the human brain weighs 1.5 kg (1.5 liters by volume). The human brain's 86 billion neurons contrast with a gorilla's 30 billion. A gorilla needs to eat for about 8 h a day in order to meet the energy requirements of its brain. Humans need to eat substantially less (9, 10). The evolution of human brain size is probably a function of evolutionary changes in diet, foraging for food, and optimizing energy metabolism. One explanation is the invention of fire and the consumption of cooked food – food efficiency (10). Homo erectus (the upright man) first began using fire in areas of South Africa and present-day Kenya about 1.5 million years ago (11). Beyond the impact of cooking on brain architecture, it is likely that environmental pressures and social competition have played a significant role in brain volume development and an increase in the number of neurons (12). Cooked food is more easily digested and yields more calories than raw food (13). The human brain makes up 2% of body mass, but it consumes about 20% of daily energy, which is linearly related to the number of neurons and the quality of neural connections. The energy consumption of a neuron is constant and does not depend on the size of the brain (14). Figure 1 illustrates the evolutionary increase in brain volume.

The expansion of the neocortex through primate evolution parallels the greater cognitive capacity of the human brain (Figure 2). Neuroanatomical experiments have shown that exercise can increase dendrites, spines, and other structures, indicating that functional activity drives the anatomical reshuffling of neurons and areas. For example, motor training induces experience-specific patterns of plasticity across the motor cortex and spinal cord (16). Humans have the largest frontal cortex of all primates and the entire cerebral cortex of humans in proportion to body size is larger than in other primates (9, 10, 13, 16). It is human fetal development of the neocortex and subsequent cellular organization and connectivity between brain areas that distinguishes it from the brains of other primates in terms of intellectual capacity (17).

1.2 Building brain architecture

During the first years of our lives, over a million new neural connections are formed every second. This rapid rate of synapse formation highlights the high brain plasticity during early childhood, which is crucial for significant learning potential. The rate of connection formation and brain plasticity decreases with age (18).

The stages of brain development include neurogenesis, cell migration, differentiation, maturation, synaptogenesis, cell death and pruning, and myelogenesis. Neurogenesis begins in the early embryonic stage and is usually completed 5 months after birth. Neurogenesis in the hippocampus, however, continues through life, not only in the hippocampus but also in the subventricular zones, rostral migratory stream, and olfactory bulb network, playing a crucial role in learning and memory (19).

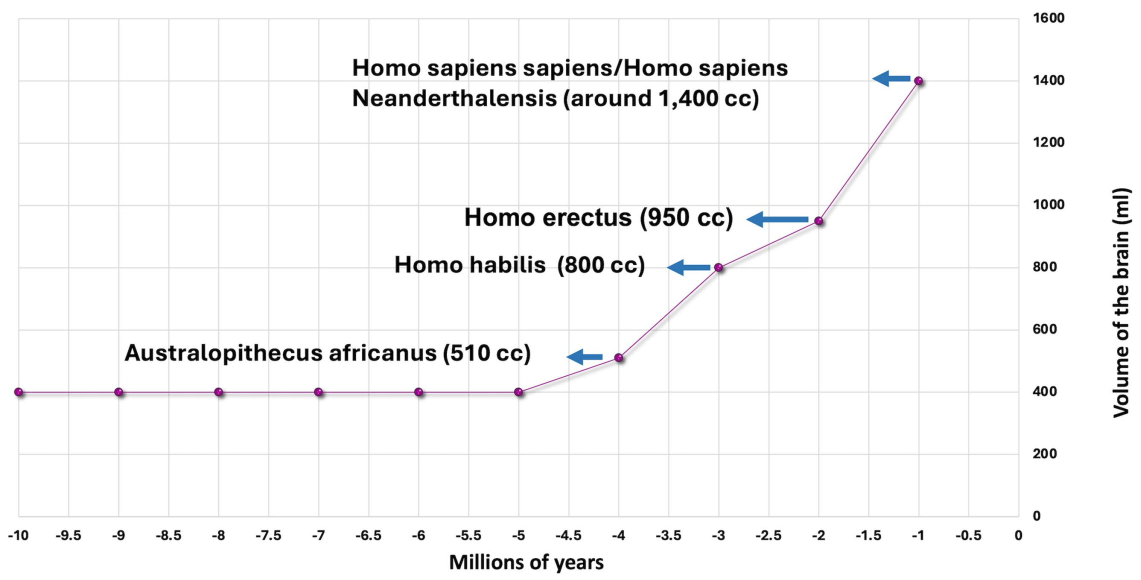


FIGURE 1
The increase in brain volume among primates.

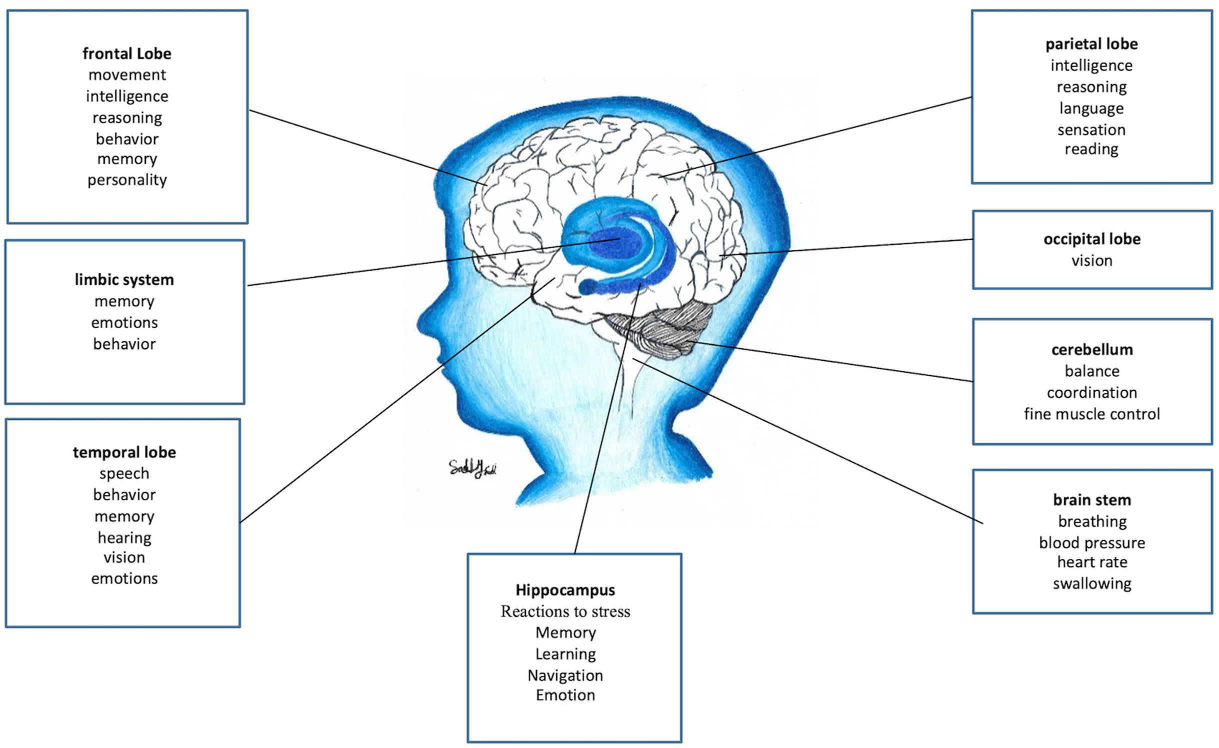


FIGURE 2
Overview of brain functions. This simplified summary highlights major brain regions and their primary functions. Note that many functions involve interactions across multiple areas. Key regions include the hypothalamus, which has a major role in reactions to stress (15), brainstem (pain modulation and sympathetic outflow), and the reward system (VTA, nucleus accumbens, prefrontal cortex) (figure drawn by Sally Saadi).

Each of the stages of development is affected by neurohormonal and environmental factors. Dendrites in babies protrude from the cell body and extend dynamically over the first 2 years of life. Axons grow much faster than dendrites and, therefore, through contact with the dendrites of other neurons, influence dendrite differentiation and neuronal connectivity. An increased and redundant number of neurons and connections are formed in the first 2 years – more than needed; thus, cell death and synaptic pruning take place. After a period of rapid proliferation and the construction of neural pathways and networks, neural connections are reduced through pruning so that electrical circuits in the brain can operate more efficiently (19).

Experiences in early childhood - the critical period – determine the process of neurological development and the architecture of neural networks – the wiring in the brain (6, 20, 21). Networks that are continuously used are strengthened while unused networks are pruned (22, 23). Every active thought, feeling, or behavior leads to the activation of thousands of neurons that connect together. Repetitive patterns of behavior or thought result in automatic neural activation. On the other hand, patterns of behavior and thought that are suppressed or interfere with established network formation disappear. The creation of environments that stimulate neural networks that support learning is crucial. Equally, shielding children from negative environmental factors substantially impacts cerebral plasticity (24). Thus, a child's first years significantly affect the architecture of the continually developing and changing brain as the child's experiences shape the formation and pruning of connections through the process of developmental synaptogenesis (6, 25, 26). A key neurotransmitter implicated in embryonic development is gamma-aminobutyric acid (GABA), controlling cell migration. Glutamate and glycine receptors appear from the first phases of cortical development, and while a detailed study of neurotransmitters is beyond the scope of this article, interference with neurotransmitter signaling has been implicated in several neurodevelopmental disorders (27–29). Dysregulation in neuronal differentiation and signaling with abnormal synaptic function are similarly associated with dopaminergic (and other neurotransmitter) pathways in early brain development implicated in cognitive, behavioral, and psychiatric disorders.

Impaired connectivity between neurons has an immediate effect on cognitive, behavioral, and emotional function, which, in turn, affect learning (5, 6), and emotional regulation (30). When an individual vocalizes a word after reading, distinct neural networks are activated compared to when the word is spoken after being heard. This difference is highlighted in studies utilizing functional MRI (fMRI) and electrophysiological measurements, which show that reading and auditory processing engage different cortical areas, reflecting the various pathways involved in language processing and cognitive functions (6, 31, 32). The stimulus and subsequent processing of information are different. Thus, several stimuli modify cortical organization and connectivity in specific and different ways. Understanding which parts of the cortex are involved in a process is complex but functional MRI (fMRI) and electrophysiological measurements of cortical oscillations are of value. Electrophysiological analysis involves the study of types of brain electrical activity and their intensity and distribution over the cortical surface. In fact, EEG has been used to evaluate brain maturity from newborns to infants, where specific patterns of activity such as the occurrence of posterior rhythm, sleep spindles, and vertex waves represent markers of adequate electrographical development (especially when these events occur between 6 and 8 weeks after birth) (31). Some neural correlates of behavior and cognition can be associated with EEG activity. EEG activity across different frequency bands is associated with a variety of cognitive and physiological states, but these associations are complex and multifaceted. For instance, gamma waves are often linked to cognitive processing and problem-solving activities. Beta waves are associated with active thinking and focus, while alpha waves are related to relaxation and calm states. Theta waves are typically observed during meditative, drowsy, or creative states, and delta waves, while prominently associated with deep sleep, can also appear during focused attention and certain cognitive tasks (Figure 3) (5–8, 33, 34). Thus, it should be possible to see whether a child is calmly learning by monitoring electroencephalography (EEG) activity. In contrast, previous studies of children exposed to toxic stress showed patterns of neural activity that reflect cortical hypoactivation, including reduced alpha power with increase power of the theta band (35). Therefore, EEG can be a valuable tool in evaluating neurophysiological markers of brain maturity in the context of cognitive and behavioral function. Recent advances in signal analysis methods have been used to generate predictive models, where cognitive processing, emotional states, or behavioral performance are correlated with biological markers of EEG activity, to monitor cognitive behavioral development in children or to assess responses to therapeutic interventions.

1.3 Developmental plasticity

Most of the human behavior result from social interactions and exposure to the environment. Some, however, are found to be prewired into the brain, such as the capacity to develop language. Similarly, the brain's ability to process and integrate visual stimuli exist almost immediately after birth (36). Nevertheless, the expansion of brain development is further boosted as the newborn is exposed to new sensorial and emotional experiences. It is during this developmental stage that neural networks, primed to receive new stimuli, compete for survival by becoming more efficient and precise in response to environmental demands. The neuronal mechanisms supporting the formation of new memories and learning consist of use-dependent long-term modifications of synaptic transmission. Moreover, this synaptic connectivity must be strengthened by repeated temporal firing to promote long-term potentiation (LTP) (37). It has been confirmed that tetanic stimulation of excitatory pathways led to long-lasting enhancement of the efficacy of the synapses between the activated fibers and the respective postsynaptic neurons (38), this increase in synaptic efficacy occurs only if the postsynaptic neurons respond by generating action potentials to the ongoing tetanic stimuli, thus fulfilling the criterion of contingent pre and post synaptic activation (39). When postsynaptic neurons are prevented to respond to the stimuli, synaptic strengthening is void, leading to a decrease in synaptic efficacy, this phenomenon is known as long-term depression (LTD). The molecular basis supporting the generation of LTP and LTD are beyond the scope of this chapter, yet, it has been shown these synaptic modifications are calcium dependent and that the polarity of the modifications depends on the rate of rise, and the amplitude of this calcium increase (40). Thus, fast, and strong intracellular increase of calcium lead to LTP, while slow and smaller increases trigger LTD (41). Therefore, stimulus-induced, and self-generated neuronal synchronized activity, plays a crucial role in the activity-dependent shaping of the neuronal architecture during development. This has a direct impact in the formation of cognitive skills in humans, as LTP/LTD activity must be finely tuned to promote synaptic strengthening and synaptic consolidation during learning experiences.

Hence, endogenous and exogenous factors influence how neuronal circuits develop early in life. Exposure to a nurturing

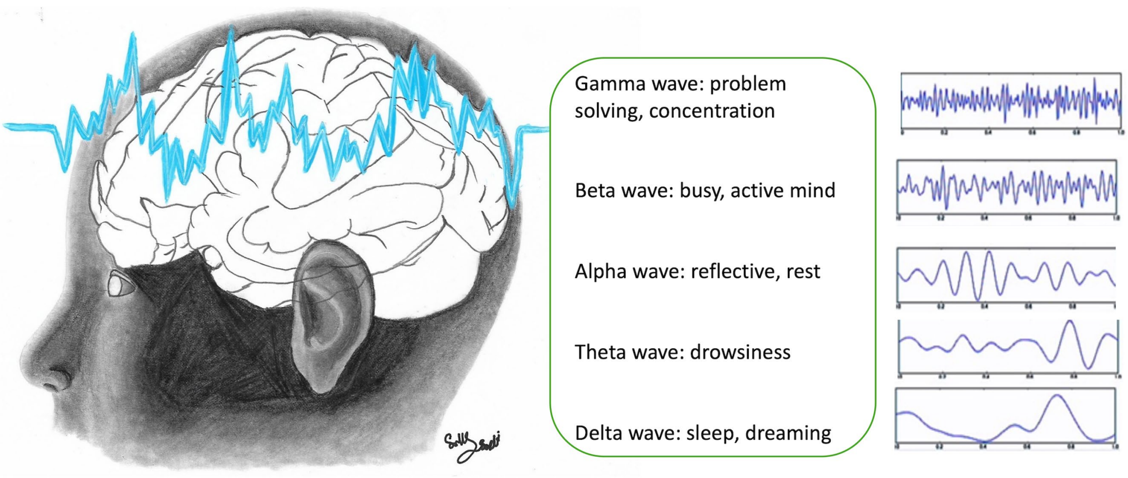


FIGURE 3
Electroencephalogram (EEG) waves in the brain (figure drawn by Sally Saadi).

environment can further facilitate neuronal growth and refinement, while exposure to adverse conditions will have a detrimental effect.

Consequently, families must be supported by their societies to provide the most favorable – econeurobiology – environment for development, so children can have the opportunity to achieve their physical and intellectual potential.

1.4 The capacity for learning

Understanding an individual's cognitive abilities, temperament and behavior depends on an understanding of neuroscience and neurological function (33). The brain contains about 86 billion neurons, 16 billion of which are in the cerebral cortex. This number of neurons is unique to humans and explains the high-energy requirements of the human brain compared to other living creatures. The human brain constantly changes and renews itself in response to new experiences, knowledge, and information from the environment – brain plasticity (7, 8, 10). Neurons are the basic units of information processing and decision-making. The large number of neurons in the human cerebral cortex and neural networks are responsible for brain connectivity and higher functioning (10, 13). Neurons connect with each other through a process called synaptogenesis, with electrical transmission resulting in the secretion of neurotransmitters. One neuron may form as many as 10,000 new connections (8, 10, 13). It is the formation of these connections that is crucial to the process of learning. Plasticity allows people to learn and adapt. Thus, while at birth, all individuals have approximately 86 billion neurons, the environment and an individual's social interactions shape the structure and architecture of the brain and facilitate cognitive and learning processes. These processes include the formation of ideas, the solution of multivariate problems, strategies to navigate daily activities, contingency planning, and the expression of character, emotion, and behavior. The capacity for learning and self-regulation (moderation of one's behavior) are essential to resilience in childhood and adult life. It is the processing of information in the cerebral cortex and connectivity, especially with the limbic system, that makes it possible for an individual to weigh information, draw conclusions, judge good and evil, remember events and their significance, learn from mistakes, plan ahead and change these plans as circumstances change, and form patterns of behavior and personality. The organization of the cerebral cortex is dependent on the individual's exposure to environmental factors and personal life experiences that affect gene expression; thus, the environment of a child at home and in school influences the creation of neuroproteins and transmitters that promote brain connectivity (42). The more frequently a process of experience takes place, the stronger the connections between neurons. Conversely, a failure to stimulate a child and the withholding of affection diminish connectivity and result in the loss of neurons, a reduced capacity to learn, and an inability to self-regulate emotions and behavior. Even in childhood, provided children are loved and supported, the brain is shaped by challenges, adversity and failures, as well as successes. This builds resilience and the capacity to learn and adapt.

Neural pathways in cognition describe the complex interaction between various brain regions, including the limbic system, the prefrontal cortex, and the reward system. The limbic system, traditionally associated with emotions and memory, plays a significant role in both conscious and unconscious processing, influencing behaviors that range from instinctive to deliberate. The prefrontal cortex, on the other hand, is linked to reasoning and analytical thinking. Kahneman's dual-process theory categorizes these functions into 'fast' and 'slow' systems, but this dichotomy remains a topic of debate in cognitive psychology and neuroscience, with emerging research suggesting more integrated and overlapping roles of these systems (43).

Both pathways are crucial to effective learning in the classroom, influencing concentration, focus, memory, and the evaluation of what is learned. Figure 4 illustrates how these neural pathways influence classroom learning, using the example of writing a story. The optimal development of connectivity between these systems is essential for fostering both quick, intuitive thought and slower, more considered analysis, contributing to what is termed the 'optimized brain.' Creating conditions that support this connectivity is vital for developing resilience and adaptive capacities in children, enabling them to manage adversity more effectively. Furthermore, the 'reward' pathways of the brain, primarily mediated by dopamine produced in the ventral

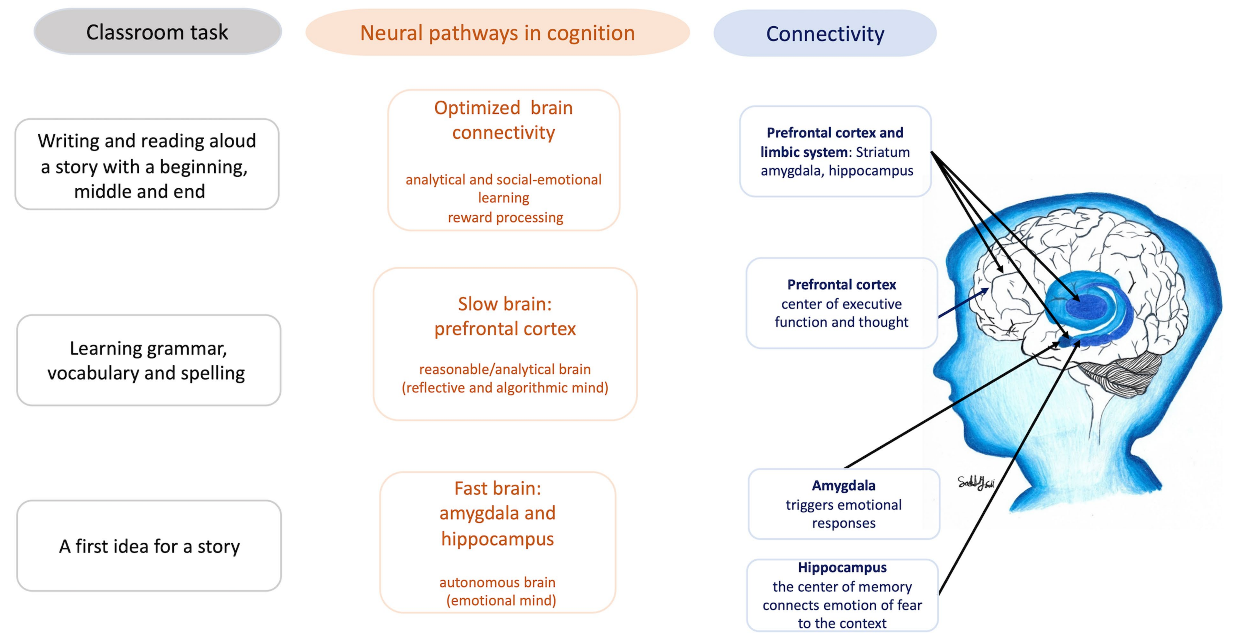


FIGURE 4
Connectivity between areas of the brain during a typical classroom task (figure drawn by Sally Saadi).

tegmental area (VTA) of the midbrain, connect with the limbic system, including the nucleus accumbens, amygdala, and hippocampus. Engaging in pleasurable learning activities, music, and aerobic exercise, alongside receiving positive feedback and praise, activates these motivation and reward pathways, driving the formation of memories, social–emotional learning, and behaviors essential for effective learning and socialization (5, 6, 10, 44).

The interaction of these brain systems forms a complex and integrated network essential for learning and behavior regulation. The reward system, which includes the VTA, nucleus accumbens, amygdala, hippocampus, hypothalamus, and striatum, plays a crucial role in regulating motivation toward specific objects, persons, or actions. Motivation is vital for learning and other functions, as it drives the engagement and persistence necessary for acquiring new skills and knowledge. The VTA connects with the limbic system and nucleus accumbens, which are in turn connected to the amygdala, hippocampus, hypothalamus, and striatum. These interconnected networks form a comprehensive system for behavior regulation, linking different hubs from the prefrontal cortex to the brainstem. This underscores the importance of a balanced and well-connected neural network for optimal cognitive and behavioral functioning.

This article reviews the evolution of human brain development and explains the conditions for optimal brain architecture, plasticity, and childhood learning. The influence of environmental factors – econeurobiology – is discussed in the context of the social determinants of health and their influence on intellectual potential.

2 Environmental enrichments at different developmental stages

Research has consistently shown that environmental enrichment at different developmental stages positively influences brain plasticity, leading to improvements in health and achievement. Studies reveal that both physical and social enrichment can cause functional, structural, and molecular changes in the brain, such as increased growth factor expression and neurogenesis (45, 46). This is evident in investigations of early environmental enrichment in rats. Environmental enrichment in these studies typically involves providing animals with a stimulating environment that includes a variety of objects, opportunities for physical activity, and social interactions. Such enrichment has been shown to influence brain development and function by enhancing neuroplasticity and promoting the expression of growth factors. For instance, these studies highlight sex-specific responses in oxytocin (OT) and brain-derived neurotrophic factor (BDNF) expression (45, 46). For instance, while physical enrichment enhances motor and cognitive functions and hippocampal BDNF expression in both sexes, combined physical and social enrichment is particularly beneficial for females. This suggests an OT-based mechanism that selectively stimulates BDNF response in a region-specific manner, depending on the type of enrichment (45).

Further studies in male mice post-weaning indicate that environmental enrichment increases social behavior, moderates stress-related physiological markers, and boosts BDNF levels in the prefrontal cortex. Conversely, removing female rats from enriched environments leads to behaviors indicative of psychiatric disorders, such as increased passive coping and hyperphagia, along with signs of HPA axis dysregulation (46). These findings underscore the potential of environmental enrichment in early life to affect parental care and offspring outcomes, possibly extending to transgenerational effects. However, translating these paradigms from animal models to clinical settings, such as in stroke patients, requires more alignment for effective implementation. Environmental enrichment shows promise for a wide range of neurological and psychiatric conditions (46).

In terms of aging, environmental enrichment (EE), even without exercise, can prevent cognitive decline and reduce age-related brain deterioration. This is particularly significant for populations where physical exercise is impractical. EE alone has been found to reduce anxiety, enhance memory, and potentially be more effective in older animals. This suggests that EE can mitigate cognitive loss with age independently of physical activity (47).

Moreover, EE enhances performance in various behavioral tasks, like spatial memory and anxiety-related behaviors in adult Wistar rats (48). While EE reduces anxiety and improves spatial memory accuracy, its impact on attentional tasks is less pronounced. Notably, EE also affects brain functional networks, promoting more efficient connectivity (49).

Lastly, a comprehensive review of 375 studies, focusing on 142 of higher quality, reveals the significance of non-cognitive skills acquired early in life on later outcomes. These skills show consistent effects on academic achievement, psychosocial, language, and cognitive outcomes. The findings highlight the need for better study design and reporting, especially in randomized controlled trials and observational studies. Interventions targeting the development of non-cognitive skills could be particularly beneficial for disadvantaged children, suggesting a broader societal impact (49). Altogether, these findings show how dramatic the influence exerted by the environment can be on brain plasticity. Studies using the EE paradigms have indicated several molecular mechanisms that might emerge as possible ways of accession for a successful treatment of neuropathological conditions affecting the juvenile and adult CNS (50). These studies also reveal how EE influence cognitive development as everyday experiences can potentially enhance or inhibit cognitive plasticity and therefore the ability to learn (51).

In summary, environmental enrichment at various developmental stages offers profound benefits for brain plasticity, ultimately enhancing achievement and health outcomes.

3 The negative impact of trauma and toxic stress on plasticity

Toxic stress, as observed in children's brains, is characterized by an adverse response to early life challenges and can exert far-reaching negative effects on physical, psychological, and behavioral well-being (52). This type of stress can result in persistent alterations to the brain's stress response systems, which may compromise an individual's ability to manage stress and regulate emotions in the future (53). The implications of toxic stress extend to epigenetic modifications, potentially leading to enduring alterations in gene expression and subsequent child development (54). Furthermore, the family setting plays a critical role, with the implementation of physical punishment by parents being identified as a significant source of toxic stress that can impact brain architecture and function (55).

Adverse childhood experiences (ACEs) – that generate toxic stress – are defined as traumatic events that occur before the age of 18 years that can have major consequences for behavioral, cognitive, and physiological development affecting one's life-course health trajectory (56) ACEs can include maltreatment, severe household dysfunctions, the loss of one or both parents for any reason, and other events such as severe bullying, natural disasters, extreme poverty, or exposure to warfare. These traumatic experiences elicit strong physiological stress responses that prepare the body to face dangers or hazards, conditioning it into a fight, flight, or freeze mode (57).

Emotional trauma can profoundly affect brain plasticity by altering neuronal circuits and synaptic connections (58). The stress induced by trauma typically activates the neural systems related to attention and memory, which leads to a temporary increase in synaptic plasticity within the hippocampus (59). Initially, this response may enhance memory, but over time, the hippocampus often becomes less responsive to new excitatory plastic changes (60). The enduring nature of traumatic memories, particularly those resistant to extinction that are characteristic of posttraumatic stress disorder (PTSD), is likely a consequence of these changes in plasticity (61). Moreover, chronic exposure to ACEs have been linked to inflammation in childhood, adolescence, and across adulthood (62). Chronic inflammation has been established as an overlying mechanism in which the immune system contributes to the development of later disease (63). Cytokines, which coordinate inflammatory processes, are often used as biomarkers to assess levels of inflammation. Children who were exposed to toxic stress between the ages of 6–8 years were found to have higher levels of C-Reactive Protein (CRP) and Interleukin-6 (IL-6) at 10 years. In addition, ACEs prior to 9 years were associated with higher levels of CRP at age 15 (62). The negative impact that chronic inflammation has in a developing brain, particularly during the maturation of cognitive and emotional functioning, may be considered an important factor for the presentation of disease or psychopathology later in life. It has been demonstrated that exposure to psychosocial deprivation early in childhood, is associated with smaller gray and white matter volume and global reductions in cortical thickness (64). Moreover, these structural abnormalities were correlated with impaired cognitive functioning and increased development of psychopathology (65, 66). However, when children are removed from their adverse environment – removed from toxic stress – by placing them in a safe and caring environment, these changes reverse, predominantly in the lateral and medial prefrontal cortex and white matter tracts that connect the prefrontal and parietal cortex (67), which are cortical structures associated with cognition and emotional regulation.

The detrimental impacts of prolonged trauma and stress on brain plasticity are well-established (68–70). Chronic stress can lead to reduced metabolism and synaptic density in the hippocampus and prefrontal cortex, which then necessitates behavioral adaptations (71). Additionally, chronic stress can lead to systemic changes that contribute to allostatic load, but the brain retains a degree of resilience and can react positively to interventions aimed at promoting plasticity and thus aid recovery (72). Research also shows that acute stress can modify inhibitory neurotransmitters, such as gamma-aminobutyric acid (GABA), influencing the stress axis and potentially affecting plasticity (72).

In conclusion, understanding the effects of trauma and stress on neural plasticity is essential for developing therapeutic strategies. These strategies not only aim to foster resilience but also address the persistent adverse effects of stress, thereby contributing to healthier brain function and mitigating the long-term consequences of stress-related disorders.

3.1 The catastrophic effects of violent conflicts on econeurobiology

War and violent conflicts often result in devastating consequences, including loss of life, displacement of civilians, destruction of infrastructure, and long-lasting socio-economic impacts. Communities endure trauma, and the conflict can exacerbate existing political, ethnic, or religious tensions, making post-war recovery challenging. Humanitarian crises may arise with limited access to basic necessities, hindering the overall development of the affected regions. Regrettably, war and violent conflicts disproportionally affects the most vulnerable populations, children, women, and the older adult, who in addition to be exposed to death, injury, disabilities, illness, and rape, they also suffer from intense and continuous psychological suffering. Children are exposed to situations of terror and horror that have detrimental effects on neural development and may leave enduring cognitive deficits and psychopathology such as posttraumatic stress disorder (PTSD), depression, and anxiety. Furthermore, these negative effects may be prolonged by exposures to further privations and violence in refugee situations (73).

Although the ideal action would be the complete removal of children from war, and to place them in a supportive and caring environment, the socio-political realities, frequently prevent any moral and/or humanitarian effort to achieve this goal. Therefore, humanitarian organizations are left with limited option to mitigate the terrible consequences of these violent conflicts have on children. The destruction of the econeurobiology must be considered a war crime, as the devastating effects on neural development will adversely affect the life trajectory of those children who survive and prevent them to reach their full potential.

4 Education as a determinant of health and social mobility

The adolescent brain becomes capable of performing more complex functions but loses adaptability in terms of lifestyle change or behavior. This decline in brain plasticity emphasizes the importance of investment in positive learning environments in early childhood. Risk factors for poor academic attainment accumulate well before a child begins school (5, 7). An early nurturing environment where children are exposed to positive interactions and encouraged to learn determine literacy, numeracy, motor skill, cognition, and emotional development in school (5, 7, 74). By the age of 3 years, the children of high-income professionals have been found to have twice the vocabulary of children from low-income families (71). One dollar invested in early childhood yields a benefit of $ 16.14 (Figure 5), while an investment of $ 1 in those over 21 years of age yields only $ 4.10 (5, 8, 23).

This paper acknowledges the significant influence of country and culture on educational theory and practice, particularly in the sections on early childhood programs, elementary curriculum, and STEAM education. The costs and benefits of early childhood programs presented in Figure 5B were estimated primarily for the United States. However, it is crucial to recognize that institutional and economic circumstances vary widely between nations, impacting the applicability and effectiveness of these programs.

Motivation and skill for those engaging with young learners in school are essential. Schools require investment and teachers require training and support. Class sizes should be smaller, and lessons should engage each child, fire the imagination, and allow them to explore what there is to learn about the world within a safe and supportive environment. Extracurricular education and activity are as important as classroom learning (75). Integrating sport, music, art, and activity into classroom lessons and effectively timing lessons, breaks and the school day add to the quality of education, how a child learns, what they learn, what they remember, and how they learn to learn (76–78). While standardized tests of knowledge acquisition and critical thinking (based on Bloom's taxonomy of critical thinking, which categorizes cognitive skills from basic recall of facts to higher-order thinking skills such as analysis and evaluation) are used to assess the attainment of educational milestones, class attendance, participation, levels of substance abuse, crime, teenage pregnancy, and child employment are important markers of the effects of education as a determinant of health, future employment, economic security, and social mobility. Bloom's taxonomy classifies educational learning objectives into six hierarchical levels: knowledge, comprehension, application, analysis, synthesis, and evaluation. This framework helps educators structure and evaluate the effectiveness of their teaching by focusing on the development of higher-order cognitive skills (77–79). Poorly performing schools are in themselves a determinant of the failure of a child to meet his or her educational potential and life goals. Funding educational programs that target early school-age children is important but, in reality, the education of the poorest children in society remains inadequately funded and badly managed. Addressing the determinants of poverty are a priority in improving education from early childhood (80). Education remains the single most important factor in lifting children out of poverty (81).

5 Econeurobiology: key factors that influence the developing brain

A child's environment and the social determinants of health influence the biological mechanisms that shape an individual's cognitive, social, psychological and behavioral development (23).

5.1 The nurturing and loving environment

Nurturing, loving, supportive and caring environments are powerful factors in child development and positive neuroplasticity (82–86). The 'serve and return' reciprocal interaction between children and their parents has been shown to be effective in "brain building" as early as infancy. The model, developed by Harvard University (87), uses a tennis analogy where an infant serves (focuses his or her attention on an object), and the parent returns the serve (sharing the child's attention and building on this). Learning continues in a supportive and encouraging environment as the child plays, develops language skills, and gains an understanding of the context and meaning of the world around them. In the absence of responsive caregiving — or if responses are unreliable or inappropriate — brain architecture does not develop as expected. It is easier to form strong neural networks in early childhood than it is to intervene or "fix" them later (88, 89). Adverse Childhood Experiences (ACE) and "toxic stress" such as exposure to domestic violence, emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect affect physical and mental health, and substantially affect the ability to learn, school attendance, and academic attainment (83, 90, 91). Toxic stress is cumulative and results in uncontrolled pruning processes, especially in the hippocampus, neuron loss, impaired synapses, damage to neural connectivity, and poor development of the prefrontal area of the brain responsible for thinking, problem-solving, the control of behavior (Figure 6) (83, 86, 88). This is negative neuroplasticity (23, 86).

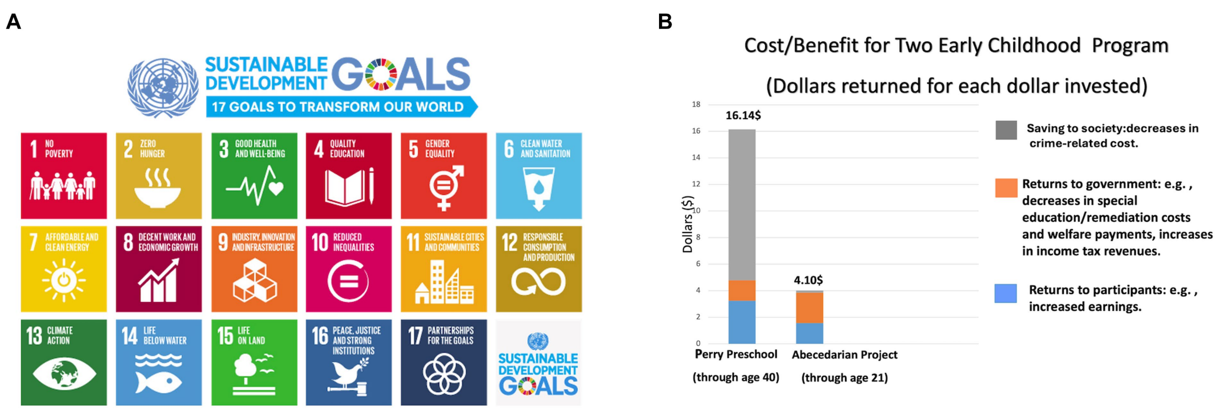


FIGURE 5
(A) Education as a sustainable development goal. Adapted with permission from the illustration: "2030 Sustainable Development Goals." © Courtesy of the United Nations (1). **(B)** The return on investment of early childhood education. Adapted with permission from the illustration: "Cost/Benefit for Two Early Childhood Programs." © Center on the Developing Child at Harvard University (5).

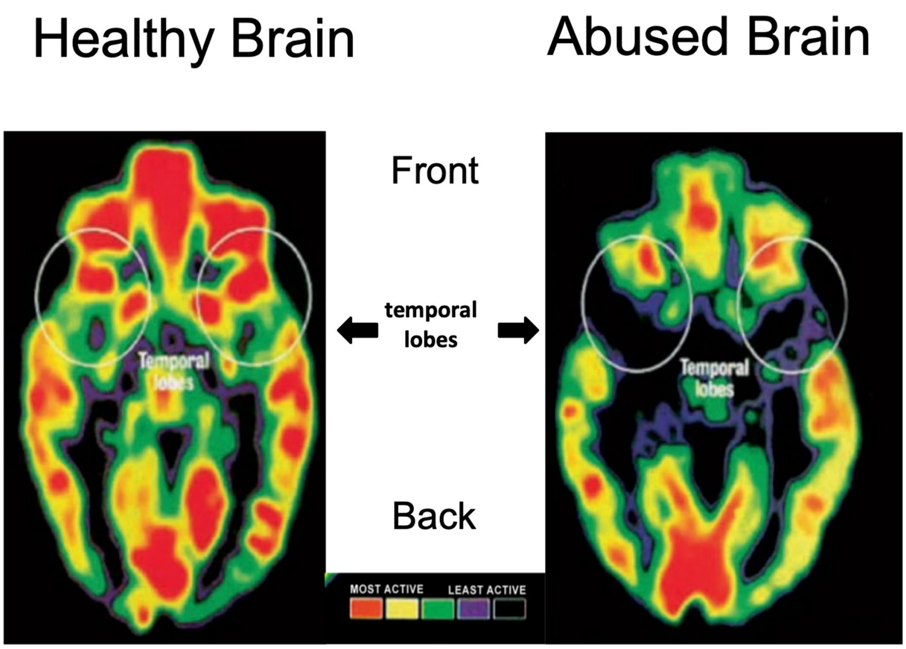


FIGURE 6
The effect of toxic stress on the healthy brain. The PET scan of the brain activity of a normal, healthy brain shows regions of high activity (red) and low activity (blue and black). In the abused brain under toxic stress, there is a significant decrease in activity in the temporal lobes, which regulate emotions. Adapted with permission from Chungani (92).

The effects on the child increase the longer exposure to the toxic environment is allowed to continue, and the risk of long-term health complications increases as the ACE score increases. For example, exposure of children to their mother's physical abuse and their own experience of physical and emotional abuse adds up to an ACE score of 3. This is higher than an individual with an ACE score of 0 or 1. There is a direct link between the ACE score and toxic stress in children, with a significant increase in the risk of long-term physical and mental health complications (93). The effects of fear and anxiety on cognition and memory (especially declarative memory that has an emotional impact) may be mediated through glucocorticoid effects on the hippocampus (94). Stress hormones and catecholamines are implicated in the consolidation of emotion-laden memories through arousal-induced activation of noradrenergic mechanisms within the amygdala (95). Children may display obvious signs of trauma in the classroom such as aggression or falling asleep in class; but more subtle signs such as the inability to concentrate or an unwillingness to learn are less easily discerned and less often attributed to abuse. Investment in small class sizes and real facetime with individual pupils are essential to identifying the problems that affect a child's performance in class. Tackling environments of toxic stress and child protection are global health and education imperatives (96–98).

There is a positive correlation between clean, well-maintained, calm, ordered school environments and academic performance

(99–101). Cognitive performance is reduced in 'busy' (distracting) visual environments compared to 'non-busy' visual environments (99). Poor lighting in classrooms affects both children's health and their ability to learn (100). The availability of greenspace in the learning environment is positively associated with cognitive performance. Learning outdoors, and even watching nature from the classroom, are associated with a decrease in heart rate and cortisol levels (101). Therefore, a pedagogy of love rooted in empathy for oneself, others, and nature is essential for a child's development, as well as for the integrity, well-being, social harmony, and economic prosperity of society.

5.2 Nutrition and a healthy diet

The infant gut microbiome (the genetic material of gut microorganisms) influences neurodevelopment from birth via the gut-brain axis (Figure 7). The gut-brain axis involves the vagus nerve, immune system, hypothalamic–pituitary axis, tryptophan metabolism, and synthesis of neuroactive peptides, metabolites, short-chain fatty acids and neurotransmitters (102–111). Complete bacterial colonization is achieved within the first 3 years of life and is affected by the child's diet, the existence of gastrointestinal disease, and exposure to antibiotics (112). A crucial function is the homeostatic mechanism of gut permeability and protection from enteric pathogens. Diarrheal diseases alone result in under-5-year mortality of up 20%, and episodes of diarrhea (three or more unformed stools per day) in the first 2 years of life may result in malnutrition-related cognitive deficits before children begin school (113).

The effects of malnutrition on brain development are profound. Chronic undernutrition and poverty in childhood are primarily measured by stunting (linear growth retardation and cumulative growth deficit). Stunted children have impaired cognition, learning, and motor function that affect school attendance, classroom participation, and learning and educational attainment (114). Fatty acids, choline, iron, zinc, cholesterol, phospholipids, and sphingomyelin play essential roles in myelination – key to white matter and cortical development (115, 116). Up to one-third of preschool children worldwide have vitamin A deficiency, 1% of whom develop night blindness (115). Nutritional inputs from infancy to school age (including breast-feeding, iron supplementation, iodine fortification, zinc, micronutrient and vitamin supplementation, and protein-energy supplementation) in community-based programs have had some success. The role school meals play in the nutrition of school age children is crucial to cognitive development and the quality of learning in schools - Learning Adjusted Years of Schooling (LAYS) (116–118). The cost of providing school meals for approximately 70 million vulnerable children is an average of $ 64 per child per year (119).

5.3 Physical activity and socialization

Development of the brain is affected by movement and exercise (77, 120–122). Effortless movement for only 10 min has been shown to improve the ability to remember and concentrate at all ages - from kindergarten to university (77). Ten minute breaks in class for gentle exercise may significantly improve classroom learning and performance in examinations, and are a relatively low-cost and easy intervention in the school timetable (77). Improvement in key educational competencies, especially higher orders of cognition in Bloom's taxonomy of critical thinking, has been demonstrated after

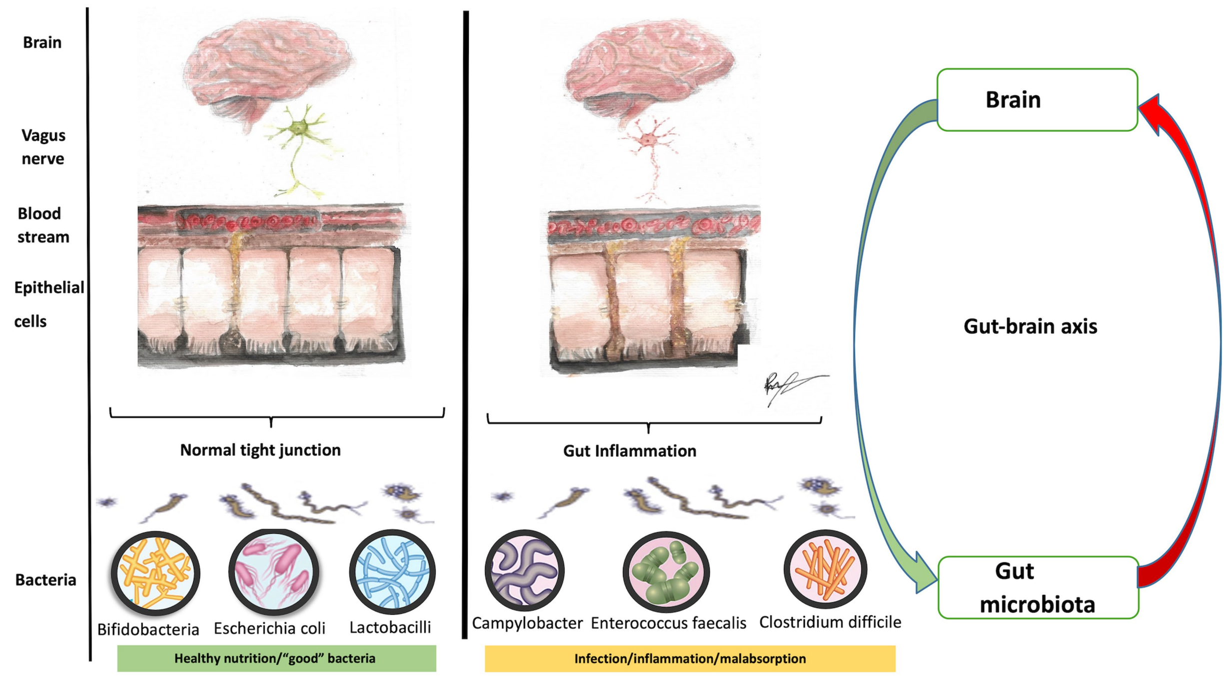


FIGURE 7
A healthy gut and the gut-brain axis (figure drawn by Roaa Mohamed).

small intervals of aerobic exercise (77, 120, 121). The mechanism may be related to the relationship between movement and the secretion of BDNF. Increased BDNF secretion increases the production of mRNA which produces neurotropin, proteins, and neurotransmitters, such as dopamine, which increase anterior hippocampal volume, improve mood, motivate learning, and improve spatial memory (122, 123).

Physical activity improves cognition, increases brain volume in children with cerebral palsy, and improves phonemic skills (122). In students with visual impairment, the relationship between cognitive function and physical activity, especially in adolescents with disabilities, suggests that moderate-intensity exercise is important for brain plasticity at this age (122). Exercise may be important in developing resilience and dealing with stress (124, 125). Children who exercise as a means of coping with pressure at school should have access to sporting facilities in school that are safe, supervised, and accessible after the school day.

Prolonged periods of sitting are associated with the digital age. While unhealthy in terms of a lack of physical activity, they are also associated with other dangers, detailed discussion of which is beyond the scope of this article. Violent video game content has been shown to increase aggression, violence, depression, lack of empathy and the spectator phenomenon (126, 127). Prolonged sitting, especially in front of LED screens, leads to fatigue, disrupts sleep, biological rhythms, and reduces cognitive function (128–132). An over-reliance on screen-based learning in the classroom at the expense of writing, drawing, hands-on tasks, outdoor learning, play, and movement, especially where there is physical and social interaction between the teacher and pupils and among the pupils, is to be discouraged. Screen time is recommended to be limited to 90 min in total during the school day (133).

5.4 Music

The positive impact of music on cognitive development, including fetal development, has been extensively studied (78, 134). Listening to Mozart has been found to significantly help mothers cope with stress and improve their temperament (134–138) which, in turn, may positively impact the child's home environment. Music also encourages calm and restful sleep (134, 136, 139). Music is an important stimulus for the growth of functional neural networks throughout the brain in the first 3 years of childhood (6, 134–140). The effect on brain development remains significant in school-age children and is, therefore, of considerable interest in improving learning conditions in the classroom, with evidence of improvement in spatial intelligence of up to 43% among students learning to play the piano versus 11% among students studying computer science without music (136). Music also impacts intellectual development, in particular the ability to listen to and absorb language (138). There is a debate as to whether these effects are only in the short term (with no lasting effect on intelligence) but positive effects on academic achievement associated with music may be seen in the teenage years (134, 137, 139). Relatively short periods of music training have strong implications on brain plasticity (141) and have strong implications for promoting the development of music-based correction strategies for children with language-based learning disabilities (142). Further, training children in music leads to a long-term improvement in visual spatial, verbal, and mathematical performance (143). Music skills also enhance language development, literacy, literature, intelligence metrics, creativity, fine motor coordination, concentration, self-confidence, emotional sensitivity, social skills, teamwork, self-discipline, general achievement, and relaxation. Early exposure to music improves personal and social development within the context of a fun and rewarding experience (144, 145). The effects on the limbic system of pleasure and enjoyment are important motivators of learning. Playing music to children for 10 min has been shown to increase gamma waves involved in thought processes and alpha waves representing a feeling of calm (78) (Figure 8). At least 6 months of musical training in primary school is required to significantly improve behavior and influence the development of neural processes reflected in specific brain wave patterns (146, 147).

5.5 Sleep

Sleep cycles begin in the womb at 23 weeks of gestation. In infancy, while the number of new neural connections formed is very high, more hours of sleep are needed for pruning and consolidation processes by which recent memories become crystallized into long-term memories (148–151) (Figure 9). By school age, the establishment of a sleep schedule becomes important. Rapid eye movement (REM) sleep is essential for the processes of short-term memory (148, 152–154). Sleep that includes REM, as well as non-REM states, is crucial to synaptic development, the support of cognitive functions, memory and plasticity (memory encoding, unification and reunion) (155–157). The process of pruning during sleep converts short-term to long-term memories. Pruning involves the clearance of amyloid, an insoluble protein precipitate, formed after the development of synapses by glial cells (148, 149). The restorative function of sleep may result from the removal of potentially neurotoxic waste products that accumulate in the central nervous system (158).

Non-REM sleep may be seen on electroencephalogram in the form of sleep spindles and K-complexes. Functional magnetic resonance imaging shows thalamic and limbic system activity during sleep, indicating their role in memory consolidation. Variations in brain activity during sleep are associated with fluctuations in cerebral oxygen demand and perfusion (159, 160).

Sleep deprivation reduces alertness, reduces the motivation to learn, limits concentration and memory formation, and affects mood (161); indeed, sometimes children fall asleep in class. Scheduled naps during the school day in kindergarten have been shown to enhance cognition and learning (162). Keeping children awake and attentive in class is a teaching challenge at any age, but shorter lessons, interesting and stimulating learning activities, inclusion and active participation, and seating struggling children closer to the teacher (or in the teacher's eyeline) are key strategies to improve learning. The identification of problems at home, anxiety or night terrors that may result in sleep deprivation is crucial.

Melatonin is secreted by the pineal gland in the evening and night. Its secretion is stimulated by darkness and inhibited by light along the retino-hypothalamic tract (Figure 9). Infants have the highest levels, and, as a child grows, melatonin levels reduce, and secretion becomes delayed (163). Melatonin may promote deeper sleep, leading to better

A

	Without music N=60	With music N=60		
Aspects of cognition	Average ±SD	Average ±SD	% Change	t-test
Knowledge and recall	69.0±8.81	89.23±6.23	29.3%	12.25***
Understanding and application	65.22±8.49	85.63±7.42	31%	13.32***
Evaluation and synthesis	60.23±6.20	80.80±7.10	34%	16.70***
Overall score	64.81±7.44	85.22±6.46	31.5%	15.25***

***$p<0.001$

B

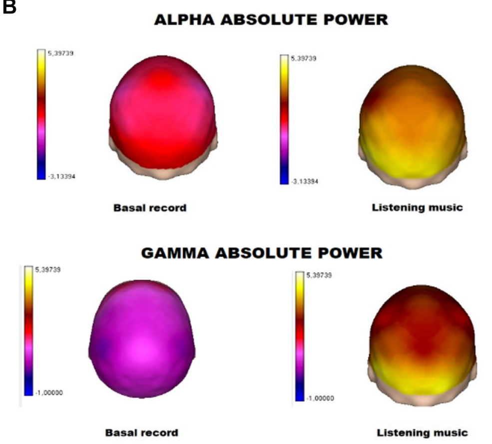


FIGURE 8
(A) Levels of cognition and academic performance with and without music (scale from 0–100) (78). **(B)** Changes in brain activity when listening to music (absolute power from alpha and gamma band) (78). Adapted with permission from (78), licensed under CC BY.

A

Age	Hours of sleep
0-3 months	14-17
4-11 months	12-15
1-2 years	11-14
3-5 years	10-13
6-13 years	9-11

B

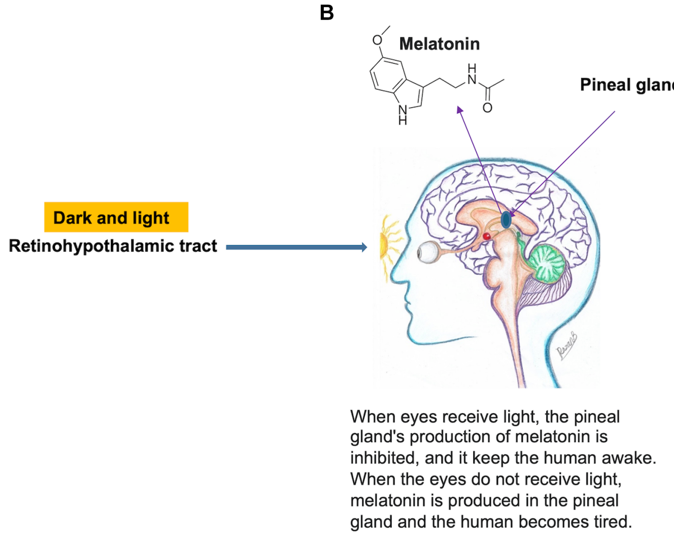


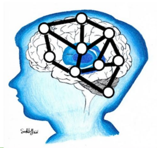
FIGURE 9
(A) Recommended hours of sleep based on childhood age (Data Source: 151). **(B)** Mechanism of inhibition of melatonin secretion from the pineal gland (figure drawn by Razan Bakir).

memory consolidation (164). Metabolites of melatonin are involved in DNA repair and free radical scavenging (165, 166). Supplementation may be effective for children with sleep disorders.

5.6 Brain connectivity – Gardner's theory of multiple intelligences

Intellectual potential is determined by the optimization of connections in the brain and the activation of multiple areas of the brain. Gardner's theory of multiple intelligences sheds light on the importance of connectivity between areas of the brain and the importance of connectivity in learning (Figure 10).

While Gardner describes the existence of multiple intelligences which include verbal and linguistic, logical and mathematical, visual and spatial, musical, naturalist, body kinesthetic, interpersonal, and intrapersonal, it is crucial to understand that these diverse abilities contribute to the creation of a unified sense of self (167, 168). Gardner demonstrated that when one area of the brain is activated, another area of the brain is affected. Improvement in one particular area of the brain that expresses a particular intelligence affects the other intelligences, i.e., logical-mathematical intelligence can be improved through musical intelligence (169–171). The synthesis of various brain systems, such as the frontoparietal network, limbic system, default mode network, and attentional networks, results in the cohesive perception of being 'one person.' This unified experience is



Gardner's multiple intelligences	Verbal Linguistic	Logical Mathematical	Visual Spatial	Musical	Naturalist	Body Kinesthetic	Interpersonal	Intrapersonal
Learning objectives	Finding the correct words to express thoughts and feelings Understanding what others are saying	Counting Quantifying Calculating Creating and testing hypotheses	3-D visualisation Hand-eye coordination	Discerning sound, pitch, tone, rhythm and timbre	Understanding living creatures Understanding human interaction with nature and the planet	Understanding one's own biology, nutrition and metabolism Understanding the body's response to exercise, stress, the need to relax and sleep	Relating to classmates and school staff Understanding nuances in communication Teamwork	Social and emotional awareness Self-reflection Personal plans and objectives
Class task examples	Writing stories and poems Reading aloud Reading comprehension exercises	Mathematical problem solving with real-world examples Mental arithmetic Mathematical puzzles	Drawing Sketching models and plans Painting Graphic design	Singing solo and in a choir Playing a musical instrument solo and in an orchestra Listening to music Writing music	Identifying trees and plants on outdoor excursions Tending a class garden of flowers and vegetables Caring for a class pet	Exercise Competitive and non-competitive sport and games Dance and movement to rhythm	Groupwork School plays and concerts Clubs Debating societies Community service as classroom activity	Keeping a diary Describing future plans and ambitions Describing hobbies, family and friend activities Self-reflection

FIGURE 10
Neural networking (brain connectivity) illustrated by Gardner's multiple intelligences in the classroom.

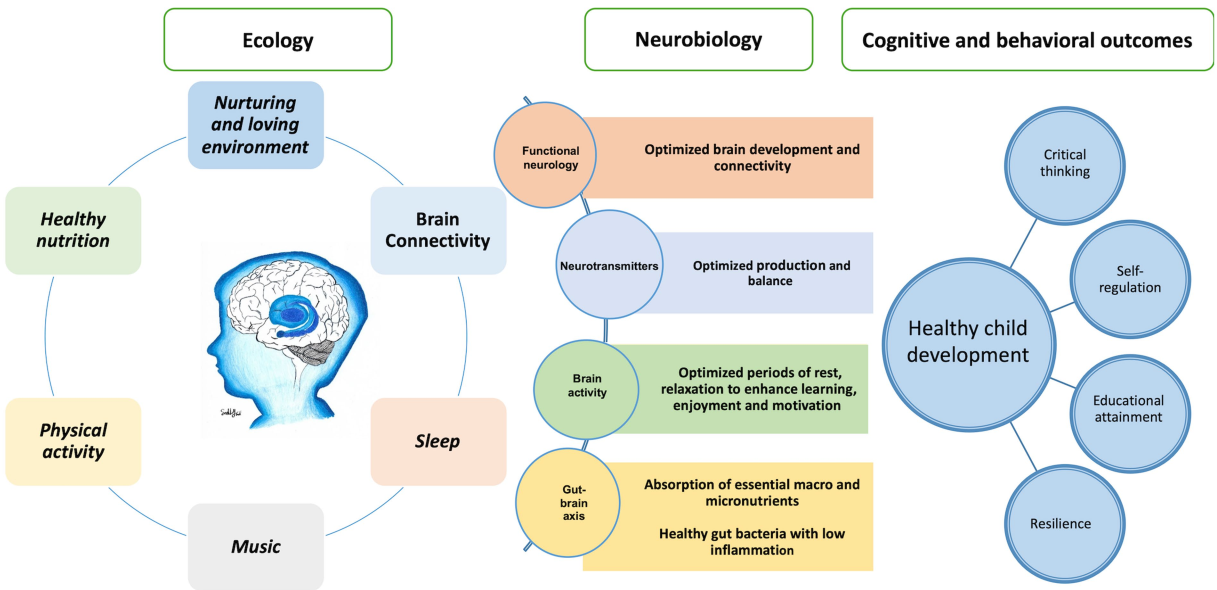


FIGURE 11
The econeurobiology of the brain for healthy child development.

similar to how different chemical senses (olfaction, taste, trigeminal sensitivity) collectively create the perception of the 'aroma' of food, where the contribution of each sense is indistinguishable from the whole percept. Therefore, while Gardner's model is useful for organizing educational activities (e.g., music, physical education, literature), it is essential to balance these activities to foster the development of a harmonious and integrated individual.

6 Using econeurobiology to tackle the social determinants of health

We propose a model that describes the impact of a child's ecological environment on neurological function – the 'econeurobiology' of brain development – Figure 11. The model refers to the ecological environment in which a child grows and the factors that shape cognition and social and emotional learning in early childhood. The model should be considered in tackling the social determinants of health, education, and child development, and creating effective and supportive environments for learning toward realization of the intellectual potential of individuals and the human capital of communities. Education lifts children out of poverty – "The fight against poverty starts with quality education for every child" (172). Music, exercise, rest and quality sleep, healthy food, and calm, ordered and nurturing environments are important in the preschool and elementary school curriculum to foster critical thinking, socialization and behavior that builds human capital.

7 Application of Gardner's intelligence model, economic biology strategies, and connection to the environment of school curriculum

It is important to consider that the application of Gardner's intelligence model and economic biology strategies may vary significantly across different cultural and institutional contexts. For example, educational policies and economic resources in the United States differ greatly from those in developing countries. Therefore, while our model provides a general framework, educators and policymakers should adapt these strategies to fit the specific needs and circumstances of their countries. This includes acknowledging the diverse educational challenges and opportunities that arise from varying economic, social, and cultural backgrounds.

Integrating Gardner's Multiple Intelligences model into educational curricula has been shown to effectively cater to diverse student learning styles. By acknowledging students' dominant intelligences, educators can apply Gardner's theory across all learning types, not just those traditionally emphasized, such as verbal–linguistic and logical-mathematical intelligences (173). This approach facilitates an all-encompassing educational experience that acknowledges the significance of teachers understanding and analyzing the intelligences their students possess. The aim is to enhance learning outcomes by adopting a Multiple Intelligences-based approach tailored to each child's unique abilities, thus improving learning achievement (173).

The educational impact of Gardner's theory is also apparent in its ability to enrich student learning experiences at the upper elementary level (174). Analysis of its application revealed improvements in student capabilities, enabling deeper analysis and connection with previous knowledge — essential for constructing meaningful learning. By addressing the diverse learning styles and preferences, the use of multiple intelligences in the classroom promotes a more inclusive and productive educational environment (174).

When teaching strategies are tailored to the assessed multiple intelligences of students, educators are better equipped to meet the diverse needs of their classrooms, which, in turn, promotes greater academic engagement (175). Students have shown enhanced involvement and motivation when their intellectual strengths are the focus of instruction. This tailored approach not only facilitates comprehension but can also positively influence academic performance. Further studies examining the correlation between students' achievements and their predominant intelligences could lend more credibility to these findings (175).

In summary, the integration of Gardner's theory into educational practices allows for a nuanced approach to teaching. By adopting strategies sensitive to individual differences, educators can enhance student understanding and performance, particularly in complex areas such as physics (176).

How can econeurobiology and what we know about the psychology of cognition and learning be applied in the classroom to improve educational attainment and foster behaviors that shape healthy communities? Addressing investment in education and teaching is crucial. Under-resourced and overworked teachers would struggle to motivate and stimulate children using the best of learning and psychological strategies. Education should be seen within the context of community building and a global strategy toward prosperous and cohesive societies. Investment in teaching should be commensurate with the importance of successful child development. The importance of quality teaching and investment in school in early and mid-childhood for all children should be emphasized over the prevailing focus on higher education for the select few. Education strategies must identify and prioritize the social determinants of learning in children and optimize learning in early childhood when brain plasticity is maximal. Creating a positive and safe environment in school and addressing problems at home are fundamental. Healthy, affordable school meals that address genuine nutrition needs (vitamin A and iodine deficiency, for example) should be available to children who are malnourished.

Ten minutes of relaxing music or aerobic exercise before class can prime children for their lessons (Figure 12). In class, four strategies have been found to stimulate learning and promote memory formation (177, 178): (1) retrieval practice (questioning pupils to elicit their recall and retrieval of information rather than lecturing to passive listeners); (2) feedback (pupils become self-aware of what they know and understand and the gaps in their learning). This stimulates and focuses new learning and increases depth of understanding; (3) spaced-practice (knowledge and understanding consolidated in stages over time so that pupils can process, reorganize and apply what they have learned). This facilitates the formation of lasting memories; (4) interleaving (acquiring new information through a variety of teaching and learning methods – a mix of skills that stimulate brain connectivity and memory formation).

8 The importance of science, technology, engineering, art and mathematics

STEAM education plays a vital role in preparing students for the future, but its implementation can be influenced by cultural and economic factors. For instance, the emphasis on different subjects within STEAM may vary depending on national priorities and resources. In some countries, there might be a greater focus on technology and engineering due to industrial needs, while others might prioritize science and mathematics based on educational traditions. Additionally, the availability of resources for hands-on learning and extracurricular activities can differ, affecting the overall effectiveness of STEAM programs. By considering these cultural and economic variations, we can better tailor STEAM education to meet the unique needs of students globally.

Children have fallen behind in science, technology, engineering, art and mathematics (STEAM) education, in reading, and in literacy (179, 180). We now have a reduced adult STEAM workforce, reduced

Time of Day	5-8 years old	8-12 years old
08.30-09.00	Breakfast at school	Breakfast at school
09.00-09.30	Catch up and singing together in class	School assembly
09.30-10.30	Mathematics\Science	Mathematics\Science
10.30-11.00	Playtime	Break in playground
11.00-11.30	Language and literacy	Language and literacy
11.30-12.00	Music	Music
12.00-13.00	Outdoor learning (STEAM)	Science (STEM)
13.00-13.30	Lunch at school	Lunch at school
13.30-14.30	Nap	Outdoor learning
14.30-15.00	Nap	Outdoor learning
15.00-15.30	Physical activity	Art
Afternoon	Community Service\ social activity	Community Service \social activity

FIGURE 12
Optimizing the elementary school schedule – a typical day for children aged 5 and 10 years (a combination of stimulation and relaxation to optimize learning).

adult literacy and reduced engagement with book reading (181). Literacy, science, and mathematical skills are essential to industrialization, a productive workforce, and the economic prosperity of nations. Children from vulnerable backgrounds are particularly disadvantaged and less likely to pursue STEAM subjects in higher education (182). Yet, effective teaching of STEAM subjects can stimulate and fire the imagination of children. These subjects lend themselves to practical teaching strategies that translate theories into tangible and real experiments, drama classes, drawing, and model-making that are fun and engaging – enhancing brain connectivity for optimal learning. They introduce real-world examples into the classroom where the relevance of STEAM concepts are obvious and learning is translational and modular. Theoretical concepts that are time-consuming, boring, laborious and difficult to explain become practical problem-solving exercises, explorations and analyses of everyday (real-life) activities that interest motivate and stimulate learning – augmenting connectivity between cortical and social and emotional learning centers from an early age.

Scientific and technological literacy are the basic tools and strategies employed in research and discovery. They develop skills of critical thinking and enable students to generate new knowledge. Education of STEAM subjects is crucial to the overall development of the brain architecture, specifically in the prefrontal cortices and the strengthening of top-down self-regulation pathways. Through STEAM education, students learn how to think, rather than being taught what to think - promoting independent and analytical thinking.

9 Conclusion

Brain connectivity is engaged at all levels of Bloom's taxonomy of critical thinking, both simultaneously and cumulatively. Active inquiry-based learning strategies surpass traditional passive didactic methods in enhancing brain connectivity, leading to more effective educational outcomes. Contextual learning strategies, particularly those incorporating real-world examples and outdoor experiences, serve to bolster cognition and memory. They add relevance and a sense of achievement, making learning more rewarding.

Competency-based educational strategies test the application of knowledge, skills, and attitudes, providing critical feedback for teachers and learners. This feedback catalyzes the acquisition of new knowledge and the reinforcement of successful behavioral models, which then evolve into essential life skills. Through such strategies, children learn the meta-skill of learning itself—a fundamental tool for lifelong education.

The relevance of school curricula to the communities they serve is paramount to ensuring that children remain engaged in their education. Extracurricular activities should complement and extend classroom learning, incorporating low-cost sports and team-building exercises into a broader curriculum framework. Opportunities such as sporting events, drama clubs, choirs, bands, debating societies, school journals, and community service projects should not be exclusive to well-funded schools. Instead, they should be leveraged to address educational determinants and meet community needs, especially in underprivileged and unstable environments (183–188).

We call upon policymakers and international institutions to recognize the critical role of designing supportive econeurobiological environments within communities and schools. Safe and nurturing settings enable children to acquire skills essential for building healthy, caring, and prosperous societies. We also call for the immediate action to remove children from war and violent conflicts, and to establish effective strategies to mitigate the negative effects of war by re-establishing healthy and functional econeurobiology.

In summary, the convergence of econeurobiology and educational strategy presents a pivotal opportunity for transformation. By leveraging insights into brain development within educational and community contexts, we can cultivate environments that not only bolster learning and cognitive growth but also contribute to forging more resilient, healthier, and united societies.

Author contributions

RM: Conceptualization, Writing – original draft. LM-Q: Conceptualization, Writing – original draft. RF: Writing – original draft. SS: Writing – original draft. DB: Writing – original draft. SC: Writing – original draft. LM: Writing – original draft. NS: Writing – original draft. RY: Writing – original draft. YZ: Writing – original draft. IW: Writing – original draft. SB: Conceptualization, Writing – original draft.

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Conflict of interest

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