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Challenges, opportunities, and actions for improved maternal and child nutrition

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Challenges, opportunities, and actions for improved maternal and child nutrition

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Table of contents

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Editorial: Challenges, opportunities, and actions for improved maternal and child nutrition

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Editorial on the Research Topic
Challenges, opportunities, and actions for improved maternal and child nutrition

Maternal and child nutrition remains a significant public health challenge globally, especially in low- and middle-income countries. Despite advancements in understanding the importance of nutrition during the first 1,000 days, implementation of interventions and their outcomes show considerable gaps. This Research Topic features nine original research articles that address critical issues, including a description of the magnitude of the problem of malnutrition in countries, the inadequate consumption of vitamins and minerals during pregnancy, the response to prevent malnutrition in emergency settings, and the high consumption of ultra-processed foods during the first 1,000 days and its impact on health and cognitive development and the effects of integrated health interventions on malnutrition. The studies urgently call for targeted nutritional interventions, comprehensive policy reforms, and community-driven strategies to combat malnutrition and its consequences. They align with target 2.2: "End all forms of malnutrition" (1) of the United Nations' Sustainable Development Goals for 2030.

The Research Topic aims are to (i) synthesize globally recognized definitions and tools for assessing nutritional quality and health outcomes; (ii) explore epidemiological trends related to malnutrition and the effects of ultra-processed foods on cognitive development; (iii) evaluate the effectiveness of nutrition interventions in various contexts; and (iv) highlight the socio-cultural, economic, and environmental determinants influencing caregivers' health-seeking behaviors and pregnancy outcomes.

The importance of promoting and ensuring the adequate intake of vitamins and minerals in the diet of toddlers (1–2 years) and preschoolers (3–5 years) is highlighted by the study conducted by Burgard et al. in Germany. In this study, in addition to showing inadequate vitamin D, iodine, and iron intake, there are also high intakes of saturated fatty acids. The authors analyzed data from the representative cross-sectional Children's Nutrition Survey KiESEL conducted between 2014 and 2017. The authors underscore the need for further research into extending vitamin D supplementation beyond infancy and call for enhanced public health initiatives to increase the use of iodized salt and reduce the intake of SFA and sugars in children's diets to address these imbalances.

The findings of Zhang et al.'s study underline the critical global challenge in child nutrition that transcends geographical boundaries. This study examined child malnutrition and its associated factors among 18,503 children aged 3 to 14 in Beijing and Tangshan from September 2020 to January 2022. The prevalence of malnutrition was 10.93%. Multivariable analysis identified seven significant predictors: parental education (OR 1.52), family income (OR 1.23), fast-food intake frequency (OR 1.14), night meals frequency (OR 1.09), eating speed (OR 1.01), and maternal and paternal obesity (both OR 0.97). These factors strongly predicted child malnutrition, emphasizing the need to address these risk factors to improve child nutrition and public health.

The study carried out by Naila et al. investigates the healthcare-seeking behaviors of caregivers for critically malnourished children under 5 years old among forcibly displaced Myanmar Nationals (FDMNs) in Bangladesh. The study's main conclusion stresses the importance of culturally sensitive interventions to promote caregiver awareness of severe wasting, enhanced healthcare accessibility, and increased community volunteer engagement, which have the potential to facilitate early identification of severely wasted children and mitigate delays in treatment. These insights align with findings from studies in Germany and China, emphasizing the need to address socio-cultural factors to enhance maternal and child nutrition in vulnerable populations.

Furthermore, Liu Y. et al. examined the associations between nutritional trace metals (NTMs) during pregnancy and the risk of preterm birth (PTB) in women experiencing recurrent pregnancy loss. The research demonstrated that higher maternal exposure to copper (Cu) and zinc (Zn) was inversely associated with PTB risk, suggesting that increased levels of these metals may lower the likelihood of PTB, with Cu identified as a significant factor. The study highlights the importance of NTMs in understanding PTB risk and offers insights for personalized care and preventive strategies to improve maternal and infant health outcomes.

This Research Topic also includes studies highlighting the effectiveness of health programs in various contexts, particularly in the most vulnerable settings. One such study by Pedrero-Tomé et al. evaluated a health program in the Tama health area of Bouza, Tahoua, and Niger, designed to combat high malnutrition rates in children under two amid severe food insecurity and high infant mortality. The program, involving 6,962 participants, included vaccinations, malaria prevention, and nutritional supplementation for children over 6 months. Results showed a decline in the proportion of children without anthropometric failure, dropping from 59.5% to 40.2% ($p < 0.001$). The study highlights the need for integrated approaches addressing both infectious diseases and malnutrition in vulnerable young children.

Similarly, the study by Sánchez-Martínez et al. focuses on the treatment of moderate acute malnutrition (MAM) in emergency settings, particularly in the Diffa region of Niger. It evaluates a simplified treatment protocol administered by Community Health Workers (CHWs) compared to the standard protocol provided by nursing staff. In a non-randomized controlled trial, the intervention group ($n = 483$) exhibited a significantly higher recovery rate (99.6% vs. 79.56%, $p < 0.001$), faster recovery times, and better anthropometric gains compared to the control group ($n = 181$). Additionally, treatment coverage in the intervention group increased from 28.8% to 84.9%, declining in the control group from 25.3% to 13.6%. Importantly, recovery rates were similar for children treated by CHWs and nursing staff, indicating that the simplified protocol can be effectively administered in emergencies. The findings highlight the need for innovative actions for the prevention and treatment of MAM in emergency contexts, integrating the participation of CHWs with the use of valid and precise indicators, such as Mid-upper arm circumference, as a risk and monitoring indicator of the nutritional status of children.

This topic also highlights the pervasive influence of ultra-processed food consumption across different life stages, emphasizing the need for targeted interventions to improve dietary habits and health outcomes for mothers and children. Granich-Armenta et al. investigated the contribution of ultra-processed foods (UPFs) to total energy intake during pregnancy, focusing on pre-gestational BMI and hemoglobin (Hb) levels in the MAS-Lactancia Cohort in Mexico. UPFs comprised about 27% of total energy intake during the second and third trimesters, with no significant changes between these periods. Women with pre-gestational obesity and low Hb levels had higher UPF energy contributions (23.1% to 44.7%) compared to those with normal BMI and higher Hb (18% to 38.6%). The high intake of sugars, saturated fats, and sodium raises maternal and child health concerns, highlighting the need for better nutrition during pregnancy.

Along the same lines, Liu S. et al. investigated the harmful effect of consuming ultra-processed foods, which goes beyond health issues, showing how these products have a negative impact on cognitive function in preschool children in China. The study examined 325 children aged 4–7 from the Guangxi Zhuang Birth Cohort. It used interviews and a Food Frequency Questionnaire to evaluate their intake of ultra-processed foods like candy and sugary drinks. The findings showed that frequent consumption of candy and sweet baked goods was significantly linked to lower full-scale IQ scores, with candy also increasing the risk of cognitive deficits. Additionally, children who consumed more than two types of ultra-processed foods had lower Verbal Comprehension Index scores.

All the studies above underscore the importance of comprehensive recommendation guidelines prioritizing maternal nutrition. The Ancira-Moreno et al. study contributed to emphasizing this dimension. This research sought to identify clinical practice guidelines (CPGs) addressing maternal malnutrition prevention, diagnosis, and treatment. Guidelines for women in the preconception period were reviewed, and their quality was assessed using the AGREE II tool. Of the 30 guidelines screened, 20 were fully evaluated, with an overall quality score of 73%. Only 55% were classified as high quality (score $> 70\%$). The highest scores were in the "Scope and Purpose" (98.5%) and "Clarity of Presentation" (93%) domains. The study underscores the need to improve the quality of guidelines for managing women's malnutrition.

Challenges, opportunities, and strategic actions

Advancing maternal and child nutrition requires addressing persistent and complex challenges, including socio-economic inequalities, gaps in healthcare infrastructure, and cultural determinants of health behaviors. These challenges are compounded by the pervasive influence of ultra-processed foods, insufficient adherence to clinical practice guidelines, and limited integration of evidence-based interventions into healthcare systems. However, these barriers also create opportunities for transformative solutions. Strategic actions include the development of robust policies that integrate nutrition-specific and nutrition-sensitive interventions, applying advanced technologies to enhance monitoring and evaluation systems, and strengthening multisectoral collaboration to optimize resource allocation and impact. Furthermore, prioritizing the training and deployment of community health workers, alongside scaling culturally sensitive approaches, can enhance early detection and treatment of malnutrition. By implementing these targeted and evidence-driven strategies, substantial progress can be achieved in mitigating the global burden of maternal and child malnutrition.

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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 ultraprocessed foods consumption and cognitive function among children aged 4–7 years: a cross-sectional data analysis

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Background: Sugar-sweetened beverage (SSB) consumption has shown associations with cognitive function in preschool children, but effects of other ultraprocessed foods consumption are rarely discussed in China. This study aimed to investigate the relationship between ultraprocessed food consumption and cognitive function among preschool children in China.

Methods: A total of 325 children aged 4–7 years were included from Guangxi Zhuang Birth Cohort in Guangxi Zhuang Autonomous Region, China. Face-to-face interviews with parents using the Food Frequency Questionnaire (FFQ) was conducted to investigate the status of seven ultraprocessed foods consumption (i.e., chocolate, biscuits, candy, fast-food, ice cream, SSBs, and sweet bakery products). The mandarin-language version of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI, Fourth Edition) was applied to assess the cognitive function of children. Multiple linear and logistic regression models were used to assess the associations between ultraprocessed food consumption and the full-scale intelligence quotient (FSIQ) and different domains and risk of cognitive deficit, respectively.

Results: We found that frequent consumption of candy ($\beta = -3.34$, 95% CI: $-5.62 \sim -1.06$; $p = 0.004$) and sweet bakery products ($\beta = -2.77$, 95% CI: $-5.58 \sim 0.04$; $p = 0.054$) were significant associated with decreased FSIQ scores in the linear regression models. However, only frequent consumption of candy was statistically significantly associated with an increased risk of cognitive deficit (OR = 2.05, 95% CI: 1.11~3.79; $p = 0.023$) in the logistic regression models. For the different domains, we found frequent consumption of candy ($\beta = -3.85$, 95% CI: $-6.28 \sim -1.43$; $p = 0.002$) and sweet bakery products ($\beta = -3.48$, 95% CI: $-6.47 \sim -0.49$; $p = 0.023$) was also significantly associated with lower Verbal Comprehension Index (VCI). When combining the seven ultraprocessed foods, we found children who frequently consumed more than two kinds of ultraprocessed foods had a significant decrease of VCI scores ($\beta = -2.66$; 95% CI: $-5.12 \sim -0.19$; $p = 0.035$) too.

Conclusion: Our results suggested that frequent consumption of individual (candy and sweet bakery products) and multiple ultraprocessed foods may decrease VCI scores and thereby impact cognitive function in children aged 4–7 years.

KEYWORDS

ultraprocessed foods consumption, children, cognitive function, candy, cross-sectional

1. Introduction

Cognitive ability is a set of higher mental functions, including memory, learning, and attention, and is demonstrated to be a significant predictor of a child's academic achievement (1). Globally, an estimated 200 million children under five are not reaching their potential for cognitive development (2, 3). Among them, 45 million are from China, which would place China the second largest number of children with cognitive delay in the world (4–6). Previous studies have shown that delayed cognitive development affects the academic performance and mental health of children, such as an increased risk of attention deficit hyperactivity disorder and emotional symptoms (7). Maintaining the healthy development of cognitive function has emerged as an important public health issue in children.

Childhood is a crucial period for the development of cognitive function, as the brain develops most rapidly at this stage. Brain development requires essential nutrients, implying that nutrition plays a key role in early childhood development (8, 9). A series of studies have focused on the relationship between dietary patterns, micronutrients, and cognition function in children (10–14). Among these factors, ultraprocessed food consumption, such as junk food, and snacks, especially chocolate, candy, biscuits, cake, ice creams, and salty snacks, has become of great interest to both academic research and the public (15, 16). Several studies have shown that ultraprocessed snacks, sugar-sweetened beverage (SSB), and chocolates were inversely associated with the cognitive function of children (17, 18). In addition, children with higher consumption of fast-food and SSBs at age 3 had poorer academic achievement at age 10 (19). An ultraprocessed dietary pattern with high fat, sugar, and processed food in early childhood has been associated with lower scores in verbal ability (20, 21) and increased odds of mathematical difficulties (22). Collectively, ultraprocessed food consumption may hinder the development of cognitive function in children.

In China, snacks and SSBs consumption is very common among preschool children (23–25). However, previous studies have only focused on the effects of SSB consumption on cognitive function (7, 26). To our knowledge, the effects of other ultraprocessed food consumption on children's cognition function are rarely discussed. To address this gap in the literature, we used a cross-sectional data from the Guangxi Zhuang birth cohort in China to estimate the individual and overall effects of consuming seven common ultraprocessed foods (i.e., chocolate, biscuits, candy, fast-food, ice cream, SSB, and sweet bakery products) on cognitive function in children aged 4–7 years.

Abbreviations: SSB, sugar-sweetened beverage; FFQ, Food Frequency Questionnaire; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; GZBC, Guangxi Zhuang Birth Cohort; VCI, Verbal Comprehension Index; VSI, Visual Spatial Index; FRI, Fluid Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; FSIQ, full-scale intelligence quotient; MICE, multivariate imputation by chained equations.

2. Materials and methods

2.1. Study participants

Study participants were from the Guangxi Zhuang Birth Cohort (GZBC), which was conducted in county-level hospitals of six major counties of the Guangxi province in China from June 2015 (27). From July to September 2021, we successfully followed up 325 children born to the mothers of GZBC in Debao and Pingguo county. During the follow-up study phase, face-to-face interviews with parents were conducted to investigate the consumption status of seven ultraprocessed foods (i.e., chocolate, biscuits, candy, fast-food, ice cream, SSB, and sweet bakery products) for the children using a Food Frequency Questionnaire (FFQ). The Mandarin-language version of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI, Fourth Edition) was applied to assess the cognitive function of children. Among them, a total of 97 children were excluded which included 4 children who did not complete the food consumption survey and 93 children who did not finish the cognitive function assessment. Finally, 228 children were included for the further analysis. Ethical approval was granted by Guangxi Medical University, China (No. 20140305-001), and maternal informed consent was provided.

2.2. Cognitive function assessment

Children's cognitive function was assessed using the Mandarin-language version of the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (28), which has been widely used in cognitive function assessments because of its high reliability and validity (29). The specific cognitive function domains included Verbal Comprehension Index (VCI, a measure of the ability to understand, learn, and retain verbal information, as well as to use language to solve novel problems), Visual Spatial Index (VSI, a measure of the ability to understand visual information and to solve novel abstract visual problems), Fluid Reasoning Index

(FRI, the test measures fluid intelligence, non-verbal concept formation, analysis, and problem-solving, and integration ability, etc.), Working Memory Index (WMI, a measure of the ability to hold verbal information in short-term memory and to manipulate the information), and Processing Speed Index (PSI, a measure of mental speed that may also be affected by factors such as attention) (30). The Full-Scale Intelligence Quotient (FSIQ) is a composite score of the above five domains scores (VCI, VSI, FRI, WMI, and PSI), which represents the general intellectual ability of the subject. The FSIQ and single index was standardized to have a mean of 100 and a standard deviation of 15, ranging from 40 to 160 (31). Higher values of the FSIQ or the single index represent a better test performance, and therefore stronger cognitive abilities. In addition, an FSIQ of less than 80 scores were defined as having a cognitive deficit (8, 32, 33). Regarding assessments, all examiners were trained professionally and certified before the test. The assessments were administered by well-trained examiners one-on-one, without any guidance from teachers or guardians in a standard and quiet assessment room.

2.3. Ultraprocessed foods assessment

Through face-to-face interviews, children's consumption of common ultraprocessed foods in the past 3 months was determined from mothers' responses to the Food Frequency Questionnaire (FFQ). The ultraprocessed foods in the present study included chocolate, biscuits, candy, fast-food (French fries or hamburgers), ice cream, sugar-sweetened beverage (SSB), and sweet bakery products. The food consumption frequency was reported as "never," "once a week," and "more than twice a week." Finally, we defined "never" and "once a week" as "infrequent" and "more than twice a week" as "frequent" (34).

2.4. Covariates

Sociodemographic and family characteristics were collected via a face-to-face interview questionnaire, including child sex (male or female), child age (years), residence area (rural or urban), siblings (0. $\geq$ 1), parental education levels (junior high school or below, senior high school or above), annual household incomes (low = $\leq$ 5.99 w/year, medium = 6–14.99 w/year, high = $\geq$ 15 w/year), outdoor exercise time (h/day), parental accompaniment time (h/day), breastfeeding duration (months), daily sleeping time (h), and secondhand smoke (no = never, infrequent = 1–2 times/week, frequent = more than 3 times/week).

2.5. Statistical analysis

Categorical variables were described in frequencies and proportions, while continuous variables were described in terms of means and standardized deviations. Two variables with missing data in our analysis included daily sleeping time (18%) and secondhand smoke (7%). They were assumed to be missing at random and imputed with the multivariate imputation by chained equations (MICE) method for five times. Continuous variables were imputed using predictive mean matching, and categorical variables using logistic regression factor (2 levels) (35). The Chi-square test and Wilcoxon rank sum test was used to determine whether there were any statistically significant differences of the covariates between cognitive deficits and non-cognitive deficits. The multiple linear regression and logistic regression models were applied to analyze the relationship between ultraprocessed food consumption and cognitive function and the risk of cognitive deficit, respectively. Specifically, two models were constructed. Crude model did not adjust any factors. Adjusted model adjusted the potential confounders. A Directed Acyclic Graph[1] was used to inspect possible pathways for confounders (36). In addition, covariates were selected *a priori* based on the previous literature (37). Finally, the following variables were selected as confounders: child age, residence area, siblings, parental education levels, annual household incomes, outdoor exercise time, parental accompaniment time, daily sleeping time, breastfeeding duration, and secondhand smoke (**Figure 1**). All statistical analyses were performed using R 4.03 software. The p-value < 0.05 were considered statistically significant. Forest plots were produced using the GraphPad Prism 8.0.1 software.

3. Results

3.1. Participants characteristics

A description of the participants (n = 228) characteristics is presented in **Table 1**. Of the 228 children, 50.88% were boys, of which, 30.70% were frequently exposed to secondhand smoke. Most of the children were from urban environments (76.75%), have siblings (73.25%), had mothers (61.40%), and fathers (62.72%) with a senior high school education or above, and less than 2 h of outdoor exercise time per day (70.18%). Among them, 45.61% had low annual household incomes. A total of 83 (36.40%) children had cognitive deficits. The distributions of residence area, siblings, parental education levels, and annual household incomes ($p < 0.05$) were significantly different between cognitive deficits and non-cognitive deficits. Especially, higher incidence of cognitive deficit was observed among children who were from urban environments, had siblings, had parents with junior high school or below education level, and had lower annual household incomes.

3.2. Association between frequent ultraprocessed food consumption and cognitive function among children aged 4–7 years

First, we applied a multiple linear regression model to assess the association between frequent ultraprocessed food consumption (independent variables) and FSIQ scores (dependent variables) (**Table 2**). In the crude model, we found children who frequently consumed candy had lower FSIQ scores compared with infrequent

1 http://dagitty.net/

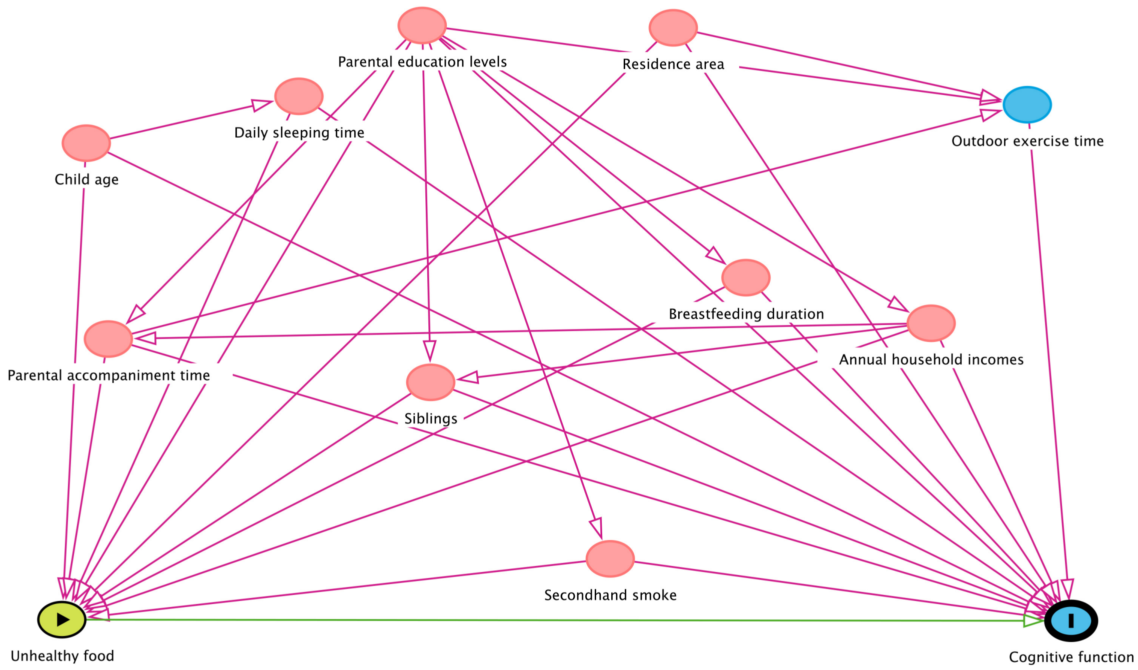

FIGURE 1
Directed acyclic graph (DAG) for the relationship of ultraprocessed foods consumption with cognitive function of children at age 4–7 years.

consumers (β = −2.49, 95% CI: −4.79∼−0.18; p = 0.035). After adjusting for potential confounders, we found that frequent consumption of candy (β = −3.34, 95% CI: −5.62∼−1.06; p = 0.004) and sweet bakery products (β = −2.77, 95% CI: −5.58∼0.04; p = 0.054) were significantly associated with lower FSIQ scores.

Second, we applied logistic regression models, including all children, to examine the association between frequent consumption of ultraprocessed foods (independent variables) and risk of cognitive deficit (dependent variables) (Table 3). In the crude model, children who frequently consumed candy showed an association with an increased risk of cognitive deficit (OR = 1.61, 95% CI: 0.94∼2.78; p = 0.085), whereas children who frequently consumed biscuits showed an association with a decreased risk of cognitive deficit (OR = 0.59, 95% CI: 0.34∼1.05; p = 0.072), both close to the level of significance. After adjusting for potential confounders, however, children who frequently consumed candy was associated with a significantly increased risk of cognitive deficit (OR = 2.05, 95% CI: 1.11∼3.79; p = 0.023).

The associations between frequent ultraprocessed food consumption and the specific cognitive domains, including VCI, VSI, FRI, WMI, and PSI scores, are also shown in Figure 2. In the crude model, children who frequently consumed candy showed a significant decrease in VCI scores (β = −3.20, 95% CI: −5.66∼−0.74; p = 0.011) while a not fully significant decrease in PSI scores (β = −2.63, 95% CI: −5.64∼−0.37; p = 0.085). However, children who frequently consumed biscuits showed an increase in FRI scores (β = 2.94, 95% CI: −0.14∼6.01; p = 0.061), which was close to the level of significance.

After adjusting for potential confounders, the associations between frequent candy consumption and lower VCI scores remained statistically significant (β = −3.85, 95% CI: −6.28∼−1.43; p = 0.002). In addition, a new significant association was found between lower VCI scores and frequent consumption of sweet bakery products (β = −3.48, 95% CI: −6.47∼−0.49; p = 0.023).

In order to analyze the combined effects of frequent consumption of the seven ultraprocessed foods on the cognitive function of children, we calculated the number (0–7) of frequent consumption of ultraprocessed foods and divided the children into frequent consumption of 0–1 and 2–7 ultraprocessed foods. Table 4 shows the multiple linear regression analysis of the associations between the numbers of ultraprocessed foods types of frequent consumption and specific cognitive function domains. In the crude models, we did not find any significant associations. However, in the adjusted models, we found that children who frequently consumed more than two kinds of ultraprocessed foods were significantly associated with decreased VCI scores (β = −2.66; 95% CI: −5.12∼−0.19; p = 0.035). Furthermore, we also analyzed the association between the numbers of ultraprocessed food types of frequent consumption and cognitive function and found there were no significant associations no matter FSIQ scores or risk of cognitive deficit (Table 5).

4. Discussion

In the present study, we employed a cross-sectional data from the Guangxi Zhuang birth cohort to assess seven common ultraprocessed foods in the cognitive function of Chinese children aged 4–7. We found children who frequently consumed candy and sweet bakery products had a significant decrease in both VCI and FSIQ scores. However, only frequent consumption of candy was significantly associated with an increased risk of cognitive

TABLE 1 Characteristics and distribution of sample children by cognitive deficit (n = 228).

Characteristics	Total (%)	Cognitive deficit		χ^2/z	*P*
		Yes (%)	No (%)		
Child sex				0.376	0.540
Boy	116 (50.88)	40 (48.20)	76 (52.40)		
Girl	112 (49.12)	43 (51.80)	69 (47.60)		
Child age (year)	228	5.00 ± 0.50	4.95 ± 0.42	−0.800	0.425
Residence area	228			4.775	0.029
Rural	53 (23.25)	26 (31.30)	27 (18.60)		
Urban	175 (76.75)	57 (68.70)	118 (81.40)		
Siblings				6.510	0.011
0	61 (26.75)	14 (16.90)	47 (32.40)		
≥ 1	167 (73.25)	69 (83.10)	98 (67.60)		
Father's education level				13.813	0.000
Junior high school or below	85 (37.28)	44 (53.00)	41 (28.30)		
Senior high school or above	143 (62.72)	39 (47.00)	104 (71.70)		
Mother's education level				15.589	0.000
Junior high school or below	88 (38.60)	46 (55.40)	42 (29.00)		
Senior high school or above	140 (61.40)	37 (44.60)	103 (71.00)		
Annual household incomes[a]				23.084	0.000
Low	104 (45.61)	55 (66.30)	49 (33.80)		
Medium	80 (35.09)	16 (19.30)	64 (44.10)		
High	44 (19.30)	12 (14.40)	32 (22.10)		
Outdoor exercise time (h/day)				0.456	0.499
≤ 2 h/day	160 (70.18)	56 (67.50)	104 (71.70)		
> 2 h/day	68 (29.82)	27 (32.50)	41 (28.30)		
Time spent with children (father) (h/day)		7.14 ± 5.20	7.35 ± 5.64	−0.034	0.973
Time spent with children (mother) (h/day)		15 ± 7.76	13.11 ± 7.62	−1.557	0.120
Daily sleeping time (h/day)		10.31 ± 1.02	10.30 ± 0.10	−0.302	0.763
Breastfeeding duration (months)		9.77 ± 3.15	10.26 ± 3.98	−0.710	0.477
Secondhand smoke[b]				0.442	0.802
No	113 (49.56)	39 (47.00)	74 (51.00)		
Infrequent	45 (19.74)	18 (21.70)	27 (18.60)		
Frequent	70 (30.70)	26 (31.30)	44 (30.30)		

[a]Annual household incomes: Low = ≤ 5.99 w/year; Medium = 6–14.99 w/year; High = ≥ 15 w/year.
[b]Secondhand smoke: No = never, Infrequent = 1–2 times/week; Frequent = more than 3 times/week.

deficit. Furthermore, frequently consuming more than two kinds of ultraprocessed food showed a significant association with decreased VCI scores. These findings suggested the individual and combined effects of the seven ultraprocessed foods on cognitive function among children aged 4–7 years, providing new evidence from China on the association between ultraprocessed food consumption and child cognitive development.

The ultraprocessed foods in this survey are mainly those high in saturated fat and added sugar. We showed a combined effects of these ultraprocessed food intake on children cognitive function in VCI domain, which was in line with findings of several prior epidemiology studies that ultraprocessed diet patterns with high fat and sugar content impact cognitive function (17, 18, 20, 21, 38). Animal evidence also supports the findings that these ultraprocessed food intakes may adversely influence cognitive development. For example, added sugars, especially high-fructose corn syrup, may adversely influence hippocampal function during critical periods of development in adolescent rats (39). Consuming a "Western Diet" with high saturated fat (such as chocolate, ice cream, and fast-food) has also showed adverse effects on neurocognitive function, particularly for memory processes that rely on the integrity of the hippocampus (40, 41). However, we found only frequent consumption of candy and sweet bakery products was associated with decreased cognitive scores. Results

TABLE 2 Associations between frequent ultraprocessed foods consumption and FSIQ scores among children aged 4–7 years.

Ultraprocessed foods	Crude model[a]		Adjusted model[b]	
	β (95% CI)	*P*	β (95% CI)	*P*
Chocolate	−1.61 (−6.60∼3.38)	0.526	−1.34 (−6.36∼3.69)	0.601
Biscuits	0.32 (−2.05∼2.70)	0.788	−1.05 (−3.51∼1.41)	0.402
Candy	−2.49 (−4.79∼−0.18)	0.035	−3.34 (−5.62∼−1.06)	0.004
Fast-food	−0.83 (−6.01∼4.36)	0.753	−2.35 (−7.54∼2.84)	0.374
Ice cream	−0.51 (−2.87∼1.85)	0.668	−0.24 (−2.68∼2.19)	0.844
SSB	−0.05 (−2.73∼2.62)	0.969	−0.31 (−2.97∼2.35)	0.818
Sweet bakery products	−1.48 (−4.29∼1.33)	0.301	−2.77 (−5.58∼0.04)	0.054

FSIQ, Full-Scale Intelligence Quotient; CI, confidence interval; SSB, sugar-sweetened beverage.
[a]Crude model was not adjusted for any variables.
[b]Adjusted model was adjusted for child age, residence area, siblings, parental education levels, annual household incomes, outdoor exercise time, parental accompaniment time, daily sleeping time, breastfeeding duration, and secondhand smoke.

TABLE 3 Associations between frequent ultraprocessed foods consumption and the risk of cognitive deficit among children aged 4–7 years.

Ultraprocessed foods	Crude model[a]		Adjusted model[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Chocolate	1.54 (0.50∼4.73)	0.455	1.13 (0.32∼3.96)	0.848
Biscuits	0.59 (0.34∼1.05)	0.072	0.78 (0.41∼1.48)	0.442
Candy	1.61 (0.94∼2.78)	0.085	2.05 (1.11∼3.79)	0.023
Fast-food	1.81 (0.56∼5.79)	0.320	2.53 (0.69∼9.22)	0.160
Ice cream	1.42 (0.82∼2.46)	0.207	1.30 (0.69∼2.42)	0.418
SSB	0.84 (0.44∼1.57)	0.578	0.84 (0.42∼1.69)	0.619
Sweet bakery products	1.02 (0.53∼1.96)	0.957	1.52 (0.72∼3.20)	0.277

OR, odds ratio; CI, confidence interval; SSB, sugar-sweetened beverage.
[a]Crude model was not adjusted for any variables.
[b]Adjusted model was adjusted for child age, residence area, siblings, parental education levels, annual household incomes, outdoor exercise time, parental accompaniment time, daily sleeping time, breastfeeding duration, and secondhand smoke.

from SSB consumption were different from previous research, in which the authors suggested SSB consumption was negatively associated with executive function (26, 37). Executive function is a generic term for a range of interrelated, higher-level of cognitive abilities that are necessary for complex reasoning, goal-oriented activity, and self-regulatory behavior. The inconsistent findings may be due to the difference of population (e.g., age and lifestyles) and the assessment tools. The latest studies have shown that that candy is the most common sources of added sugar among children and adolescent (42, 43). Recently, animal studies have shown that the potentially harmful effects of long-term candy consumption on memory deficits and hippocampal neurogenesis were sufficient to reduce hippocampal levels of brain-derived neurotrophic factor (BDNF) and spatial learning performance (44). Given these finding together with the impact of candy on cognitive function, we should pay much more attention to the regulation of these food sources.

In the present study, we observed that individually the categories candy and sweet bakery products and combined effects of the seven ultraprocessed foods on cognitive function were mainly associated with decreasing VCI scores, which represented the ability to understand, learn, and retain verbal information, as well as to use language to solve novel problems. Our findings are also in line with two previous studies (20) showing that ultraprocessed dietary pattern (snack pattern) was negatively associated with lower cognitive ability, especially in verbal ability. During childhood, parenting and the family environment significantly impact verbal skills more than other performance abilities (45). Evidence shows that the prefrontal cortex and hippocampus region are critical role in verbal communication and comprehension (46, 47). Animal studies have shown that sugar could induce increases in inflammation mediators in the hippocampal (such as IL-6 and IL-1β), as well as decrease antioxidant enzymes in the frontal cortex (37). These findings lend some support to the results of the present study potentially suggesting that ultraprocessed food consumption may impact regions of the brain associated with verbal function. However, more sensitive measures such as functional magnetic resonance imaging (fMRI) techniques should be employed to assess this potential relationship further.

5. Strengths, limitations future research

The present study provides new evidence of the association between ultraprocessed foods consumption and cognitive performance among children aged 4–7 years. However, the following limitations should be taken into consideration when interpreting the results. First, the study relies on a cross-sectional

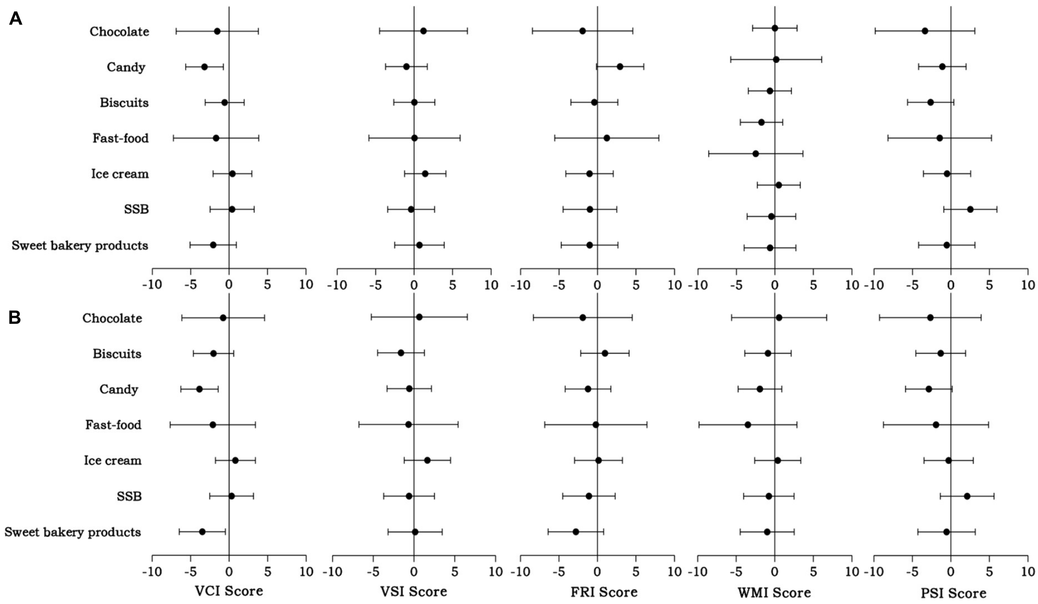

FIGURE 2
Associations between frequent consumption of ultraprocessed foods and different domain scores of the Wechsler Preschool and Primary Scale of Intelligence test among children aged 4–7 years. Crude model **(A)** was not adjusted for any variables. Adjusted model **(B)** was adjusted for child age, residence area, siblings, parental education levels, annual household incomes, outdoor exercise time, parental accompaniment time, daily sleeping time, breastfeeding duration, and secondhand smoke. SSB, sugar-sweetened beverage; VCI, Verbal Comprehension Index; VSI, Visual Spatial Index; FRI, Fluid Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index.

TABLE 4 Associations between the numbers of ultraprocessed foods types of frequent consumption and specific cognitive function domains among children aged 4–7 years.

Cognitive function domains[a]	Crude model[b]		Adjusted model[c]	
	β (95% CI)	*P*	β (95% CI)	*P*
VCI Scores	−1.77 (−4.24∼0.70)	0.160	−2.66 (−5.12∼−0.19)	0.035
VSI Scores	−0.54 (−3.19∼2.11)	0.689	−1.11 (−3.84∼1.62)	0.422
FRI Scores	0.56 (−2.47∼3.58)	0.717	−0.56 (−3.54∼2.42)	0.711
WMI Scores	−0.39 (−3.14∼2.36)	0.780	−0.76 (−3.63∼2.10)	0.600
PSI Scores	−0.05 (−3.05∼2.96)	0.975	0 (−3.07∼3.07)	1.000

VCI, Verbal Comprehension Index; VSI, Visual Spatial Index; FRI, Fluid Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index.
[a]The results showed the effects of frequent consumption of 2–7 ultraprocessed foods compared with 0–1.
[b]Crude model was not adjusted for any variables.
[c]Adjusted model was adjusted for child age, residence area, siblings, parental education levels, annual household incomes, outdoor exercise time, parental accompaniment time, daily sleeping time, breastfeeding duration, and secondhand smoke.

TABLE 5 Associations between the numbers of ultraprocessed foods types of frequent consumption and cognitive function among children aged 4–7 years.

Models[a]	FSIQ scores		Risk of cognitive deficit	
	β (95% CI)	*P*	OR (95% CI)	*P*
Crude model[b]	−0.75 (−3.06∼1.57)	0.524	1.00 (0.59∼1.72)	0.990
Adjusted model[c]	−1.72 (−4.04∼0.61)	0.147	1.22 (0.66∼2.24)	0.525

FSIQ, Full-Scale Intelligence Quotient; OR, odds ratio; CI, confidence interval.
[a]The results showed the effects of frequent consumption of 2–7 ultraprocessed foods compared with 0–1.
[b]Crude model was not adjusted for any variables.
[c]Adjusted model was adjusted for child age, residence area, siblings, parental education levels, annual household incomes, outdoor exercise time, parental accompaniment time, daily sleeping time, breastfeeding duration, and secondhand smoke.

data, which could not infer the causal relationship between ultraprocessed food consumption and cognitive development. Second, the questionnaire method in this study may cause recall bias, so we measured the frequency of consumption of ultraprocessed foods on a weekly basis, rather than monthly or yearly, mainly to reduce the influence of recall bias. Finally, assessing the cognitive performance at a single point in time may influence misclassification bias. This is because a child's performance varies and is contingent upon the testing environment. However, in order to avoid the risk of bias as much as possible, we required testers to undergo strict training and obtain official certification. We ensured that all testers followed the evaluation procedures strictly, such as evaluating children individually in a standardized testing room. Future studies are needed to establish the causal relationship between ultraprocessed food consumption and cognitive development perhaps using more sensitive techniques such as brain imaging.

6. Conclusion

The results of this study suggested that the frequent consumption of the category "candy" and "sweet bakery products" and multiple ultraprocessed foods may decrease VCI scores and thereby impact cognitive function in children aged 4–7 years. It is necessary for scientists and policymakers to make targeted efforts to reduce ultraprocessed food consumption in children due to their potentially harmful effects on both physical and brain health including cognitive and emotional function.

Data availability statement

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

Ethics statement

This study was approved by the Ethical Committee of Guangxi Medical University (No.20140305–001). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

SL: Data curation, Funding acquisition, Project administration, Resources, Supervision, Writing-review and editing, Writing–original draft. CM: Investigation, Methodology, Visualization, Writing–original draft. LL: Formal analysis, Methodology, Software, Writing–review and editing. JL: Supervision, Writing–review and editing. FL: Supervision, Writing–review and editing. XX: Supervision, Writing–review and editing. PL: Data curation, Supervision, Writing–review and editing. GW: Data curation, Supervision, Writing–review and editing. XH: Supervision, Writing–review and editing. XQ: Data curation, Funding acquisition, Resources, Writing–review and editing. XZ: Writing–review and editing.

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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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A scoping review and critical evaluation of the methodological quality of clinical practice guidelines on nutrition in the preconception

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Introduction: Clinical practice guidelines (CPGs) contain recommendations for specific clinical circumstances, including maternal malnutrition. This study aimed to identify the CPGs that provide recommendations for preventing, diagnosing, and treating women's malnutrition. Additionally, we sought to assess the methodological quality using the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.

Methods: An online search for CPGs was performed, looking for those that contained lifestyle and nutritional recommendations to prevent, diagnose and treat malnutrition in women during the preconception period using PubMed and different websites. The reviewers utilized the AGREE II instrument to appraise the quality of the CPGs. We defined high-quality guidelines with a final score of > 70%.

Results: The titles and abstracts from 30 guidelines were screened for inclusion, of which 20 guidelines were fully reviewed for quality assessment. The overall quality assessment of CPGs was 73%, and only 55% reached a high-quality classification. The domains in the guidelines classified as high-quality had the highest scores in "Scope and Purpose" and "Clarity of Presentation" with a median of 98.5 and 93%, respectively.

Discussion: Further assessment is needed to improve the quality of the guidelines, which is an opportunity to strengthen them, especially in the domains with the lowest scores.

KEYWORDS

AGREE II, clinical practice guidelines, nutrition, preconception, methodological quality appraisal

1. Introduction

Maternal malnutrition is associated with irreversible negative health outcomes for the mother–child binomial in the medium and long term (1). Women's health and nutrition status before pregnancy is crucial in determining gestational weight gain, pregnancy health, and birth outcomes (2). Nevertheless, the preconception nutritional status has been overlooked despite its importance; poor+ nutrition in the preconception period is women's least studied stage of life (3).

Globally, more than one billion women experience at least one form of malnutrition. The prevalence of underweight in women of reproductive age in 2014 was 9.7%, and substantial burdens persist across Asia and Africa, reaching 24% in South Asia (4). In Southeast and South Asia, maternal short stature (< 150 cm) affects 40–70% of women. Latin America and the Caribbean, Pacific Islands, and the Middle East bear a significant burden of overweight and obesity, with even higher prevalence observed in regions like South Asia (5). In addition, one-third of women of reproductive age in lower-middle-income countries are anemic, and vitamin D deficiency is re-emerging as a significant global health issue (6, 7). Recent studies have linked the above-mentioned conditions with several clinical conditions in pregnancy (e.g., preeclampsia, gestational diabetes, higher incidence of cesarean section, preterm birth, etc.) (8).

Clinical practice guidelines (CPGs) provide recommendations that are designed to aid healthcare providers, physicians, and patients in making informed decisions regarding appropriate healthcare for specific clinical circumstances, such as the supplementation with folate, iron, and folic acid, and weight management of women with obesity in pregnancy (9); as well as recommendations for nutritional assessment, healthy diet, dietary modifications, nutritional supplementation, or any nutritional or lifestyle recommendations given in primary care and other health care areas. However, CPGs vary among countries or regions, and some of them do not meet the basic quality standards (10, 11). Furthermore, there is often a lack of regular updates to guidelines, which means that they may not always remain up-to-date and fail to incorporate the most current evidence (8).

The Appraisal of Guidelines for Research and Evaluation Instrument (AGREE II) was developed to address the issue of quality variability in CPGs. Its main objectives are to establish a framework for assessing guideline quality, offer a methodological approach for guideline development, and provide guidance on what information should be included and how it should be reported. The AGREE II instrument can be applied to any health or disease-related guidelines, including preconception, pregnancy, the postpartum period, and other stages of women's lives (12).

High-quality CPGs benefit the reduction of issues related to poor nutrition in the preconception period. This study aimed to identify the CPGs that include recommendations for preventing, diagnosing, and treating women's malnutrition and to evaluate the methodological quality of the included guidelines using the AGREE II instrument.

2. Materials and methods

2.1. Data sources and search strategy

We thoroughly assessed CPGs, including lifestyle and nutritional recommendations to prevent, diagnose and treat malnutrition in the preconception period. Our study incorporated CPGs, standard references, and position statements that provided recommendations on various aspects of nutritional assessment (including anthropometric measurements, biochemical data, clinical history, and lifestyle factors), healthy diet, dietary modifications, nutritional supplementation, and other nutritional or lifestyle recommendations.

The review process consisted of five stages. For our study, we utilized the framework initially proposed by Arksey and O'Malley (13), which was further refined by Levac et al. (14) and the Joanna Briggs Institute (15). We added one last step to assess the quality of the CPGs using the AGREE II instrument (12).

We performed two types of searches for our study. The first search involved a systematic search in a single bibliographic database [1] using the algorithm outlined in Table 1 and filters for guidelines and practice guidelines. The second search involved a manual search on guideline-related websites of national and international agencies and societies focused on child health and nutrition. We used key terms from the PubMed algorithm, individually and combined in English and Spanish, for this manual search.

2.2. Studies selection

2.2.1. Inclusion criteria

The included documents met the following eligibility criteria: (i) they were international and national CPGs, standard references, or position statements; (ii) they were written in English or Spanish; (iii) they were published between January 2008 and February 2021, considering the publication of The Lancet's Maternal and Child Undernutrition Series.

2.2.2. Exclusion criteria

The exclusion criteria encompassed opinions or editorials, articles published as communication tools, and clinical practice guidelines (CPGs) focused solely on lifestyle and nutrition recommendations

1 PubMed: https://ncbi.nlm.nih.gov/pubmed

TABLE 1 Search algorithm.

Algorithm	Limits
("preconception period" OR preconception) AND ("Preconception Care"[MeSH[†]] OR "Nutrition Assessment"[MeSH] OR "Nutrition Therapy"[MeSH] OR "prevention and control" [Subheading] OR "Health Promotion"[MeSH]) AND ("Malnutrition"[MeSH] OR "Body Weight"[MeSH] OR "Anemia"[MeSH] OR "Deficiency Diseases"[MeSH] OR "Nutrition Disorders"[MeSH] OR "Nutritional Physiological Phenomena"[MeSH])	Article Type (Guideline, Practice Guideline); Languages (English, Spanish); Publication date (From 2008/1/1 to 2021/2/1)

[†]MeSH, Medical subject headings.

TABLE 2 The Appraisal of Guidelines for Research and Evaluation Instrument II domains and content.

Domain	Content
1. Scope and purpose	Related to the overall aim of the guideline
2. Stakeholder involvement	Measures the extent to which the guideline was developed by the appropriate stakeholders
3. Rigour of development	Focuses on the methodology employed for evidence collection and synthesis the evidence
4. Clarity of presentation	Assesses the language, structure, and format of the guideline
5. Applicability	Examines the practical implications of implementing the guideline
6. Editorial independence	Evaluates if the formulation of the recommendations is unbiased by competing interests

Extracted from the AGREE II instrument (16).

related to a specific pathology or its associated complications. After importing the identified studies into Excel, any duplicate entries were removed.

2.3. Quality assessment

The evaluation process involved the participation of authors, including dietitians and physicians. Two of the authors (CMM, MAM) independently reviewed the titles and abstracts of each study to determine their eligibility for inclusion. In the event of disagreements, another author (SBM) evaluated the guideline to provide a final decision. We obtained full-text copies of the potentially eligible documents; one of them was independently assessed by two authors to determine if they met the inclusion criteria. In case of disagreements, a third author was assigned to determine the final inclusion of the study.

The AGREE II instrument assesses a CPG's development in terms of its quality, rigor, and transparency. It comprises six domains (Table 2) consisting of 23 key items in total. Each item within the instrument is assessed using a seven-point Likert rating scale, ranging from one (Strongly Disagree) to seven (Strongly Agree), as defined in the AGREE II User's Manual (10). The overall scores of each of the six domains were calculated by adding all their corresponding items and scaling the total as a proportion of the maximum possible score for that domain (max score = 100). An overall assessment score of > 70% indicated high quality in the guidelines (10). The quality of each CPGs was independently evaluated by two authors (SES, LTC, AT, FAA, MAM) using the online AGREE platform "My AGREE PLUS."

2.4. Data analysis

The means and median scores for each domain of the AGREE II instrument were computed to determine the most critical domains across the different guidelines. The overall quality of each guideline was assessed by applying a threshold of 70% for the final score of each domain. Data collection and extraction were performed using Microsoft Excel 2021, version 16.57. This study did not require ethical approval or consent.

3. Results

A summary of the results is shown in Figure 1, which was yielded by the keyword combinations with PubMed and other websites. We started the eligibility process after collecting all the results and omitting duplicated articles. The titles and abstracts from 30 guidelines were screened for inclusion, of which 20 guidelines were fully reviewed for quality assessment.

Of the 20 PCGs, six were related to prenatal care for pregnancy and six to weight control, overweight and obesity in women of reproductive age and during pregnancy, five of the guidelines were focused on supplementation of iron, folic acid, calcium or vitamin K, and the rest of the guidelines provided recommendations for healthy eating and lifestyle and for preconception management in women with diabetes.

Supplementary material 1 shows the general characteristics of the included guidelines, such as reference clinical guidelines, supporting organization, year, region, number of references and target audience. The main supporting organization is the World Health Organization (WHO) (17–21) NICE (22–24), the Royal College of Obstetricians and Gynecologists (25, 26) and other Societies, Colleges and Departments of Health.

Studies were published from 2009 to 2021. Of the 20 guidelines, six were internationally developed (17–21, 27), and the others were created in six different countries, including the United Kingdom (22–26), Canada (28–30), the United States of America (USA) (31, 32), Australia (33, 34), Latvia (35) and Poland (36) with one each.

The mean of references was 89.3 (Min:13 Max:239); however, three guides by NICE did not specify their references (22–24). The guidelines were designed for different target audiences, and the main ones were healthcare providers. Some guides directed their guidelines towards policymakers, expert advisers, government officials, scientists, the food industry and organizations of nutrition actions for public health.

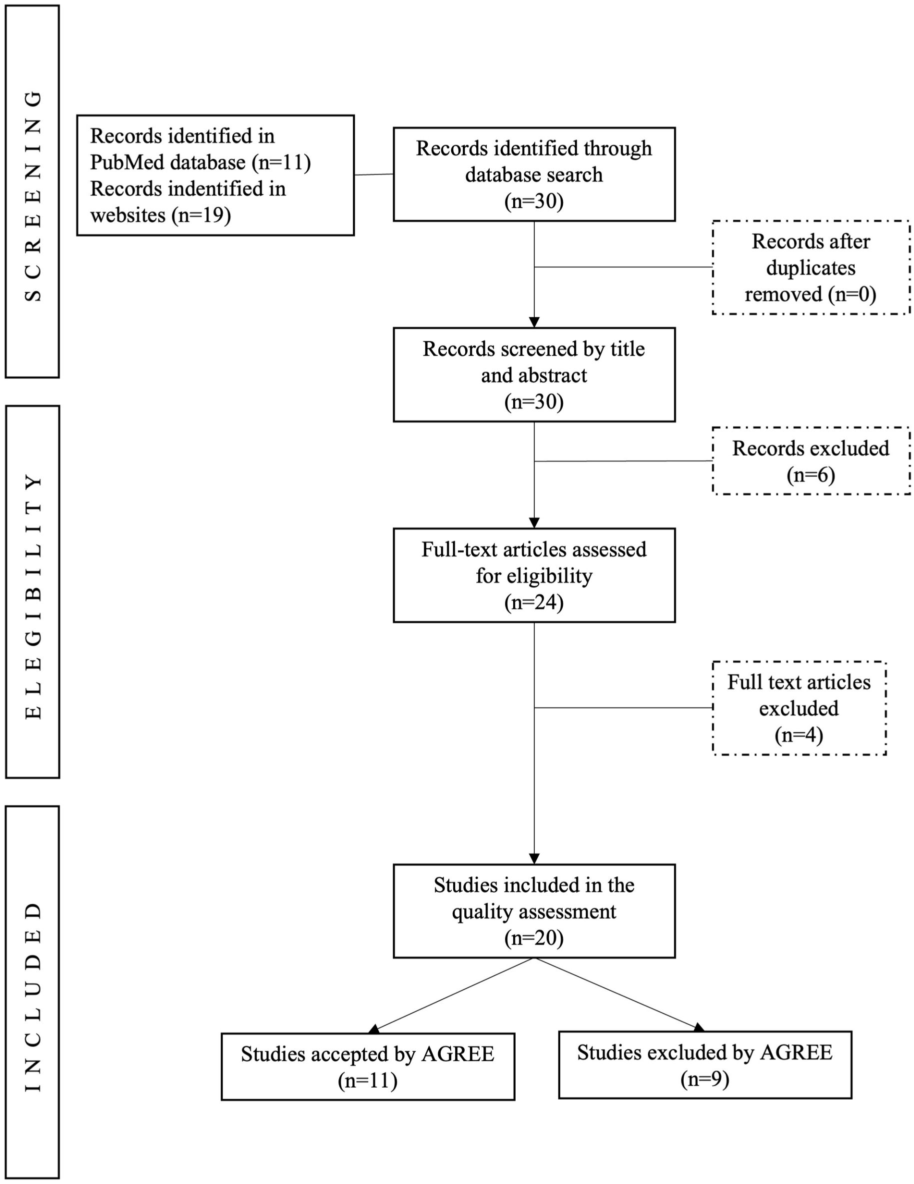

FIGURE 1
PRISMA flow diagram of literature sources and review process.

3.1. Quality of guidelines according to the AGREE II domains.

Table 3 presents the scores for each domain and the final quality evaluation of all CPGs. The overall quality assessment was 73% (range = 39–100), and the median was 83% (range = 17–100). 75% (n = 15) reached a high-quality classification. About the domains, three of them had a score of >70%. The domain with the highest score was "Clarity of presentation," with a mean of 88.5% (range = 50–100), and "Scope and purpose," with a mean of 87% (range = 39–100), while the lowest was "Applicability" with a mean of 69.9% (range = 4–100). High-quality guidelines had a higher evaluation in "Scope and Purpose" and "Clarity of Presentation" with a mean of 97.3% (range = 39–100) and 94.9% (range = 50–100), respectively; meanwhile, the domain with the lowest score was "Applicability" with a mean of 81.5% (range = 60–100). In the guidelines classified as low quality, the domain with the lowest score was "Applicability" with a mean of 35% (score = 4–100) and "Rigour of development" with 36.8% (score = 21–100).

Two clinical guidelines developed by NICE, "Antenatal care for uncomplicated pregnancies" in 2019 (22) and "Weight management before, during, and after pregnancy" in 2010 (24), had the highest score (more than 90% in all the evaluated domains); while the clinical guidelines by Bomba-Opoń D. et al. (36), the Royal Australian and New Zealand College of Obstetricians and Gynecologists (34), the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine (32), McAuliffe FM et al. (27) and Australian Government Department of Health (33) had an overall low quality with 39, 50, 56, 67 and 69%, respectively. Therefore, they are not recommended according to the AGREE II assessment tool. The average quality scores of each domain of the AGREE II instrument by all guidelines, high-quality guidelines, and low-quality guidelines are shown in Figure 2.

TABLE 3 Appraisal of Guidelines for Research and Evaluation (AGREE) II version result for clinical practice guidelines.

Clinical guideline	AGREE II domains (%)							
	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence	Overall assessment	Quality of guidelines
Antenatal care for uncomplicated pregnancies (22)	100	97	100	100	94	92	100	High quality
Canadian Adult Obesity Clinical Practice Guidelines: Weight Management Over the Reproductive Years for Adult Women Living with Obesity (30)	94	86	75	92	88	58	94	High quality
Care of Women with Obesity in Pregnancy: Green-top Guideline No. 72 (26)	86	58	97	97	65	96	86	High quality
Clinical Practice Guidelines: pregnancy care (33)	69	56	56	83	48	71	69	Low quality
Diabetes in pregnancy: management from preconception to the postnatal period (23)	100	100	84	100	98	92	100	High quality
Folate supplementation during the preconception period, pregnancy and puerperium. Polish Society of Gynecologists and Obstetricians Guidelines (36)	39	28	21	64	4	8	39	Low quality
Guideline No. 391-Pregnancy and Maternal Obesity Part 1: Pre-conception and Prenatal Care (29)	97	83	100	94	60	83	97	High quality
Guideline: intermittent iron and folic acid supplementation in menstruating women (17)	100	83	96	92	100	83	100	High quality
Guideline: optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects (18)	100	81	99	97	100	92	100	High quality
Guideline: sodium intake for adults and children (19)	100	83	98	100	88	100	100	High quality
Guideline: sugars intake for adults and children (19, 20)	100	83	98	100	100	100	100	High quality
Management of Women with Obesity in Pregnancy (25)	100	89	92	94	83	92	100	High quality
Obesity and reproduction (28)	94	56	75	83	40	50	94	High quality
Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding (31)	100	81	73	92	75	75	100	High quality
Pre-pregnancy counseling (34)	50	50	49	50	38	50	50	Low quality
Pre-pregnancy counseling (32)	56	53	34	86	52	100	56	Low quality
Prevention of noncommunicable diseases by interventions in the preconception period: A FIGO position paper for action by healthcare practitioners (27)	67	53	24	64	33	96	67	Low quality
Proper maternal nutrition during pregnancy planning and pregnancy: a healthy start in life (35)	89	81	63	83	63	96	89	High quality
Weight management before, during, and after pregnancy (24)	100	100	92	100	94	100	100	High quality
WHO recommendation on calcium supplementation before pregnancy for the prevention of pre-eclampsia and its complications (21)	100	83	96	100	75	100	100	High quality
Mean (range)	**87.0 (range 39 – 100%)**	**74.2 (range 28 – 100%)**	**76.1 (range 21– 100%)**	**88.5 (range 50 – 100%)**	**69.9 (range 4 – 100%)**	**81.7 (range 8 – 100%)**	**73.0 (range 17 – 100%)**	
Median (range)	**98.5 (range 39 – 100%)**	**82 (range 28 – 100%)**	**88 (range 21 – 100%)**	**93 (range 50 – 100%)**	**75 (range 4 – 100%)**	**92 (range 8 – 100%)**	**83 (range 17 – 100%)**	

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3.1.1. Scope and purpose domain

For the "Scope and Purpose" domain, 75% (n = 15) of the guidelines received a score > 80%. The lowest scores (below ≤ 50%) were achieved by "Folate supplementation during the preconception period, pregnancy and puerperium" (2017) (36) with 39%, "Pre-pregnancy counseling" by The Royal Australian and New Zealand College of Obstetricians and Gynecologists (2021) (34) and The American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine (2019) (32) with 50 and 56%, respectively.

3.1.2. Stakeholder involvement

Domain 2, the mean score was 74.2% (range = 28–100) and the median score of 82% (range = 28–100%). Of the guidelines, 10% (n = 12) had a maximum score of 100% in "Diabetes in pregnancy: management from preconception to the postnatal period" (2020) (23) and "Weight management before, during, and after pregnancy" (2010) (24). The "Folate supplementation during the preconception period, pregnancy and puerperium" (2017) (36) was the only guideline that scored below 50%.

3.1.3. Rigour of development

For the 20 sets of guidelines, the mean AGREE II score for the domain "Rigour and development" was 76.1% (range = 21–100). The highest score for this domain was observed in two CPGs (10%): "Antenatal care for uncomplicated pregnancies" (22) and "Guideline No. 391-Pregnancy and Maternal Obesity Part 1: Pre-conception and Prenatal Care" (29), both in 2019. Of the guidelines, 70% received a score higher than 70, and 15% (n = 3) scored below 50% (27, 32, 34). "Prevention of noncommunicable diseases by interventions in the preconception period: A FIGO position paper for action by healthcare practitioners" (2020) (27) had the lowest score in this domain.

3.1.4. Clarity of presentation

Compared with the others, this domain obtained the highest score with a mean of 88.5% (range = 50–99) and median score of 93% (range = 50–100). The scores established for this domain were high for all the guidelines; 85% (n = 17) of them scored > 70%.

3.1.5. Applicability

This domain obtained the lowest score with a mean of 69.9% (range = 4–100%) and a median score of 75% (range = 4–100). Half of the guidelines (50%) analyzed received a score > 70%. The nine reached an evaluation > 70% and "Obesity and Reproduction" (2018) (28), "Pre-pregnancy counseling" (2019) (34), "Prevention of noncommunicable diseases by interventions in the preconception period: A FIGO position paper for action by healthcare practitioners" (2020) (27) and "Folate supplementation during the preconception period, pregnancy and puerperium. Polish Society of Gynecologists and Obstetricians Guidelines" (2017) (36) had a score lower score with 40, 38, 33, 4%, respectively.

3.1.6. Editorial independence

On the "Editorial independence" domain, the guidelines obtained a mean AGREE II score of 81.7% (range = 8–100). Fourteen (70%) received a score higher than 80%. Bomba-Opoń D et al. (36) 's guideline was the only one that scored equal to 8%.

4. Discussion

Most of the CPGs we found included recommendations for managing obesity and the prescription of supplements. Nevertheless, few guidelines have been developed to make recommendations about iron and folic acid supplementation, even though anemia is one of the

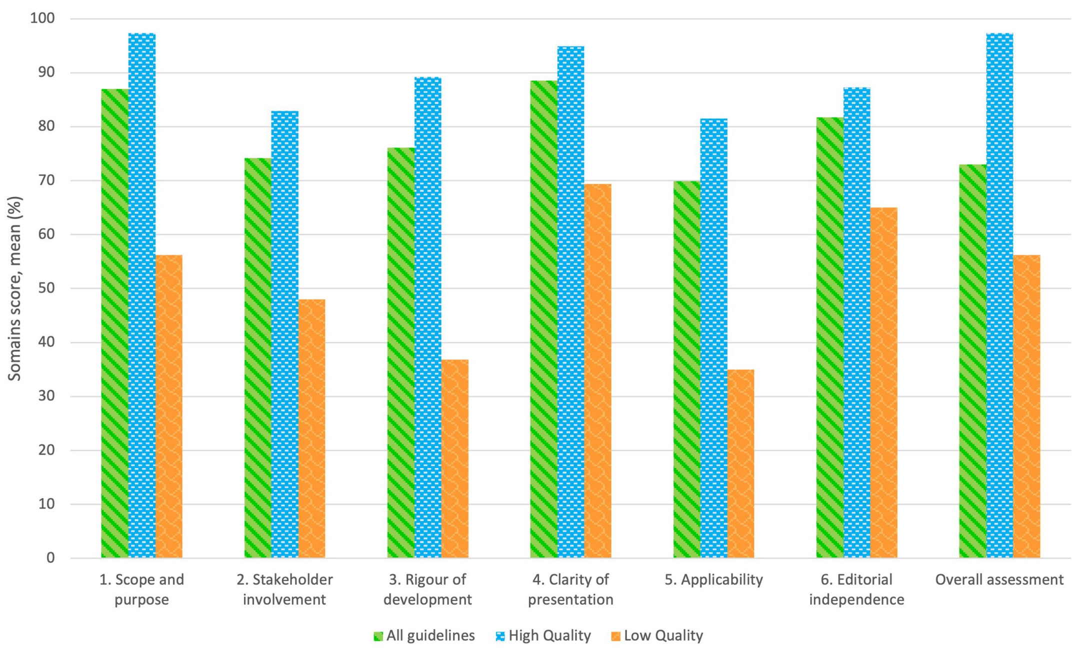

FIGURE 2
Average quality score by each domain of AGREE II for all included guidelines.

most common forms of malnutrition in this group of women (6, 7). In addition, elaborated guides for optimizing weight were not identified despite the important role that nutritional status during preconception plays in determining health outcomes in pregnant women (2).

Our main findings revealed that only 55% of the CPGs were evaluated as high quality, while the domain scores were between high- and low-quality CPGs. High-quality CPGs had a higher evaluation in the classifications of "Scope and Purpose" (median = 98.5%, range = 39–100) and "Clarity of Presentation" (median = 93%, range = 50–100). Low-quality CPGs had a higher score in the classification of "Clarity of presentation" (median = 93%, range 50–100) and "Editorial Independence" (median = 92%, range 8–100). In the guidelines classified as high quality and low quality, the domain with the lowest score was "Applicability," with a median of 48% (range = 60–100) and 75% (score = 4–100%), respectively. Our results agree with other quality assessments of CPGs using the AGREE II instrument (37).

According to the AGREE II instrument, several quality domains need to be improved and prioritized; in this context, domains 5 and 2, which are "Applicability" and "Stakeholder involvement," obtained the lowest mean (69.9 and 74.2%, respectively) in most of the guidelines. The "Applicability" domain has been reported to be related to implementing the guidelines by health professionals in daily clinical practice (12). This situation may be a key to understanding the gap between knowledge and implementation of CPGs, in addition to the potential implications on the clinical practice and the nutritional status of women. In our context, it is necessary the development of robust, comprehensive, and high-quality guidelines for a healthy lifestyle in the preconception period (38).

This study has different limitations. First, our systemic search was exclusively conducted in one database (PubMed) which may have limited the search for developing countries. Secondly, the search was restricted to CPGs published in Spanish or English. It is important to acknowledge certain limitations when interpreting these results because the geographical generalizability may be limited considering the under-representation from low and middle-income regions such as Asia, Africa, Latin America and Caribe.

Only a few methodologies have been designed to assess the quality of CPGs. AGREE II provides elements that allow for developing and implementing initiatives to improve healthcare quality. We recommend this instrument that guideline developers, clinicians, researchers, and policymakers consider and utilize the AGREE II tool, as it is a comprehensive and user-friendly instrument that can be adapted to specific populations, injuries, or diseases (39).

There is a gap in the evidence of the different forms of malnutrition in the preconception period, and sometimes, the guidelines have yet to be adapted to new contexts, like the pandemic caused by Coronavirus SARS-CoV-2 in 2020 (8). To our knowledge, this is the first study that evaluates the quality of CPGs for the preconception period and the importance of including different health professionals, such as dietitians, related to the preconception in this evaluation process.

5. Conclusion

AGREE II tool provides a framework to develop guidelines and an instrument to review their quality. Further assessment is needed to improve the quality guidelines, which is an opportunity to strengthen them, especially in the domains where the scores were the lowest. We recommend using the AGREE II instrument by all health professionals since it can be applied easily and in detail. This instrument also allows an analytical evaluation before implementing the given guidelines, which would support the making of decisions around the health system of a country or region. We need increased rigor in formulating guidelines to prevent, diagnose and treat malnutrition in all its forms during preconception, a critical period of life.

Data availability statement

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

Author contributions

SB-M, MA-M, NS, and CM-M conceptualized the study. NS, SB-M, MA-M, and IO-G conducted the methodology. SH-C, AT-D, and IO-G conducted the formal analysis. CM-M, NS, LT-C, FA-A, SE, KM-S, LI-G, and CM-A appraisers with experience in quality assessment of guidelines, scored each guideline using the AGREE II instrument. MA-M, NS, and SB-M conducted data curation. SB-M, MA-M, IO-G, and EH-L wrote the first draft on the manuscript. SB-M, MA-M, NS, IO-G, EH-L, and SH-C critically revised the manuscript. MA-M, SB-M, NS, IO-G, and SH-C supervised the project. MA-M and IO-G administered the project. MA-M funding acquisition. All authors have read 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1122289/full#supplementary-material

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Impact of integrated preventive and curative health package on nutritional status of children under 2 years of age in the health area of Tama, Tahoua region (Niger)

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Background: Niger, relevant in light of current political coup, is one of the countries with the worst human development indicators, characterized by high fertility rates and extremely high infant mortality rates. Food insecurity in the region is alarming, leading to high malnutrition rates in children. This study aimed to evaluate an integral preventive-curative health program targeting children aged under 2 years in the health area of Tama, district of Bouza, Tahoua.

Methodology: Anthropometric follow-up data of 6,962 children aged under 2 years were included in this study. These children received complete vaccination and malaria chemoprevention, and those older than 6 months received nutritional supplementation with a small quantity of lipid-based nutrient supplements. Fundamental growth indicators (height-for-age, weight-for-height, weight-for-age, and middle-upper arm circumference) and the Composite Index of Anthropometric Failure were calculated at the beginning and end of the program (mean time spent in the program: 14.5 ± 6.6 months) The evolution of these indicators was compared with those of a sample from a vertical vaccination program conducted in the neighboring region of Madarounfa on similar dates.

Results: The proportion of children without anthropometric failure decreased from 59.5 to 40.2% ($p < 0.001$), with the categories that included stunting increasing the most. When analyzing the anthropometric indicators according to the months of compliance with the program, there was a slight improvement in the indicators of acute malnutrition, whereas those of chronic malnutrition worsened significantly. However, when compared with the Madarounfa sample, the children in the present study registered a significantly lower worsening in all three indicators: height-age (–0.46 vs. -2.44; $p < 0.001$), weight-height (+0.31 vs. -0.55; $p < 0.001$) and weight-age (–0.03 vs. -1.63; $p < 0.001$) difference.

Conclusion: The comprehensive preventive-curative health program slightly slows the worsening of cumulative malnutrition in the early years of life in complex contexts, such as southern Niger.

KEYWORDS

growth, anthropometric failure, wasting, stunting, small quantity lipid-based nutrient supplement

1. Introduction

The Republic of Niger is a continental country in West Africa, with three northern quarters in the Sahara and Sahel. Desert conditions in this significant part of the territory limit the development of subsistence agriculture. Rainfall varies from region to region; however, in general, rainy periods are short and unpredictable, alternating with periods of drought. These circumstances mean that the population is permanently food insecure. Between 1996 and 2019, Niger was ranked last on the Human Development Index as the poorest country in the world. In 2021 the Human Development Index was 0.400, surpassing only Chad and the Central African Republic (1).

In the same year, the synthetic fertility index (average number of children per woman) was 6.2, and the birth rate was 45.6 births per 1,000 inhabitants. Although the mortality rate was also high (14.83‰), the country has experienced a significant demographic increase, doubling its population between 2000 (10.1 million inhabitants) and 2020 (21.4 million) (2). The life expectancy was 62.4 years, almost half its inhabitants (48.5%) were aged under 14 years, and only 16.4% lived in urban areas (3, 4).

The food security situation in Niger is alarming and mainly affects the infant population, contributing to a high rate of under-five child mortality, with 115.2 deaths per 1,000 live births (5). Exclusive breastfeeding up to 6 months reaches only 23% of children, only 6% of children between 6 and 23 months have a minimum acceptable diet, and anemia is estimated to affect 73% of children under 5 years (6). Moreover, the Nutritional and Mortality Survey published by the National Institute of Statistics and elaborated according to the Standardized Monitoring and Assessment of Relief and Transitions (SMART) methodology in 2021 (7) reported prevalence rates of 12.7, 2.7, and 43.5% for global, severe acute, and chronic malnutrition, respectively. This last figure is higher than the average for the African region (30.7%) and is categorized at an emergency level, according to the criteria of the World Health Organization (WHO) (8). For this reason, the fight against malnutrition has been a priority for several years for the Nigerian government, which has been implementing a National Nutrition Security Policy for almost a decade (7).

Doctors Without Borders (Médecins Sans Frontières, MSF) have been working in Niger permanently since 2001 and have strengthened their presence there since 2005. In response to all sorts of medical challenges, particularly measles or meningitis epidemics, during a vaccination campaign in 2001, there was a high prevalence of acute malnutrition in the Maradi region, and consequently, nutritional projects were initiated to address this problem (9, 10). In addition to expanding its capacity, it sought the intervention of other Non-Governmental Organizations, and other MSF sections came in to cover other regions of the country. Furthermore, when MSF began intervening in the Tahoua region, Community Management of Acute Malnutrition (CMAM) programs using ready-to-use therapeutic foods were established.

Approximately 60,000 severely malnourished children in Niger were treated by MSF in that year (10). As a result, MSF has shifted its understanding of the malnutrition problem, realizing that a sole focus on treatment was unsuitable. Therefore, an integrated preventive and curative healthcare package, known as the PPCSI (an acronym for "Paquet préventif et curative de soins intégrés" in French), was developed with the primary aim of decreasing mortality in children aged under 5 years in a way that, if proven effective, could be replicated in more areas of the country. This package is intended to prevent and treat malnutrition, malaria, and other common diseases. Additionally, it ensures and supports vaccination and breastfeeding (11).

Stunting is a height-for-age (HAZ) score below −2 z-score from the median of the WHO growth standard (12). A longitudinal growth retardation occurs in response to cumulative nutritional deficits. This anthropometric failure reached an all-time high in Niger in 2018 (47.8%), with Tahoua being the most affected region (42.9%). Being underweight is a determinant predictor of stunting, as highlighted in different populations in Asia and sub-Saharan Africa (13–15). Moreover, insufficient micronutrients, especially zinc, iron, calcium, and vitamin A, significantly affect longitudinal growth, which is deficient after weaning in environments of low dietary diversity, such as Niger (16, 17). Unlike acute malnutrition, which can be reversed quickly by nutritional, medical, and psycho-stimulation treatments, a meta-analysis by Goudet et al. (18) reported that nutritional interventions alone did not reduce growth retardation treating chronic malnutrition that requires a multisectoral approach over a relatively long period.

Furthermore, some studies have shown modest improvements in stunting following a lipid-enriched or flour-enriched therapeutic feed (18, 19). This effect is more positive when supplementation is accompanied by vaccination and nutritional education for mothers or caregivers (20). The present study aimed to analyze the effect of a PPCSI, which included a small quantity of lipid-based nutrient supplement (SQ-LNS) as a food complement, on the nutritional status of children aged between 6 and 24 months in Tahoua, Niger.

2. Materials and methods

2.1. Study design

The PPCSI was conceived as an operational research project with a prospective cohort methodology implemented by MSF in the Tama health area, located in the Bouza health district of the Tahoua region (Figure 1), where MSF conducted a humanitarian assistance project in agreement with the Ministry of Health of Niger. The study was also approved by the National Ethics Committee in Niger (Comité Consultatif National d'Ethique, reference 013/2014/CCNE, 2014) and the MSF Ethics Review Board (ID 1535, 2015), and compliance with the country's current health legislation was ensured.

The intervention targeted all children under 24 months of age and residing in the Tama health area during the 3 years and 9 months of the PPSCI (March 2015–December 2018), and during that time, 8,116 children aged between 0 and 23 months were admitted. This sample was recruited through all health posts located in Tama with the help of community health workers. All children under 2 years of age were invited to participate, and the exclusion criterion was that they presented acute malnutrition at the beginning since they were referred to another specific treatment program. Written informed consent of

Abbreviations: MSF, Médecins Sans Frontières; CMAM, Community Management of Acute Malnutrition; PPCSI, Paquet préventif et curatif de soins intégrés; HAZ, height-for-age; WHZ, weight/height; WAZ, weight/age; WHO, World Health Organization; SQ-LNS, lipid-based nutrient supplement; UNICEF, United Nations International Children's Emergency Fund; MUAC, middle-upper arm circumference; CIAF, Composite Index of Anthropometric Failure; SAM, severe acute malnutrition.

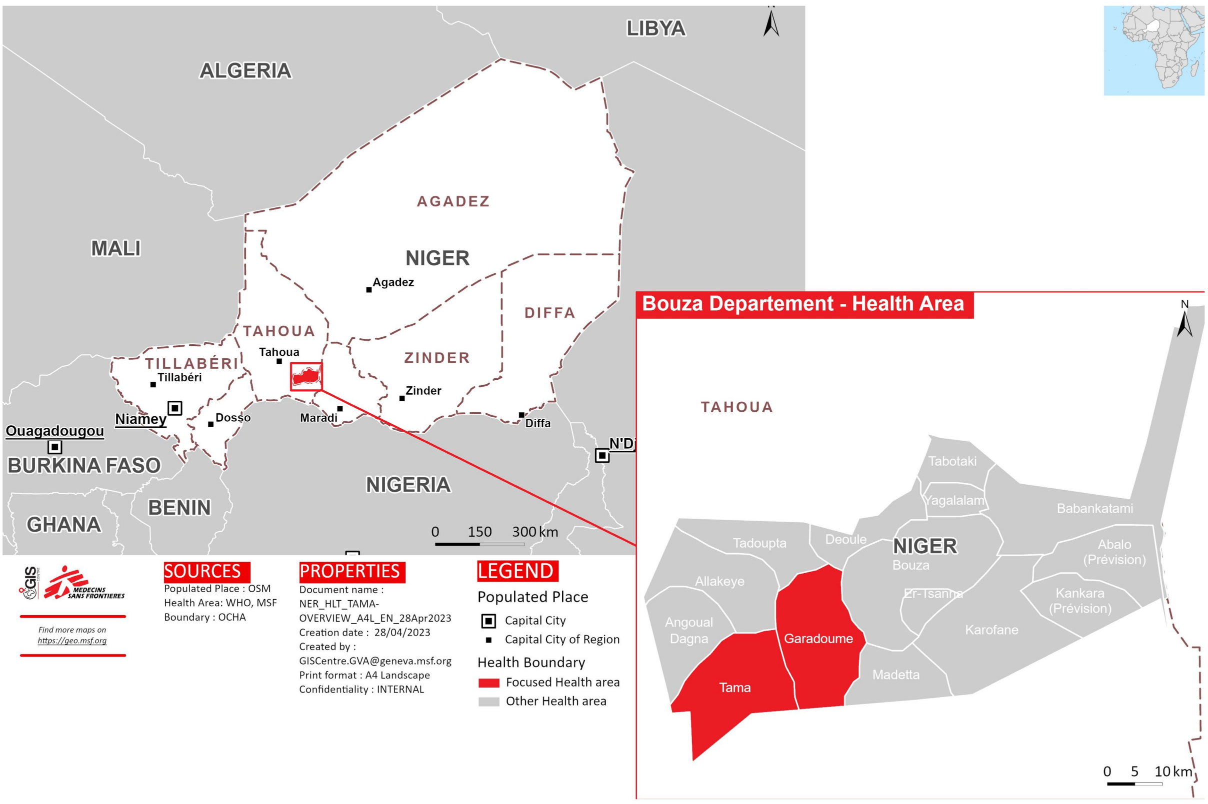

FIGURE 1
Geographic location of the health areas involved in the study (own source).

parents or guardians was obtained after explanations in the local language, guaranteeing that refusal to participate would not affect access to free care in MSF-supported facilities. On admission, the children received seasonal malaria chemoprevention and complete vaccination (polio, tuberculosis, pentavalent rotavirus, pneumonia, yellow fever, and measles). Additionally, for those aged over 6 months, deworming treatment every 6 months and supplementary feeding with one Nutributter© sachet daily (20 g, 108 kcal) were provided. This daily ration contained 2.6 g of protein and 7 g of fat (essential fatty acids) as well as vitamins A (0.4 mg), B1 (0.3 mg), B2 (0.4 μg), B3 (1.8 mg), B6 (0.3 mg) B12 (0.5 mg) C (30 mg) and folic acid (80 μg). Moreover, it incorporated minerals such as calcium (100 mg), potassium (152 mg), zinc (4 mg), iron (9 mg), selenium (10 mg), phosphorus (82 mg), magnesium (16 mg), copper (0.2 mg), iodine (90 mg) and manganese (0.08 mg) (21). At the same time, the mothers received education on breastfeeding and infant nutrition. The conveyed message was mainly about basic hygiene and the importance of breastfeeding. Giving babies under 6 months only breast milk, without other liquids such as water or tea, was recommended, a common habit in the country's cultural practices. This program has been previously described in detail (11). It should be noted that the investigators have no record of whether the sachets with the food supplement were ingested in their entirety by the child. This is an important aspect that, unfortunately, could not be controlled.

Monthly medical follow-ups (visits) were established. to check the children's health and growth; measure weight, length, or height; and middle-upper arm circumference (MUAC) to make an anthropometric diagnosis of their nutritional condition. Anthropometric measurements were performed by MSF-trained health personnel using salter-type scales (100 g accuracy), baby/infant length/height wooden measuring boards, and standard MUAC tapes. However, inter- and intra-observer controls were not performed to ensure an acceptable technical measurement error. This circumstance may perhaps explain the number of implausible observations that had to be eliminated from the database.

2.2. Data processing

Figure 2 shows the workflow used to clean the database. Firstly, data of all participants whose sex or age was not recorded were discarded, as these were considered critical variables in the analysis to establish nutritional status. Secondly, we eliminated participants who made fewer than three visits, which is the minimum time estimated to be able to appreciate the changes associated with the intervention. Finally, participants diagnosed with severe acute malnutrition (SAM) at their first visit were excluded because they were referred to CMAM treatment programs. Data from 14.4% of the initially registered participants (N = 8,116) were discarded, and the final database included 6,962 children under 24 months who attended a health post in the Tama health area.

Table 1 summarizes the results of the second data-cleaning process. In this case, the exclusion criterion does not correspond to the eliminated individuals but to anomalous data, that is, values

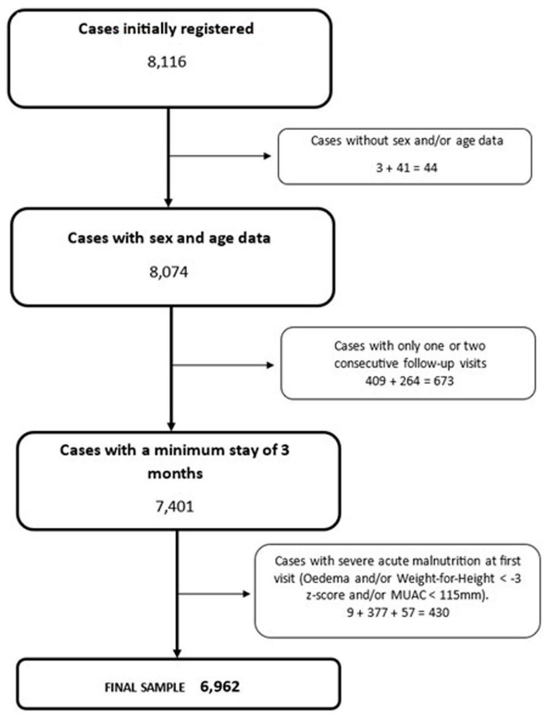

FIGURE 2
A flowchart depicting the database cleaning process.

incompatible with life according to WHO fixed exclusion criteria (22). WHO Antro software (23) was used to estimate the z-scores for the HAZ, weight-for-height (WHZ), and weight-for-age (WAZ) indicators that evaluate chronic, acute, and global malnutrition, respectively. Thus, data with HAZ values below −6 z-score or above +6 z-score, WHZ values below −6 z-score or above +5 z-score, and WAZ values below −5 z-score or above +5 z-score were eliminated. As can be seen from the amount of data eliminated, the error rate was higher in measuring body length indicators compared to body weight.

The final sample consisted of 6,962 children (3,559 boys and 3,403 girls) aged between 0 and 23 months. The mean age of entry into the nutritional program was 2.8 (inter-quartile range 1.2–9.0) months. Of the children, 65.1% started the program before 6 months of age, 17.4% between 6 and 11 months of age, 11.8% between 12 and 17 months of age, and 5.7% between 18 and 24 months of age. The mean time in the program was 14.5 ± 6.6 months. Notably, 15.2% of the children did not continue the program until a period of 6 months and 36.0% exceeded 18 months in the program.

2.3. Statistical analysis

To contrast the possible effect of the length of stay in the program, quartiles were established for this variable, and the Wilcoxon test was applied to compare the averages corresponding to the z-scores of the different anthropometric indicators (HAZ, WHZ, and WAZ) and MUAC. In contrast, the Composite Index of Anthropometric Failure (CIAF) (24) was estimated and compared for each category and the average z-scores of the different anthropometric indicators at the beginning and end of the program.

TABLE 1 Anthropometric records eliminated by indicator and follow-up visits.

	Height-for-age	Weight-for-height	Weight-for-age	Total by visit
Initial data	89,335	89,397	91,891	27,0623
Visit 1	295	481	75	851
Visit 2	316	397	40	753
Visit 3	358	479	42	879
Visit 4	35	466	42	543
Visit 5	335	372	25	732
Visit 6	270	256	30	556
Visit 7	231	153	30	414
Visit 8	194	117	22	333
Visit 9	161	82	18	261
Visit 10	118	53	17	188
Visit 11	92	34	20	146
Visit 12	60	22	18	100
Visit 13	41	16	11	68
Visit 14	29	8	10	47
Visit 15	11	6	8	25
Visit 16	11	4	3	18
Visit 17	8	4	6	18
Visit 18	10	5	6	21
Visit 19	5	3	4	12
Visit 20	0	1	1	2
Visit 21	1	1	1	3
Visit 22	0	0	0	0
Visit 23	0	0	0	0
Visit 24	1	1	0	2
Total data eliminated	2.89% (2,582)	3.31% (2,961)	0.47% (429)	2.21% (5,972)

Stunting, wasting, and underweight reflect distinct biological processes, but the same subject may exhibit more than one of these characteristics simultaneously. At the population level, CIAF is a measure that provides a single, aggregated figure for the number of children affected. This index identifies six groups in which category A encompasses children without anthropometric failure. The other five are B: wasting only; C: wasting and underweight; D: wasting, stunting, and underweight; E: stunting and underweight; F: stunting only; and Y: underweight only. The CIAF is calculated by subtracting those in group A from the total number of children in the sample.

As a comparison or proxy control group, we used the database compiled by the MSF in the work of Kohlmann et al. (25) to explore the association between chronic and acute malnutrition and its ontogenetic evolution in children under 2 years. This database grouped all individuals analyzed in a previous case–control study (26) to test the effectiveness of an oral vaccine against rotavirus, which causes gastroenteritis. That study was conducted in the health district of Madarounfa in the Maradi region (bordering the region of the present study) on nearby dates (August 2014 to December 2019). Additionally, the sample size (N = 6,567), age range (between 6 weeks and 24 months), and periodicity of visits for monitoring growth (every 4 weeks; 139,529 visits in total) were similar to those of the present study. Therefore, the Madarounfa database was considered adequate as a control series, as the children did not receive any nutritional supplementation.

Violin plots were used to establish the contrast in the progression of nutritional status over time, showing the differences in the HAZ, WHZ, and WAZ z-scores between the first and last visits and comparing the results obtained in the present study with those achieved in the Madarounfa region. All the statistical analyzes were performed using R software (v.4.3.1).

3. Results

Table 2 shows the anthropometric indicators at the beginning and end of the program for all children who completed a minimum of three visits. The z-scores for the HAZ, WHZ, and WAZ moved away from the reference toward malnutrition values at the end of the intervention. In contrast, the MUAC increased by an average of 0.5 cm. When the CIAF was analyzed, the anthropometric failure increased by approximately 20%. This increase in malnutrition was best observed in the nutritional categories that included stunting.

Table 3 shows the anthropometric results at the beginning and end of the follow-up period, separating children who complied with the complete program from those who did not. Those who had not completed the program for 24 months were children who were not enrolled at birth and, therefore, entered the program at an older age, SAM cases referred for CMAM treatment programs, and dropouts before 24 months. Table 4 shows the anthropometric changes according to the length of stay in the program. The acute malnutrition indicator improved significantly, whereas the growth retardation and underweight indicators worsened.

Finally, we compared the z-scores according to the anthropometric failure category at the beginning of the program (Table 5). About the HAZ, children who were exclusively classified as chronically undernourished achieved a slight improvement in their z-scores. In the case of the WAZ, improvement was found in children with more than one type of malnutrition (C, D and E ICAF categories).

The contrast between the present Tahoua sample and the Madarounfa series is shown in Figure 3. As can be seen from the differences in z-scores between the first and last visits, in both series, there is a nutritional deterioration of a greater depth in the case of the HAZ. However, for all indicators considered (HAZ, WHZ, and WAZ), the difference between the first and last visits was significantly smaller in the present study compared to that from Madarounfa ($p < 0.001$).

TABLE 2 Anthropometric indicators at the beginning and end of the follow-up for the whole sample*.

Indicator	*N*	Time point	Median [IQR]	Value of *p*
Height-for-age (z-score)	8,040	START	−1.30 [−2.40, −0.25]	<0.001
		END	−2.01 [−2.94, −1.11]	
Weight-for-height (z-score)	7,672	START	−0.28 [−1.12, 0.89]	<0.001
		END	−0.40 [−1.21, 0.42]	
Weight-for-age (z-score)	7,630	START	−0.92 [−1.79, −0.12]	<0.001
		END	−1.36 [−2.1, −0.65]	
MUAC (mm)	7,153	START	135 [130, 140]	<0.001
		END	140 [135, 148]	

CIAF category	Time point	% (*N*)	Value of *p*
Without anthropometric failure	START	86.2% (5,606)	<0.001
	END	28.9% (1,877)	
Wasting only	START	4.3% (277)	
	END	0.3% (21)	
Wasting + Underweight	START	1.8% (118)	
	END	2.6% (170)	
Stunting + wasting + underweight	START	0.6% (37)	
	END	9.3% (605)	
Stunting + underweight	START	2.6% (170)	
	END	27.7% (1,801)	
Stunting only	START	3.3% (215)	
	END	29.8% (1,937)	
Underweight only	START	1.2% (77)	
	END	1.4% (89)	

CIAF, Composite Index of Anthropometric Failure; IQR, interquartile range; MUAC, middle-upper arm circumference; * Includes girls and boys who entered the program at different ages. Mean time spent in the program: 14.5 ± 6.6 months.

TABLE 3 Anthropometric indicators at the beginning and end of the follow-up according to compliance with the whole program.

Children who completed the whole program (from 0 to 24 months)				
Indicator	*N*	Time point	Median [IQR]	Value of *p*
Height-for-age (z-score)	1,566	START	−1.20 [−2.30, −0.15]	<0.001
		END	−1.93 [−2.86, −1.00]	
Weight-for-height (z-score)	1,542	START	−0.22 [−1.22, 0.98]	0.068[NS]
		END	−0.41 [−1.24, 0.44]	
Weight-for-age (z-score)	1,542	START	−0.85 [−1.72, −0.07]	<0.001
		END	−1.32 [−2.10, −0.58]	

Children who did not complete the whole program				
Indicator	*N*	Time point	Median [IQR]	Value of *p*
Height-for-age (z-score)	6,474	START	−1.69 [−2.72, −0.68]	<0.001
		END	−2.40 [−3.16, −1.53]	
Weight-for-height (z-score)	6,130	START	−0.51 [−1.23, −0.61]	<0.001
		END	−0.35 [−1.10, 0.34]	
Weight-for-age (z-score)	6,088	START	−1.17 [−2.03, −0.36]	<0.001
		END	−1.49 [−2.16, −0.89]	

IQR, interquartile range; NS, not significant.

TABLE 4 Anthropometric indicators at the beginning and end of the follow-up according to the months of participation in the program.

Children with length of stay within the first quartile (< 9 months)				
Indicator	*N*	Time point	Median [IQR]	Value of *p*
Height-for-age (z-score)	1,058	START	−1.91 [−2.92, −0.94]	<0.001
		END	−2.31 [−3.18, −1.36]	
Weight-for-height (z-score)	1,066	START	−0.77 [−1.37, −0.05]	<0.001
		END	−0.50 [−1.29, 0.24]	
Weight-for-age (z-score)	1,070	START	−1.53 [−2.24, −0.66]	<0.001
		END	−1.58 [−2.41, −0.80]	
Children with length of stay within the second quartile (9–16 months)				
Indicator	*N*	Time point	Median [IQR]	Value of *p*
Height-for-age (z-score)	1,067	START	−1.62 [−2.42, −0.74]	<0.001
		END	−2.31 [−3.03, −1.39]	
Weight-for-height (z-score)	1,073	START	−0.67 [−1.29, 0.03]	<0.001
		END	−0.26 [−1.05, 0.58]	
Weight-for-age (z-score)	1,070	START	−1.34 [−2.02, −0.61]	<0.001
		END	−1.42 [−2.14, −0.73]	
Children with length of stay within the third quartile (16–21 months)				
Indicator	*N*	Time point	Median [IQR]	Value of *p*
Height-for-age (z-score)	1,054	START	−1.33 [−2.36, −0.27]	<0.001
		END	−2.29 [−3.08, −1.47]	
Weight-for-height (z-score)	1,056	START	0.50 [−0.86, 1.16]	<0.001
		END	−0.41 [−1.20, 0.33]	
Weight-for-age (z-score)	1,054	START	−0.85 [−1.72, −0.70]	<0.001
		END	−1.45 [−2.10, −0.85]	
Children with length of stay within the fourth quartile (>21 months)				
Indicator	*N*	Time point	Median [IQR]	Value of *p*
Height-for-age (z-score)	970	START	−1.01 [−2.18, 0.11]	<0.001
		END	−2.23 [−2.97, −1.48]	
Weight-for-height (z-score)	970	START	0.41 [−0.99, 1.61]	<0.001
		END	−0.59 [−1.30, 0.25]	
Weight-for-age (z-score)	970	START	−0.43 [−1.25, 0.32]	<0.001
		END	−1.53 [−2.22, −0.91]	

IQR, interquartile range.

4. Discussion

The CIAF increased by almost 20% over the 3 years of PPCSI in Tahoua. However, this does not invalidate its success, given that the program seems to reduce the potentially expected malnutrition burden compared with other preventive interventions in the Madarounfa border region on similar dates (25). Considering that children diagnosed with SAM at the first visit were referred for specific treatment, it can be affirmed that the PPCSI succeeded in reducing mild or moderate acute malnutrition. This occurred even among the children who only completed part of the program. Additionally, children diagnosed with stunting only showed significantly improved HAZ. Children with more than one type of malnutrition at enrollment also showed improved nutritional status, with their WHZ and WAZ approaching the median of the WHO reference (12).

During the development of PPCSI, the CIAF increased at the expense of categories that included stunting. This result was not surprising because longitudinal growth retardation accumulates with age in this context. This situation has been explained in detail by Victora et al. (27), who analyzed a large sample of studies in 54 countries worldwide. In this work, it was observed that, in the series of 30 countries in sub-Saharan Africa, the HAZ declined sharply up to 2 years of age (−0.10 z-score/month) and then increased slightly (0.005 z-score/month) up to 5 years of age.

This model was also described by Bhutta et al. (28), who reported that longitudinal growth retardation increases rapidly between 3 and 24 months of age, continues to increase more slowly until 36 months, and usually remains stable until 5 years of age. A meta-analysis by the authors above (28) analyzed the effects of more than 100 nutritional interventions conducted in 36 countries. Depending on the type of intervention (promotion of breastfeeding, supplementation with micronutrients, accompanied or not accompanied by community nutritional education, etc.), stunting was reduced by 10 to 33% at

TABLE 5 Anthropometric indicators at the beginning and end of the follow-up according to the initial anthropometric failure status.

Height-for-age Z-score			
CIAF category at inclusion	Time point	Median [IQR]	Value of p
Without anthropometric failure	START	−0.48 [−1.31, 0.08]	<0.001
	END	−1.57 [−2.40, −0.78]	
Wasting only	START	1.47 [0.52, 2.20]	<0.001
	END	−1.51 [−2.51, −0.60]	
Wasting + underweight	START	−0.79 [−1.49, −0.28]	<0.001
	END	−2.20 [−3.09, −1.40]	
Stunting + wasting + underweight	START	−3.13 [−3.71, −2.39]	0.584[NS]
	END	−3.27 [−4.01, −2.50]	
Stunting + underweight	START	−3.33 [−3.84, −2.67]	<0.001
	END	−3.17 [−3.81, −2.45]	
Stunting only	START	−2.76 [−3.05, −2.25]	<0.001
	END	−2.48 [−3.17, −1.80]	
Underweight only	START	−1.64 [−3.05, −1.84]	<0.001
	END	−2.35 [−1.69, −1.48]	

Weight-for-height Z-score			
CIAF category at inclusion	Time point	Median [IQR]	Value of p
Without anthropometric failure	START	0.02 [−0.89, 0.78]	<0.001
	END	−0.22 [−1.04, 0.55]	
Wasting only	START	−3.04 [−3.54, −2.30]	<0.001
	END	−0.41 [−1.37, 0.35]	
Wasting + underweight	START	−3.39 [−4.06, −2.54]	<0.001
	END	−0.76 [−1.65, 0.13]	
Stunting + wasting + underweight	START	−2.74 [−3.04, −2.21]	<0.001
	END	−1.12 [−1.93, −0.22]	
Stunting + underweight	START	−0.58 [−1.34, −0.10]	0.475[NS]
	END	−0.66 [−1.46, 0.12]	
Stunting only	START	1.31 [0.07, 2.42]	<0.001
	END	−0.25 [−1.13, 0.52]	
Underweight only	START	−1.54 [−1.84, −1.32]	<0.001
	END	−0.87 [−1.55, −0.23]	

Weight-for-age Z-score			
CIAF category at inclusion	Time point	Median [IQR]	Value of p
Without anthropometric failure	START	−0.31 [−1.02, 0.26]	<0.001
	END	−1.06 [−1.71, −0.39]	
Wasting only	START	−0.77 [−1.44, −0.23]	<0.001
	END	−1.18 [−1.82, −0.57]	
Wasting + underweight	START	−2.73 [−3.10, −2.30]	<0.001
	END	−1.79 [−2.54, −1.06]	
Stunting + wasting + underweight	START	−3.67 [−4.19, −3.10]	<0.001
	END	−2.58 [−3.25, −1.97]	
Stunting + underweight	START	−2.68 [−3.00, −2.24]	<0.001
	END	−2.22 [−2.86, −1.63]	
Stunting only	START	−1.07 [−1.64, −0.67]	<0.001
	END	−1.54 [−2.16, −0.97]	
Underweight only	START	−2.21 [−2.29, −2.06]	<0.010
	END	−1.91 [−2.43, −1.15]	

CIAF, Composite Index of Anthropometric Failure; IQR, interquartile range; NS, not significant.

24 months. However, the pattern (a faster increase up to 24 months and a slower increase up to 36 months) was maintained.

Food supplements are essential to nutritional recovery, and micronutrients are particularly effective in improving children's health, survival, growth, and functional as highlighted by a review study (29). However, a more recent meta-analysis (18) provides no evidence that complementary interventions increase HAZ in poor urban settings in countries such as Bangladesh, India or Peru. As the authors rightly state, this is a wake-up call on the need to change the structural factors (social, political) that limit the effectiveness of interventions focused on the nutritional improvement of children.

In the PPCSI developed by MSF in the Tahoua region, an SQ-LNS was provided to all children aged 6 to 24 months. This home fortification adds fatty acids and energy to micronutrient and macronutrient supplementation in an easy-to-implement and acceptable manner. The daily ration provides slightly more than one-tenth of the necessary energy and practically covers the daily requirements of micronutrients in children under 2 years (30). Additionally, the product is well accepted by children and causes little digestive discomfort compared with other supplements with similar characteristics (31, 32).

Several studies have reported the benefits of supplementation with SQ-LNS in reducing anemia and improving motor development in children. However, evidence of the effect on height growth is weak. A supplementary feeding program implemented in refugee camps in Djibouti and Kenya between 2008 and 2011 with the same SQ-LNS found that among children under 5 years, anemia decreased by between 9.3 and 29.33% (depending on the age group). In contrast, the prevalence of stunting remained similar (33). Similarly, another study of 750 children aged between 6 and 12 months in the Matlosana municipality (Northwest South Africa) showed that supplementation with SQ-LNS products improved hemoglobin and iron concentrations. These supplements reduced iron-deficiency anemia but showed only a transitory effect on longitudinal growth and failed to reduce chronic malnutrition (34).

In contrast, a study conducted in Ghana on children aged 6 to 12 months, comparing groups of children receiving three nutritional products (crushable flavored multiple-micronutrient tablets, micronutrient powders, and SQ-LNS), showed that all three groups had decreased anemia and improved motor development. However, only the children supplemented with SQ-LNS had accelerated linear growth, achieving HAZ averages closer to the median of the WHO standard (HAZ = −0.20 ± 0.54) compared with those supplemented with tablets (HAZ = − 0.39 ± 0.54) or with the tablets plus micronutrient powder combination (HAZ = −0.38 ± 0.54) (35). Similarly, the results of a trial conducted on a sample of Haitian children (n = 589; 6–11 months) recruited from the urban slum of Haitian Cap (36) are worth mentioning. In this trial, those supplemented with the same SQ-LNS for 3 or 6 months showed more accelerated growth in height than those that did not receive supplementation. Moreover, the differences with the control group were maintained for up to 6 months after the end of the intervention. Other studies have shown additional benefits of such interventions, especially in preventing wasting (37) and reducing mortality (38). Very few studies have had such an integral approach, and none involving the SQ-LNS has been implemented in Niger, which is of high public health relevance.

The World Food Program and United Nations Children's Fund (UNICEF) recommend distributing lipid-based supplements, such as those used in the present study, and others, such as fortified blended foods, to prevent acute malnutrition and stunting in situations of food vulnerability (39, 40). Beyond the nutritional value of a particular product, scientific evidence highlights that success in reducing anthropometric failure is more likely when multisectoral interventions are implemented, combining specific nutrition-sensitive methods and programs. Agricultural improvements, female empowerment, vaccination, parasite control, and other sanitation and hygiene measures maximize the impact of complementary or therapeutic foods (39, 40). Further research is needed to identify the most cost-effective interventions to ensure sustainability in complex contexts, such as southern Niger.

A comparison of the children analyzed in the present study with the Madarounfa series (25) highlighted the possible beneficial effect of SQ-LNS supplementation in the context of PPCSI on the anthropometric condition of the children. Both studies were carried out in Niger by the MSF on similar dates, with similar sample sizes and approaches to growth monitoring (present study: N = 6,962 children; visits = 92,517; Madarounfa: N = 6,567 children; 139,529 visits). The Madarounfa study used prospective data from a double-masked placebo-controlled trial to evaluate the efficacy and safety of a multivalent vaccine against bovine rotavirus and severe rotavirus gastroenteritis. It should be noted that some mothers received different types of prenatal supplements: lipid-based supplements, multiple micronutrient supplements, or iron-folic acid (41, 42). As shown in the results, the z-scores between the first and last visits indicated a deterioration in growth in anthropometric indicators that combine weight, height, and age. However, this impairment was more pronounced in the Madarounfa series, especially in the HAZ and WAZ.

The present results show that integral interventions, such as PPCSI, can positively impact complex contexts, contributing to increased vaccination rates, expanding seasonal malaria chemoprevention activities, screening and treating children with malnutrition and several diseases, and training and involving the community as a pillar of the intervention. The duration and integral approach of the program in complex settings with high levels of all forms of undernutrition need to catch up in its attempt to improve this situation. Nonetheless, all the efforts in this direction are relevant.

At this point, the authors believe it is essential to reflect on the scope of the interventions that specific organizations such as MSF carry out in contexts of humanitarian crisis and severe food insecurity. These interventions are based on improving the most vulnerable groups' nutrition and primary sanitary and hygienic conditions. As has been shown in this paper and others cited, the impact of these actions partly slows down the deterioration of nutritional status, slowing down the worsening of stunting.

However, the success of these programs is strongly limited by the fact that child growth is a process that is part of a holistic Social-Economic-Political-Emotional (SEPE) process. This concept focuses on the interaction between the biology of development and the quality of material and societal conditions (43, 44).

This means that nutritional status does not depend solely on diet and controlling infections and parasitosis. All the SEPE factors, not strictly nutritional, significantly influence human growth. In the

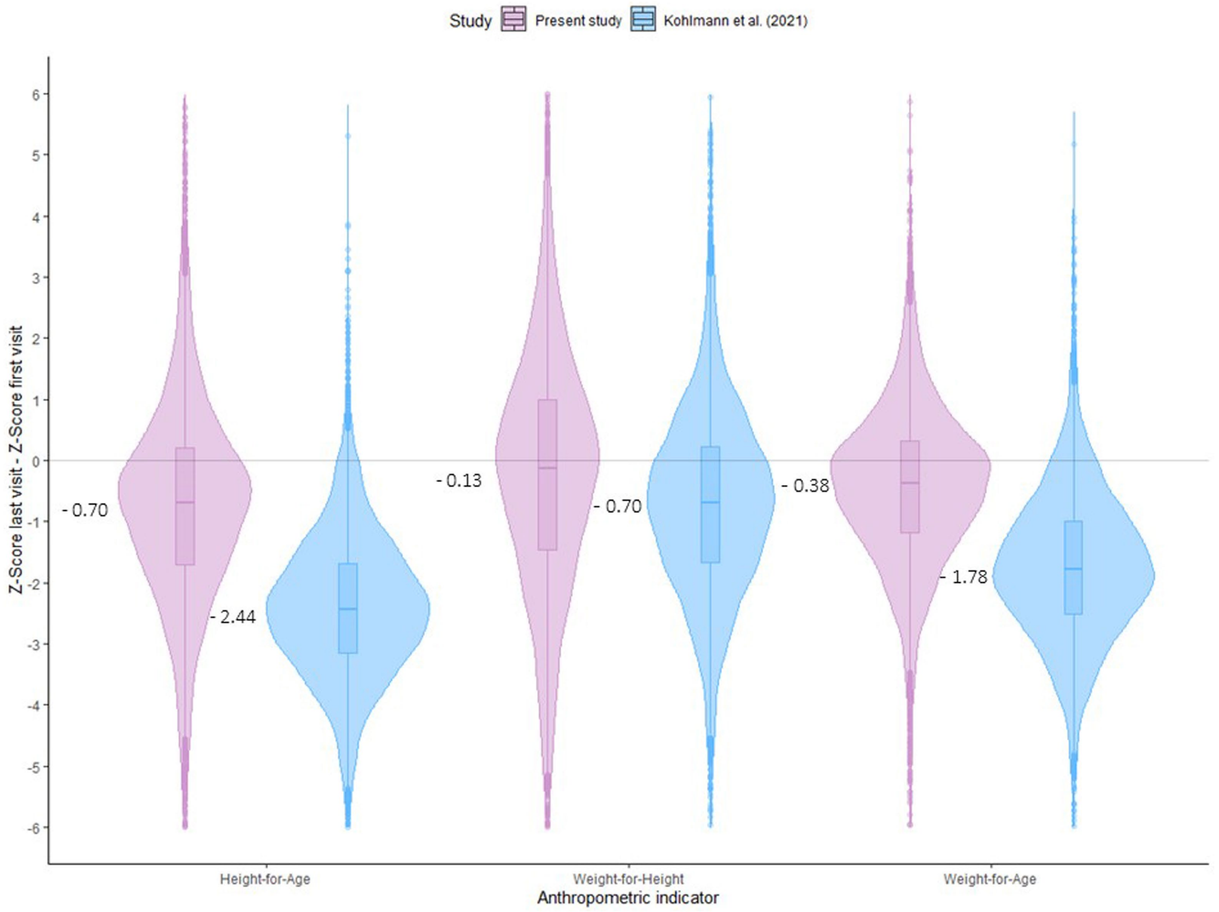

FIGURE 3
Difference between anthropometric indicators at the beginning and end of the program in two south Niger cohorts.

environments where humanitarian actions are implemented, conditions of inequity, low educational levels, insecurity, or violence are common, translating into chronic stress. All this affects children emotionally, undermining the production of hormones such as oxytocin and osteocalcin, which are involved in skeletal development and regulate height expression. In this regard, some authors (45, 46) discuss extensively how stress, education, socioeconomic, political, and emotional conditions are responsible for stunting.

We must remember that intake and disease are the immediate causes of malnutrition. However, the underlying and fundamental causes, such as the economic, political, and ideological structure of countries, primarily generate the damage. It is very complex to promote changes at this level. However, we must be aware that the programs promoted by NGOs can only succeed in addressing the problem from an ecological and global perspective. In order to have an average growth, children need proper nutrition and protection against violence, abuse, neglect, environmental threats, including air pollution, and prolonged exposure to other adversities that arise in countries in crisis or conflict situations (47). To achieve effectiveness, there is a need to strengthen the role of preventing malnutrition and other diseases, focusing on the whole context of the social determinants of health (48).

The main strengths of the present study are that it was conducted at the community level, with a large number of Community Health Workers performing home visits, recruiting children, and following up on them, thereby enhancing adherence to the program. However, this study had some limitations. This operational study was based on the anthropometric follow-up of a cohort of children participating in a new integrated healthcare program. Therefore, the main limitation of this study was the need for a formal control group (children from a neighboring health area where the program had not been implemented). To assess the program's impact, data collected in another MSF operational study in a border region with similar socio-environmental conditions were used; however, this could not be objectively assessed. Consequently, the program's impact results should be interpreted with caution.

Additionally, anthropometric follow-up was performed by the health staff of the health centers after receiving training for this purpose; however, their lack of experience may have caused measurement errors. This has resulted in eliminating several anthropometric indicators owing to their implausibility. Typing or missing information could not be prevented, and rounding up height measurements was common. Additionally, relevant information on the roles and activities of Community Health Workers was unavailable. It is still being determined whether they supervised the acceptability and consumption of SQ-LNS (except for the collection of empty supplement sachets at every visit). Furthermore, intake of other local foods was not assessed.

During data cleaning, several children who presented with SAM on admission were excluded from the analysis. However, when they returned to PPCSI after recovery from the CMAM programs, this circumstance was not recorded and could result in differential growth. A better method to follow up with children back and forth between both programs would have provided a more precise overview of the program, and an analysis of the interference between stunting and acute malnutrition could have been executed.

In conclusion, the PPCSI program, which integrates vaccination, malaria chemoprevention, identification and treatment of malnutrition and other diseases, and supplementation with SQ-LNS for all children aged under 2 years, is slightly effective in curbing the accumulated burden of malnutrition in the early years of life in complex contexts, such as that in southern Niger.

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 humans were approved by National Ethics Committee in Niger (Comité Consultatif National d'Ethique, reference 013/2014/CCNE, 2014) and the MSF Ethics Review Board (ID 1535, 2015). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RP-T: Formal analysis, Writing – original draft, Writing – review & editing. MM: Formal analysis, Writing – original draft, Writing – review & editing. NL-E: Writing – original draft, Writing – review & editing. ME: Writing – original draft, Writing – review & editing. MR: Conceptualization, Methodology, Writing – review & editing. AV: Conceptualization, Methodology, Writing – review & editing. CC: Conceptualization, Methodology, Writing – review & editing. RG: Conceptualization, Methodology, Writing – review & editing. CL: Conceptualization, Methodology, Writing – review & editing.

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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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Impact of a simplified treatment protocol for moderate acute malnutrition with a decentralized treatment approach in emergency settings of Niger

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Introduction: Of the 45.4 million children under five affected by acute malnutrition in the world, the majority (31.8 million) are affected by moderate acute malnutrition (MAM). Its treatment is particularly complex in emergency settings such as the Diffa region in Niger. This study aims to evaluate the effectiveness and coverage of a simplified treatment protocol with Community Health Workers (CHWs) as treatment providers.

Methods: This study is a non-randomized controlled trial. The control group ($n = 181$) received the standard protocol currently used in country, delivered by nursing staff only in health centres and health posts, while the intervention group ($n = 483$) received the simplified protocol which included nursing at health centres and CHWs at health post as treatment providers.

Results: The recovery rate was higher in the simplified protocol group (99.6% vs. 79.56%, $p < 0.001$) recording lower time to recover and higher anthropometric gain. Treatment coverage in the intervention group increased from 28.8% to 84.9% and reduced in the control group (25.3% to 13.6%). No differences were found in the recovery rate of children treated by CHWs and nursing staff.

Conclusion: The outcomes using the simplified protocol exceeded humanitarian requirements and demonstrated improvements compared to the standard protocol showing that the simplified protocol could be safely provided by CHWs in an emergency context. Further research in other contexts is needed to scale up this intervention.

KEYWORDS

wasting, simplified approaches, community health workers (CHWs), mid-upper arm circumference (MUAC), ready-to-use therapeutic food (RUTF), moderate wasting

1 Introduction

Globally, it is estimated that acute malnutrition currently affects 45.4 million children under the age of five. The West African region has one of the highest prevalence of global acute malnutrition (GAM) 6.9% [95% CI: (5.9%)–(8.1%)] on the African continent (1). Niger has one of the highest national rates of GAM in the region reaching 12.5% [95% CI: (11.1%)–(13.9%)] (2), which is above the 10% emergency threshold set by WHO / UNICEF indicating a high prevalence (3). The Diffa region, located in the southeast of the country, is particularly affected by the presence of chronic armed conflicts which negatively impacted food security, and has resulted in thousands of displaced people in the region who require humanitarian assistance (4).

National-level reports identify factors such as increased infant morbidity and mortality and its economic burden linked to medical treatments and loss of productivity as directly related to acute malnutrition prevalence in Niger (5). The term acute malnutrition refers to two well-known forms: severe acute malnutrition (SAM), the most extreme form which requires urgent treatment (6) due to the 9 times higher risk of death (7), and moderate acute malnutrition (MAM), precursor of SAM, with a 3 times higher risk of death compared to a well-nourished child (8), an increased risk of infectious diseases due to the deterioration of the immune system (7) but also longer term effects that affect the physical growth, cognitive development and future work capacity of the child (9). Recurrence of the condition is also a very important factor to consider as it has been shown that children who recover from MAM have high relapse rates in the year after their nutritional recovery (10).

The WHO officially recommends SAM and MAM to be treated independently following different protocols (11, 12), however there is a growing consensus that acute malnutrition should be considered as a continuous spectrum disorder, and not as two independent states (13). SAM is treated with ready-to-use therapeutic food (RUTF) in UNICEF-supplied outpatient therapeutic programmes (OTPs). Whereas MAM treatment programmes use supplementary foods, usually supported by the World Food Programme (WFP). Considerable discrepancies exist between the treatment protocols in different countries (14–18). MAM protocols may implement ready-to-use supplementary food (RUSF), fortified flours, nutrition education or counselling to improve child's nutritional status (19, 20). Differences also exist in the cut-off points of the anthropometric indicators mid-upper arm circumference (MUAC) and/or weight-for-height Z-score (WHZ) that determine admission and cure. In some countries, guidelines for the treatment of MAM are absent (13).

Despite the implementation of Community-Based Management of Acute Malnutrition (CMAM) programming which allows children affected by severe or moderate acute malnutrition to be treated in outpatient settings, treatment coverage remains very low. In a review of 34 Supplementary Feeding Programmes, coverage was found to range from (10%) to 70% in rural settings, with a mean coverage of just 34.6%, and between 20% to 70% in urban settings with a mean coverage of 40.9% (21). Furthermore, in emergency situations, funding for SAM treatment programmes is commonly prioritised, leaving MAM children untreated (22).

In recent years, several simplified approaches have been developed to make treatment of acute malnutrition more accessible. Some of the main adaptations include using (i) Family MUAC for detection of cases, (ii) involving Community Health Workers (CHWs) as treatment providers, (iii) combined protocol (MUAC as the sole criterion for admission and recovery and using RUTF to treat both SAM and MAM cases), or (iv) reduced frequency of follow-up in specific contexts. These simplifications aim to identify cases earlier, increase coverage, facilitate their management, and reduce costs for governments (23). Several research studies have demonstrated the effectiveness of the two first approaches, mainly with SAM children (24–29). More evidence is needed related to the combined protocol and the potential impact of using different simplifications in the same context (30–34).

The aim of this study is to evaluate the effectiveness and coverage of MAM treatment in emergency settings in Niger using MUAC as the only criterion for admission and discharge, RUTF as nutritional product, delivered in both at health facilities and health post level.

2 Materials and methods

2.1 Treatment design and assessment

The study consisted of a non-randomized controlled trial conducted in nine communes in the Diffa region of Niger, between December 2020 and April 2021. The total sample of the study was 664 MAM children aged 6 to 59 months, who attended treatment centres spontaneously, or were recruited through active screening in the communities.

The experimental design comprised two groups receiving decentralized treatment in health posts but differing in terms of treatment provider and treatment protocol. The control group ($n = 181$), located in the catchment area of Kablewa, included its health centre and two health posts located in Kawa and Oudi Peulh villages. Children were treated following the standard CMAM protocol used in country with nursing staff as the only health care providers. The admission criteria of the control group consisted of WHZ < -2 and > -3 (35) and/or a MUAC<125 and > 115 mm and treatment was provided as a fixed dose of RUSF of 1 sachet/day (537 kcal/day, 12.1 g of protein, 35 g of lipids and 0 g of carbohydrates) (36). Discharge criteria were both WHZ > -2 and MUAC >125 mm during two consecutive visits.

The intervention group ($n = 483$) was located in N'Guigmi health area and comprised of its health centre and three health posts located in Birzoweya, Bonégrale and N'Gagala villages. Children were treated under a simplified protocol using a different nutritional product with both nurses and CHWs as treatment providers. In this group, the only admission criterion was MUAC <125 and > 115 mm, and treatment was provided with a fixed dose of RUTF of 1 sachet/day (500 kcal/day, 12.8 g of protein, 30.3 g of lipids and 45 g of carbohydrates) (36). The discharge criterion was MUAC >125 mm only, during two consecutive visits.

During admission the presence of comorbidities and type of admission (new, relapse, transfer…) were also recorded. The main variable considered in the study was treatment outcome which included: recovery (according to the anthropometric criteria outlined by each protocol), defaulting (children not showing up for the follow-up visit for two consecutive weeks), non-response (children that lost weight or with a stagnant weight gain for two consecutive visits) or discharge errors (children who appeared as cured on the records, but their anthropometric measures did not meet the criteria established by the protocol). Other outcome variables recorded included time to recovery, number of sachets used, and weight and MUAC gain.

2.2 Socio-economic assessment

To evaluate the possible socio-economic differences and their influence on treatment outcomes between the two groups, a socio-economic survey was carried out with a subsample of participants from each treatment arm ($n = 107$ treated with standard protocol and $n = 296$ treated with the simplified protocol). The survey was administered to the caregivers at the treatment sites and consisted of four groups of questions examining the dimensions of living conditions, namely demographics, livelihoods, food security and diversity assessed through the Food Consumption Score (37) and health care access.

2.3 Treatment coverage assessment

In addition to the main study, two coverage assessments were conducted, one prior to study enrolment in November 2020 and one at the end of the study in April 2021. Both assessments used the standardized methodology Simplified Lot Quality Assurance Sampling Evaluation of Access and Coverage (SLEAC) (38) in the same communes of the study and MAM cases were defined based on the anthropometric criteria described in the standard national CMAM protocol. In the first phase of this methodology a spatial sampling method was used to select the villages according to the distribution of the health centres. A survey was then conducted to find the number of current MAM cases registered in the programme (covered cases), the number of current MAM cases not registered in the programme (uncovered cases) and the number of recovering MAM children in the programme (did not have MAM at the time of the survey but had not yet been discharged as recovered).

2.4 Statistical analysis

Statistical analyses were performed using the R software (39). To assess the post-hoc statistical power, the sample size was calculated using the Fisher's exact test for comparing two binomial proportions in two independent groups, under a 5% α error probability and a two-tail hypothesis of inequality (H_0: $p_1 = p_2$ vs. H_1: $p_1 \neq p_2$) (40):

$$n = \left[\sqrt{\overline{p}\overline{q}\left(1+\frac{1}{k}\right)}\, z_{1-\alpha/2} + \sqrt{p_1 q_1 + \frac{p_2 q_2}{k}}\, z_{1-\beta}\right]^2 / \Delta^2$$

where p_1, p_2 = projected true probabilities in the two groups. Estimated from previous studies (85% recovery for control group and 95% recovery for simplified group) (30, 41).

$$Q_1, q_2 = 1 - p_1, 1 - p_2$$

$$\Delta = | p_2 - p_1 |$$

$$\overline{p} = \frac{p_1 + k p_2}{1 + k}$$

$$\overline{q} = 1 - \overline{p}$$

$$n = \left[1.96 \cdot \sqrt{0.9 \cdot 0.1 \cdot \left(1 + \frac{1}{1}\right)} + 0.84 \cdot \sqrt{0.85 \cdot 0.15 + \left(\frac{0.95 \cdot 0.05}{1}\right)}\right]^2 / 0.1^2 = 140$$

During data cleaning negative numbers or values greater than 4 standard deviations were considered as transcription errors resulting in 12 atypical values in the time to recovery and number of consumed sachets being eliminated. Normality of the quantitative variables was assessed through the Shapiro–Wilk test.

Univariate statistical comparisons between the two protocols were conducted using Pearson's chi-square with the Yates continuity correction for the qualitative variables. Depending on the Normality of the distribution, Student's t-test or Mann–Whitney test were used for the quantitative variables. For the coverage analysis, Mantel–Haenszel chi-square test ($p < 0.05$) was used to compare the final coverage of the treatment adjusted for the initial coverage in each of the study areas.

In the multivariate analyses the principal component analysis was applied to visualize the interdependence between the variables. The two-dimensional representation of treated children, using components 1 and 2, allowed the inclusion of the protocol variable in the graph that showed if there was a pattern related to the outcomes by using colours. Building on the dependency analysis results, different multiple linear regression models were conducted for each outcome to understand the effect of the included explanatory variables upon admission on treatment and their significance. To model the probability of cure over time, a multivariate Cox regression model was used to understand the associated Hazard Ratio (HR) of the explanatory variables included and adjusted for the impact of the others. Follow-up time, used in the analysis, was calculated from enrolment date to date of recovery. A Cox model describes the relation between the event incidence, as expressed by the hazard function and a set of covariates considering censored data (in our case the event is the recovery of treatment and the covariates considered in the model were: Protocol, sex, age, MUAC, comorbidities at admission and treatment provider). Mathematically, the Cox model is written as:

$$h(t) = h_0(t) \times \exp\left\{b_1 x_1 + b_2 x_2 + \cdots + b_p x_p\right\}.$$

where the hazard function h(t) is dependent on a set of p covariates (x_1, x_2, …, x_p), whose impact is measured by the size of the respective coefficients (b_1, b_2, …, b_p) (42). A forest plot was also used for the graphic representation of the results.

2.5 Ethical considerations

The study was approved by the National Health Research Ethics Committee of Niger, reference number 013/2020/CNERS. All parents or caretakers of the children included in the study signed informed consent prior participation in the study.

3 Results

The socioeconomic characteristics of the two study groups are presented in Table 1. No significant differences were found in relevant variables in terms of demographics, food security, or access to health. However, in the intervention group a lower proportion of participants was less than 30 min away from the health centre (36.0% vs. 51.4%, $p = 0.008$). The study groups presented more differences in terms of livelihoods, with the intervention group showing a higher proportion of families not owning a household nor arable land but, instead, a higher proportion of households with access to safe water, safe sanitation and electricity compared to the control group.

The treatment coverage estimates recorded at the beginning and end of the intervention are presented in Figure 1. During the study period, the intervention group registered an increase of 56% in treatment coverage while the control group recorded a 12% decrease. After adjusting for initial coverage, there was a significant difference in the final coverage between the intervention group (84.9%) and the control group (13.6%).

Table 2 summarizes the characteristics of children treated for malnutrition at the time of admission. In both groups the majority of cases were new admissions, however, children in the intervention group had significantly more cases of diarrhea, cough, fever, and pale conjunctiva than the control group. Significant differences were found for WAZ and MUAC between the groups, although the average difference was too small to be of clinical relevance, especially in the case of MUAC.

Table 3 shows the results for anthropometric severity at admission by protocol group and treatment provider. Significant differences were found between treatment providers in simplified protocol in terms of median values of HAZ and WAZ but not for MUAC or WHZ, which are the outcome indicators with clinical relevance for acute malnutrition.

The treatment outcomes of the groups are presented in Table 4. The proportion of children cured was 20% higher in the simplified protocol group with a post-hoc calculated power of 1.000 and an alpha error of 0.010. The same group presented fewer cases of defaulting, non-response, and discharge errors compared to the standard CMAM protocol. No deaths were recorded in any of the groups. The average time to recovery was two weeks shorter for children treated with the simplified protocol, registering a higher daily gain in both weight and MUAC, compared to the standard protocol despite using stricter discharge criteria.

A comparison of outcomes between service providers was made within the intervention group (Table 5). Children treated by CHWs recovered on average 7 days earlier, consumed less therapeutic food, had higher daily weight gain which was almost double compared to children treated by health staff.

Table 6 shows the variables that influence outcome indicators and the treatment protocol of children that achieved recovery. After adjusting for explanatory variables, it was found that treatment protocol, significantly affects treatment outcomes by reducing the consumption of food product and time of recovery while increasing the daily gain of MUAC and weight. Sex did not appear to have an influence on the outcome variables and age showed an association only with daily weight gain, which was lower the older was the child. Daily weight gain was significantly influenced by all explanatory variables except sex, while the daily MUAC gain was associated only to the initial MUAC value, the treatment protocol and its provider. The study also showed a significant association between lower MUAC values at admission and increased consumption of food products, and longer time to recovery. However, no significant association was found with WHZ, HAZ or WAZ at admission.

The results of the Cox regression analysis are presented in a Forest plot in Figure 2. A hazard ratio (HR) value of 1 indicates that the variable in question does not have an impact on the probability of recovery over time and, are not significant for recovery. The factor with the greatest significance was the treatment protocol, with the simplified protocol increasing the probability of child's recovery by more than three times compared to the standard CMAM protocol. Being treated by a CHW compared to a health staff increased the probability of recovery by 77%. Lastly, every additional millimeter of MUAC presented at admission, increased the probability of recovery by 10%.

Figure 3 presents the principal component analysis (PCA) of the treatment outcomes in relation to the cured children in each study group and the treatment provider. Each child is represented by a sphere and its location within the quadrants depends on the combined effect of all the treatment variables included. Each independent variable is represented by an arrow showing the effect on the outcome, hence, the greater the influence, the more pronounced the displacement of a case will be in that direction. As expected, time to recovery and the total consumption of food product had a similar effect and were more influential for those cases treated with the standard CMAM protocol (in red). The anthropometric gain outcomes were instead associated with the cases treated with the simplified protocol (in green). Moreover, cases treated by CHWs (in dark green) were located more to the left, showing a stronger association with weight gain than MUAC gain, due to their diagonal dispersion.

4 Discussion

The present study showed that, in the emergency context of the Diffa region in Niger, the simplified protocol was able to cure more children, in less time, with greater anthropometric gain and less ready-to-use nutritional product use than the standard CMAM protocol.

The two study groups had similar socioeconomic characteristics, but differed in certain aspects, some having a positive effect on the intervention group and others on the control group, although neither group had a clear baseline disadvantage that could considerably influence treatment outcomes. No significant differences were found in anthropometric measurements; however, the simplified protocol group presented a greater number of cases with diarrhea, cough, fever, and pale conjunctiva, which could complicate recovery (43). Despite of this, the intervention group recorded better treatment outcomes with higher recovery rate and lower proportion of non-response.

After adjusting for baseline treatment coverage, the study showed a significant increase in coverage in the intervention group (+56.1%), and a decrease in the control group (−11.7%) demonstrating the influence of programme adaptations. While the simplified protocol group exceeded the 50% Sphere coverage standard for rural areas (44), the CMAM protocol group reached half of that target. As far as we know, this is the first study in west Africa to evaluate coverage of MAM treatment, if we decentralize

TABLE 1 Socioeconomic characteristics comparison between community management of acute malnutrition (CMAM) protocol group and the simplified protocol group.

Class	Indicator	Control CMAM protocol (*n* = 107)		Intervention simplified protocol (*n* = 296)		
		N° responses	Results	N° responses	Results	*p*-value
Demographics	Number of cohabiting people, mean (sd)	107	5.57 (2.59)	296	5.48 (2.24)	0.740
	Number of children under 5 years of age living with the treated child, mean (sd)	101	1.87 (1.95)	284	1.68 (1.75)	0.375
	Years of education of mother or primary caregiver, mean (sd)	69	0.77 (2.55)	173	0.60 (4.00)	0.748
Livelihoods	Type of housing	107		285		
	In propiety, % (*n*)		91.60 (98)		74.03 (211)	<0.001
	For rent, % (*n*)		0.00 (0)		7.02 (20)	0.011
	On loan, % (*n*)		8.40 (9)		18.95 (54)	0.017
	Households with access to safe water, % (*n*)	107	51.40 (55)	296	64.86 (192)	0.019
	Households with access to safe sanitation, % (*n*)	107	0.00 (0)	296	7.43 (22)	0.008
	Households with electricity, % (*n*)	107	4.67 (5)	296	13.51 (40)	0.021
	Households with arable land, % (*n*)	107	28.97 (31)	292	3.42 (10)	<0.001
	Households with livestock, % (*n*)	107	56.07 (60)	296	59.46 (176)	0.621
	N° cows, mean (sd)	60	6.28 (8.36)	176	6.94 (13.50)	0.657
	N° sheep, mean (sd)	60	3.88 (4.97)	176	1.42 (3.20)	<0.001
	N° goats, mean (sd)	60	8.13 (14.55)	176	7.73 (12.75)	0.848
	Households with construction land (concrete, cement, wood, tiles…), % (*n*)	107	0.93 (1)	287	0.70 (2)	0.999
	Households with construction roof (concrete, cement, wood, tiles…), % (*n*)	107	1.87 (2)	295	0.68 (5)	0.999
Food security	Number of meals per day, mean (sd)	102	2.93 (0.47)	268	2.77 (0.44)	0.003
	Lack of food in the last 4 weeks	107		291		
	No, % (*n*)		77.60 (83)		83.50 (243)	0.224
	Rarely, % (*n*)		22.40 (24)		15.45 (45)	0.139
	3–10 times, % (*n*)		0.00 (0)		0.70 (2)	0.952
	More than 10 times, % (*n*)		0.00 (0)		0.35 (1)	0.999
	Food Diversity (Food Consumption Score), mean (sd)	107	56.30 (21.16)	296	53.52 (19.60)	0.237
	Poor diet, % (*n*)		6.54 (7)		3.04 (9)	0.193
	Limited diet, % (*n*)		14.95 (16)		11.82 (35)	0.506
	Acceptable diet, % (*n*)		78.50 (84)		85.14 (252)	0.153
Heath care access	Behavior if the child is sick	106		296		
	Health centre or health post, % (*n*)		100.00 (106)		94.94 (281)	0.039
	Traditional medicine, % (*n*)		0.00 (0)		4.39 (13)	0.061
	Self medication, % (*n*)		0.00 (0)		0.67 (2)	0.965
	Households with difficulty to access treatment, % (*n*)	107	4.70 (5)	296	4.39 (13)	0.999
	Time it takes to get to treatment	105		294		
	30 min or less, % (*n*)		51.42 (54)		36.05 (106)	0.008
	Up to 1 h 30 min, % (*n*)		34.29 (36)		40.82 (120)	0.288
	More than 2 h, % (*n*)		14.29 (15)		23.13 (68)	0.076

CMAM: community management of acute malnutrition; sd: standard deviation; *n*: number of individuals.

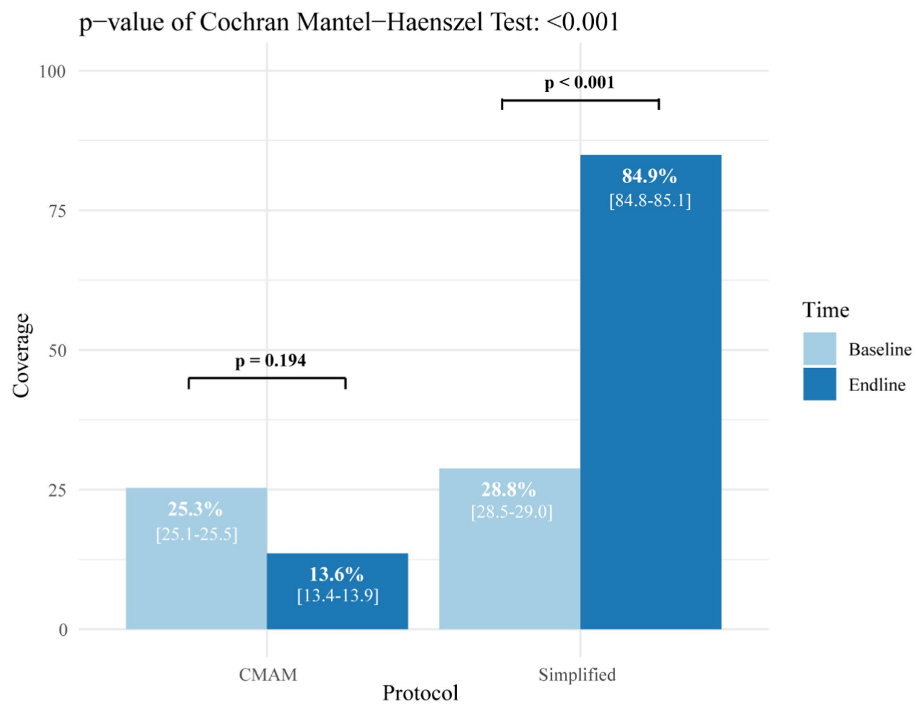

FIGURE 1
Coverage of moderate acute malnutrition treatment in the study groups before and after the intervention. CMAM: community management of acute malnutrition.

TABLE 2 Admission characteristics of children treated for moderate acute malnutrition by study group.

Characteristics	Control CMAM protocol	Intervention simplified protocol	Comparison
			p-value
Sex and age	*n* = 181	*n* = 483	
Female, *n* (%)	92 (50.83)	258 (53.42)	0.611[NS]
Age in months, mean (sd)	12.33 (4.47)	14.05 (6.09)	0.001
Presence of comorbidities	*n* = 181	*n* = 483	
Diarrheal, *n* (%)	2 (1.10)	48 (9.94)	<0.001
Vomiting, *n* (%)	2 (1.10)	6 (1.24)	0.999[NS]
Acute respiratory infection, *n* (%)	0 (0.00)	9 (1.86)	0.141[NS]
Cough, *n* (%)	4 (2.21)	59 (12.21)	<0.001
Fever, *n* (%)	2 (1.10)	25 (5.18)	0.032
Pale Conjunctiva, *n* (%)	0 (0.00)	27 (5.59)	0.002
Malaria positive test result, *n* (%)	0 (0.00)	0 (0.00)	0.999[NS]
Type of admission	*n* = 179	*n* = 476	
New admission, *n* (%)	179 (100)	472 (99.16)	0.504[NS]
Readmission, *n* (%)	0 (0.00)	0 (0.00)	0.999[NS]
Relapse, *n* (%)	0 (0.00)	3 (0.63)	0.678[NS]
Transfer, *n* (%)	0 (0.00)	1 (0.21)	0.999[NS]
Anthropometry at admission	*n* = 181	*n* = 481	
WHZ, mean (sd)	−2.18 (0.75)	−2.13 (1.17)	0.326[NS]
HAZ, mean (sd)	−1.45 (1.69)	−1.19 (1.56)	0.119[NS]
WAZ, mean (sd)	−2.37 (0.88)	−2.18 (0.91)	0.009
MUAC, mean (sd)	119.52 (1.88)	119.08 (2.03)	0.016

CMAM: community management of acute malnutrition; HAZ: height-for-age z-score; MUAC: middle-upper arm circumference; NS: Not significant *p*-value; sd: standard deviation; WAZ: weight-for-age z-score; WHZ: weight-for-height z-score; *n*: number of individuals.

TABLE 3 Anthropometry at admission between study groups and treatment providers.

Protocol	CMAM protocol	Simplified protocol		
	$n = 181$	$n = 481$		
Provider	Health staff (in health centre and health post)	CHWs (in health posts)	Health staff (in health centre)	
	$n = 181$	$n = 208$	$n = 273$	p-value
WHZ, mean (sd)	−2.180 (0.748)	−2.185 (1.121)	−2.090 (1.208)	0.112
HAZ, mean (sd)	−1.451 (1.690)	−1.423 (1.390)	−1.015 (1.664)	0.002
WAZ, mean (sd)	−2.366 (0.882)	−2.327 (0.943)	−2.070 (0.863)	<0.001
MUAC, mean (sd)	119.508 (1.529)	119.177 (1.868)	119.014 (2.037)	0.184

CMAM: community management of acute malnutrition; CHWs: community health workers; WHZ: weight-for-height z-score; HAZ: height-for-age z-score; WAZ: weight-for-age z-score; MUAC: middle-upper arm circumference; sd: standard deviation; *n*: number of individuals.

TABLE 4 Treatment outcomes comparison among children treated for moderate acute malnutrition by study group.

Treatment outcomes	Control CMAM protocol	Intervention simplified protocol	
	$n = 181$	$n = 483$	p-value
Recovery, *n* (%)	144 (79.56)	481 (99.60)	<0.001
Death, *n* (%)	0 (0.00)	0 (0.00)	–
Defaulting, *n* (%)	8 (4.42)	0 (0.00)	<0.001
Non-response, *n* (%)	18 (9.94)	1 (0.20)	<0.001
Discharge error, *n* (%)*	11 (6.08)	1 (0.20)	<0.001
Time to recovery (days) median (IQR)**	$n = 141$	$n = 472$	<0.001
	42.00 (34.00; 56.00)	28.00 (21.00; 35.00)	
Food consumption median (IQR)**	$n = 139$	$n = 474$	
RUSF sachets	60.00 (45.00; 60.00)		–
RUTF sachets		28.00 (28.00; 35.00)	
Weight gain median (IQR)**	$n = 139$	$n = 471$	
Total (Kg)	1.00 (0.60; 1.30)	0.80 (0.50; 1.20)	0.010
Daily (g/Kg/day)	3.08 (2.18; 4.52)	4.46 (2.86; 6.85)	<0.001
MUAC gain median (IQR)**	$n = 141$	$n = 472$	
Total (mm)	8.00 (6.00; 10.00)	10.00 (8.00; 11.00)	<0.001
Daily (mm/day)	0.19 (0.14; 0.25)	0.34 (0.27; 0.48)	<0.001

CMAM: community management of acute malnutrition; IQR: interquartile range; MUAC: middle-upper arm circumference; RUSF: ready-to-use supplementary food; RUTF: ready-to-use therapeutic food; *n*: number of individuals. *Cases discharged as cured but whose anthropometry does not meet the cure criteria according to each protocol. **Variables recorded only among recovered children.

the treatment at health post. An increase of coverage has been documented by other studies (27, 28, 45–47, among others) that analysed the inclusion of CHWs as SAM treatment providers outside the health centres by making treatment more accessible to communities thus eliminating possible economic barriers. Although we expect a similar effect for MAM treatment in both groups, there are currently no available studies on MAM treatment coverage that include health posts that can be used as comparison. The difference that we have found, may be attributed to the number and spatial distribution of the health posts in each health area. A geospatial study in Niger found that the geographic distribution of community health posts was inefficient, and only 22.1% of the population had access to a treatment site within a 60-min walk (48). In addition, the same study showed that the integration of CHWs in the 7,741 health posts in the country could increase coverage from 41.5% to 82.9%. As our study was not a randomized controlled trial, we cannot ensure that the distribution of the health post was the same in both arms, and this can contribute to the increase in coverage in just the intervention group. This finding could be also due to the protocol used. The control group under the standard protocol used RUSF for MAM, during the study an irregular supply of RUSF for MAM treatment programmes was noted. Management of acute malnutrition with the simplified protocol is easier to apply, could reduce the workload for health service providers, could decrease the waiting time for families, and therefore increase the number of children that can be treated.

In terms of treatment effectiveness, both protocols presented outcomes that exceeded the minimum recommendations for a humanitarian response (>75% recovery, <10% death and < 15% default) (44). The group treated with simplified protocol showed

TABLE 5 Outcomes among recovered children treated of moderate acute malnutrition with the simplified protocol compared by treatment provider within the intervention group.

Treatment outcomes	Community health workers	Health staff	
	n = 208	*n* = 275	*p*-value
Recovery, *n* (%)	207 (99.52)	274 (99.64)	0.999
Time to recovery (days)	*n* = 203	*n* = 271	<0.001
	21.00 (21.00; 28.00)	28.00 (21.00; 36.00)	
Food consumption median (IQR)	*n* = 203	*n* = 273	
RUTF sachets	28.00 (28.00; 28.00)	35.00 (28.00; 42.00)	<0.001
Weight gain median (IQR)	*n* = 201	*n* = 270	
Total (Kg)	1.10 (0.67: 1.20)	0.70 (0.50; 1.00)	<0.001
Daily (g/Kg/day)	6.57 (3.69; 7.94)	3.57 (2.44; 5.02)	<0.001
MUAC gain median (IQR)**	*n* = 202	*n* = 270	
Total (mm)	10.00 (8.00; 12.00)	9.00 (8.00; 11.00)	<0.001
Daily (mm/day)	0.46 (0.33; 0.52)	0.30 (0.23; 0.37)	<0.001

MUAC: middle-upper arm circumference; IQR: interquartile range; RUSF: ready-to-use supplementary food; RUTF: ready-to-use therapeutic food; *n*: number of individuals.

TABLE 6 Association of sex, age, admission characteristics and protocol in treatment variables of children cured from moderate acute malnutrition.

Dependent variable	Model 1: sachets consumption		Model 2: time to recovery (days)		Model 3: daily MUAC gain		Model 4: daily weight gain	
Independent variables	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value	β coefficient (95% CI)	*p*-value
(Intercept)	270.27 (210.05; 330.49)	<0.001	301.11 (238.85; 363.38)	<0.001	1.86 (1.14; 2.58)	<0.001	−20.45 (−26.29; 13.04)	0.011
Sex: male	−0.44 (−2.43; 1.54)	0.660	−1.50 (−3.56; 0.56)	0.154	0.02 (−0.01; 0.04)	0.172	−0.38 (−1.66; −0.28)	0.153
Age	−0.12 (−0.32; 0.08)	0.242	−0.15 (−0.37; 0.06)	0.152	0.01 (−0.01; 0.01)	0.230	−0.08 (−0.18; −0.04)	0.004
Comorbidities: yes	1.76 (−1.12; 4.65)	0.230	1.05 (−1.89; 3.99)	0.483	−0.02 (−0.05; 0.01)	0.193	−1.08 (−2.22; −0.20)	0.004
MUAC	−1.77 (−2.27; −1.27)	<0.001	−2.11 (−2.63; −1.59)	<0.001	−0.01 (−0.02; −0.01)	<0.001	0.19 (−0.09; 0.24)	0.005
WHZ	−1.11 (−7.32; 5.10)	0.725	−6.57 (−13.13; −0.02)	0.049	0.02 (−0.05; 0.10)	0.587	2.18 (−0.49; 3.89)	0.010
HAZ	−0.36 (−4.85; 4.12)	0.874	−4.14 (−8.88; 0.64)	0.087	0.01 (−0.05; 0.06)	0.852	1.72 (0.04; 3.22)	0.005
WAZ	1.21 (−7.51; 9.93)	0.786	8.70 (−0.48; 17.89)	0.063	−0.01 (−0.11; 0.10)	0.857	−4.28 (−7.11; −0.97)	<0.001
Provider: CHWs	−6.20 (−8.36; −4.04)	<0.001	−6.83 (−9.06; −4.59)	<0.001	0.12 (0.09; 0.15)	<0.001	2.09 (1.61; 3.10)	<0.001
Protocol: simplified	−22.03 (−24.52; −19.54)	<0.001	−15.59 (−18.17; −13.01)	<0.001	0.10 (0.07; 0.13)	<0.001	0.81 (−0.44; 1.26)	0.016
Adjusted R^2	0.47		0.36		0.29		0.19	

CHWs: community health workers; CI: confidence interval; HAZ: height-for-age z-score at admission; MUAC: middle-upper arm circumference at admission; WAZ: weight-for-age z-score at admission; WHZ: weight-for-height z-score at admission.

very high recovery rates (99.6%), while the group treated with the CMAM protocol experienced a significant drop to 79.6% recovery due to: (1) a greater number of discharge errors (6.1%), probably due to the fact that a more complex discharge criterion could increase the probability of committing errors and (2) a therapeutic food stock break event, which may have had an effect on increasing non-response (9.9%) and defaulting (4.4%) cases. All this together can be associated with the lower recovery values observed in the

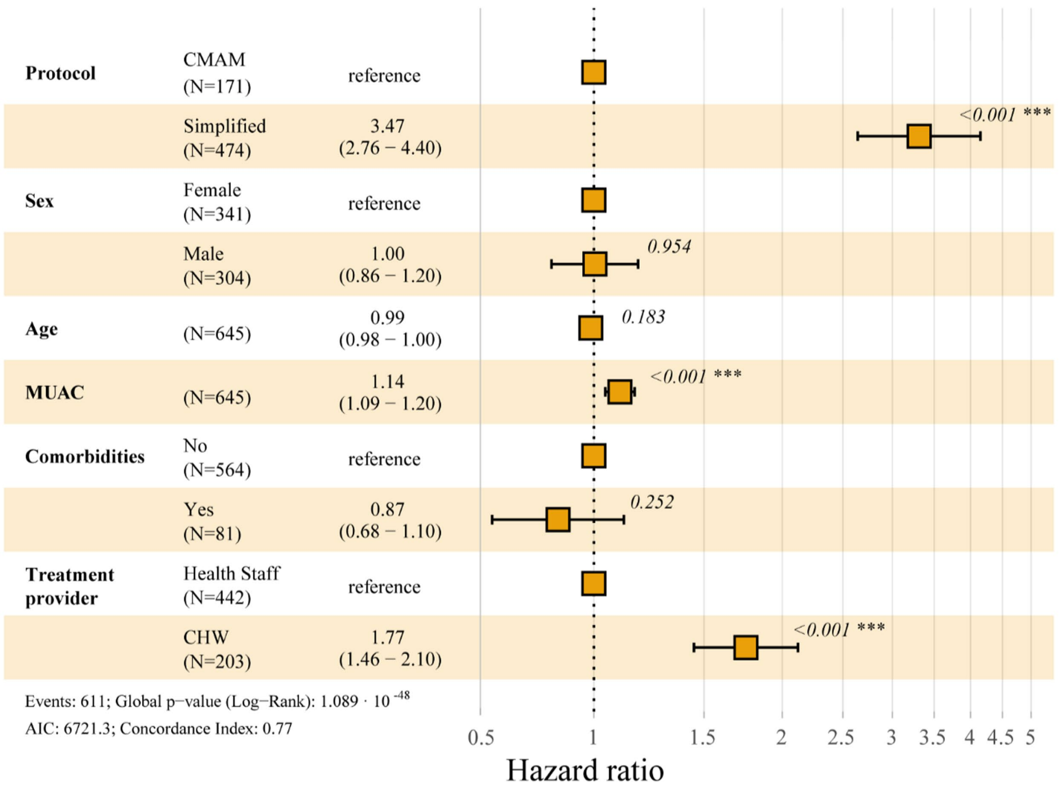

FIGURE 2
Forest plot displaying multivariate cox regression model of the probability of cure over time. CMAM: community management of acute malnutrition; MUAC: middle-upper arm circumference at admission; CHW: community health workers; N: number of individuals.

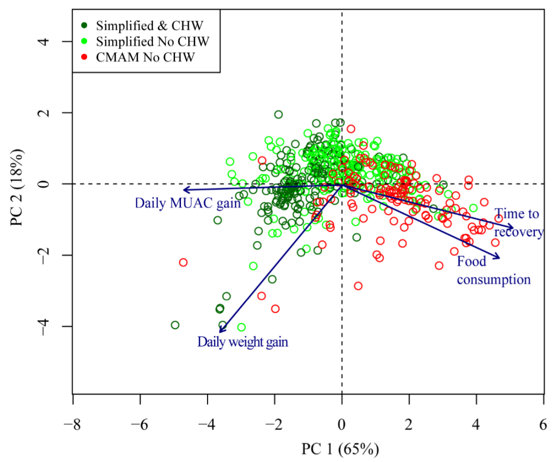

FIGURE 3
Principal component analysis showing the relationship between different quantitative results of interest and the protocol with which the patient has been treated. CMAM: community management of acute malnutrition; CHW: community health workers; MUAC: middle-upper arm circumference at admission; PC: principal component.

CMAM protocol group. Conversely, the ComPAS study by Bailey et al. (30) conducted in South Sudan and Kenya, showed non-significant differences in MAM cure rates between the standard and the same simplified protocol, presenting 85.1% (773/908) and 86.4% (860/995) recovery rates, respectively. Another study by Daures et al. (31) tested a different simplified protocol called OptiMA which consisted of the provision of a reduced RUTF dose based on three MUAC ranges (175 kcal/kg/day with MUAC<115 mm, 125 kcal/kg/day with MUAC 115-120 mm and 75 kcal/kg/day with MUAC 120-124 mm). Comparing like for like MUAC ranges, the OptiMA study presented similar recovery rates to our study (MUAC 115-124 mm: 89.48%, $n = 3699/4134$).

The same simplified protocol as the one used in the present study was tested in a large cohort in Mali which included CHWs as treatment providers in the health posts and recorded a global cure rate for MAM cases of 95.2% (17,220/18,090) (41). In the present study, time to recovery in children treated with the simplified protocol was significantly shorter (28 vs. 42 days with the CMAM protocol). This finding is very consistent with the large Malian cohort reported by Kangas et al. (41), which also recorded a time to recovery of 28 days for MAM cases treated under the same simplified protocol. Some differences have also been found between protocols in terms of consumption of ready-to-use food sachets (60 RUSF sachets with the CMAM protocol vs. 28 RUTF sachets with the simplified protocol) but these values are not directly comparable due to the differences in product composition and costs. The RUTF sachets consumed in the simplified protocol was lower than the 42 sachets recorded in the study by Kangas et al. (41). These differences could be explained by the fact that an extra ration of 7 sachets of RUTF was given to each child at discharge.

Despite a recent meta-analysis on MAM treatment (49) concluding that RUTF and RUSF showed little or no difference in recovery rate (risk ratio: 1.02 [0.98–1.05]), the influence on recovery could be indirect since RUTF may lead to an increase in daily weight gain when compared to RUSF (mean difference of 0.2 g/kg/day; 95% CI: 0.08 to 0.32). If we look at anthropometric gain presented in this study, the group with the simplified protocol far exceeded the CMAM protocol group in both anthropometric indicators (weight: 4.46 vs. 3.08 g/Kg/day; MUAC: 0.34 vs. 0.19 mm/day). These results are also consistent with those found in the Malian cohort (41) which showed a weight gain of 4.8 g/Kg/day and MUAC gain of 0.3 mm/day. In our study, the simplified protocol has been implemented by nurses and CHWs in formal health centres and decentralized health posts. Looking at the effectiveness of the simplified protocol in relation to the treatment provider within the intervention group, we found no differences between CHWs and nurses in terms of cure rate (99.5% vs. 99.6%). In the Malian cohort, the CHWs reached a slightly lower cure ratio of 95.6% (41).

The present study highlights the relevance of decentralizing treatment by involving less skilled CHWs alongside a simplified protocol to optimise effectiveness. Our results showed that children treated by CHWs had lower time to recovery than those treated by health staff (21 vs. 28 days), lower RUTF consumption (28 vs. 35 sachets), higher daily weight gain (6.57 vs. 3.57 g/Kg/day) and MUAC gain (0.46 vs. 0.30 mm/day). This improvement appeared to be gradual as presented in the first dimension of the principal components analysis showing how the simplified protocol resulted in improved outcomes, with the cloud point shifting to the left, which improved even further when including CHWs with a further shift to the left. However, although the observed pattern appears very clear, the complexity surrounding acute malnutrition must not be forgotten, which is also evident in the graph through the dispersed positions of some children.

Some studies on SAM treatment have reported improved outcomes achieved by CHWs could be related to their ability to treat malnutrition and concurrent infections in an integrated manner, thereby reducing the burden of comorbidities that hinder proper recovery. This could be explained by the increased workload of the health staff which limits the time spent diagnosing these pathologies during treatment of acute malnutrition (26, 27). A review on relapse and mortality after discharge (50) highlighted the importance of continuity of care for moderately malnourished cases through integrated and decentralized programmes implemented at the health posts closest to the high-risk populations like those included in the present study.

The multivariate Cox regression model identified treatment protocol, provider and MUAC at admission as factors significantly affecting the probability of recovery over time. The study by Gebremichael (51) also found that MUAC at admission was a significant determinant of recovery. This is because a higher anthropometric status at admission increases the probability of a successful recovery (26, 50). However, our multivariate model found that treatment protocol and provider are more influential that anthropometric status, in this case MUAC, in determining recovery due to the higher adjusted HRs (3.3 and 1.8 respectively). Therefore, treating MAM cases with a simplified protocol that uses RUTF and CHWs improves treatment outcomes. A recent study also concluded that treating high-risk MAM cases with RUTF increased their short-term recovery in terms of greater MUAC and weight gain (20).

The results of our linear regression models reveal that the recovery of acute malnutrition is a complex multifactorial process showed by the R^2 values obtained in our models (around 0.2–0.5) which are relatively low, similar to the results obtained by Maust et al. (34), which had R^2 falling around 0.15–0.5. This suggests that the explanatory variables considered in our four models are not capable of providing a very accurate prediction of the treatment outcomes in terms of time to recovery, consumption of sachets, daily weight and MUAC gain. One of the key results of this study, which aligns with the findings provided by other authors, is that children who receive an integrated treatment, meaning MUAC for diagnosis and RUTF for SAM and MAM treatment, recover faster and with greater gains in MUAC and WHZ. Furthermore, based on our study, we can say that CHWs as treatment providers contribute further improve these outcomes. Identifying other factors influencing recovery and taking them into account in programmatic designs could help improve effectiveness of treatment programmes. A recent study by Rashid et al. (52) identified higher age of the child, higher MUAC at admission, receiving deworming treatment, time taken to access services from the nearby health post (60 min or less) and use of ready-to-use supplementary food as positive predictors of time to recovery from MAM.

The results obtained in the intervention group provide evidence in favour of using a simplified protocol for the treatment of MAM. Moreover, including CHWs as treatment providers, as opposed to relying solely on specialised healthcare personnel, could significantly improve effectiveness of the treatment protocol. In addition, early treatment of malnutrition is more effective, poses less risk to the child, and is less expensive. The cost-effectiveness study of the present research concluded that the cost of treating a MAM child with the CMAM protocol was USD 165.2 (95% CI: 151.7; 179.3), whereas when using the simplified protocol treatment cost was USD 96.5 (95% CI: 87.3; 100.3) (53). Since the mid-nineties' authors have been highlighting the importance of adequately treating MAM: "there is no question the most severely malnourished children suffer the most, but they may not be contributing to most of the suffering" (54).

4.1 Limitations

There are some caveats that should be taken into account. This study is not a randomized controlled trial, so the results cannot be extrapolated to other contexts and the probability of residual confounding is increased. Another possible limitation is the difference in sample sizes between groups, whereby there was a higher incidence of cases in the intervention area. However, this fact actually reflects the field situation, where the worst socioeconomic conditions are recorded, with a higher population of 47,198 habitants vs. a population of 26,176 habitants in the intervention and control groups, respectively. Nevertheless, the statistical tests used are robust about this type of sample imbalance and the results show that the simplification of the protocol is effective even with worse baseline conditions. In this sense, due to logistical reasons, the socioeconomic assessment could not be carried out on all the treated participants, which was corrected by taking a random sample of them. The coverage surveys were carried out in different time periods, just 8 months later after the start of the project. The SQUEAC methodology suggests that this kind of survey can be implemented in periods of a minimum of 4 months after the new intervention is launched for monitoring the effect. One of the factors that may have a negative effect on treatment coverage is the overburdening of health facilities and worsening of access to treatment sites due to flooding, which means not all children in need can reach them. In our case, the period of the highest prevalence of the disease was when the final survey was conducted, and, even with this situation, an increase in treatment coverage was shown in the intervention group when we decentralized treatment to the community level.

5 Conclusion

Implementing a simplified protocol for the treatment of MAM based on MUAC as the sole criterion for admission and discharge, a fixed daily dose of one RUTF and involving CHWs as treatment providers could significantly improve the effectiveness and coverage of treatment programmes compared to standard protocols. The simplification of the protocol would facilitate training of personnel and reduce errors due to its easier implementation. In addition, eliminating the requirement to use two different products to treat MAM and SAM cases would simplify the logistics of interventions and align with the intention of treating acute malnutrition continuously and as a whole condition, which is expected to have a positive impact on reducing the therapeutic food stock break events and consequently in increasing treatment coverage since more children will be able to follow the treatment adequately. Furthermore, decentralizing treatment outside of the health centres could be particularly important in emergency settings where access is hindered by multiple barriers. The challenge would be to ensure chain supply closer to the families at the health post level.

Children affected by MAM, not only are very vulnerable due to their condition but also risk deteriorating into SAM if they do not receive timely and adequate treatment. Providing appropriate care to MAM children should be recognised as an important public health issue and prioritised in the future. More research is needed to test this simplified protocol on a larger scale in different contexts to understand its effectiveness in terms of recovery over time and avoid relapses linked to this approach.

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.

Ethics statement

The studies involving humans were approved by National Health Research Ethics Committee of Niger. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LS-M: Data curation, Formal analysis, Validation, Visualization, Writing – original draft. PC-C: Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing. AG: Project administration, Supervision, Validation, Writing – review & editing. AD: Project administration, Supervision, Validation, Writing – review & editing. AS: Supervision, Validation, Writing – review & editing. NO: Supervision, Validation, Writing – review & editing. RL: Supervision, Validation, Writing – review & editing. FT: Funding acquisition, Project administration, Validation, Writing – review & editing. AV: Funding acquisition, Validation, Writing – review & editing. CH: Validation, Visualization, Writing – review & editing. NL-E: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

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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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Caregivers' socio-cultural influences on health-seeking behavior for their wasted children among forcibly displaced Myanmar Nationals and their nearest host communities

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Introduction: A total of 19% of forcibly displaced Myanmar Nationals (FDMNs) Bangladesh fall within the age range of under five years old, while an average of 1% exhibit severe malnutrition. Cox's Bazar is the closest host community for FDMNs, with similar traditional culture and religion and shared linguistic, ethnic, and cultural ties.

Methods: A qualitative study was conducted to investigate the impact of socio-cultural factors on the healthcare-seeking behavior of caregivers of critically malnourished children in FDMN camps and neighboring host communities.

Results: The utilization of informal healthcare by caregivers in both populations can be attributed to cultural attitudes, taboos, and peer pressure. The healthcare by practices in the FDMN camps and host towns were primarily affected by household responsibilities, familial assistance in accessing medical services, decisions made by husbands or mothers-in-law, and the availability and accessibility of healthcare facilities. Certain features were identified that prompt caregivers to seek formal treatment in both groups. The efficacy of the treatment was a primary consideration. In instances where conventional remedies and informal treatments proved ineffective in restoring the health of children, others who were invested in their well-being, such as family members and neighbors, advised caretakers to pursue professional medical care.

Discussion: Enhanced caregiver awareness of severe wasting, enhanced healthcare accessibility, and increased community volunteer engagement have the potential to facilitate early identification of severely wasted children and mitigate delays in treatment.

KEYWORDS
forcibly displaced Myanmar Nationals, host community, severe wasting, healthcare-seeking behavior, Bangladesh

Introduction

The plight of the Forcibly Displaced Myanmar Nationals (FDMN) community in Bangladesh has been one of the most violent and protracted humanitarian crises in recent history, marked by restricted mobility, denial of citizenship, forcible displacements, and decades-long persecution (1). Violence erupted in Myanmar in the late 1970s, resulting in the displacement of millions of FDMN from its Rakhine state to Bangladesh (2). Currently, more than 1.1 million FDMN are residing in Bangladesh (1) and housed mostly in overcrowded settlements in the Ukhiya and Teknaf Upazilas of the Cox's Bazaar district. More than 180,000 children under the age of five in this population (3, 4). Around 19% of the FDMN population in Bangladesh (3) are children under the age of five, and around 0.7% of those children are severely malnourished (5). Severe wasting which is a form of malnutrition linked to a mortality rate of 73–187 per 1,000 children per year (6, 7). This condition is life-threatening and requires immediate medical attention (7). However, unfamiliarity with the new setting is very likely to be challenging in healthcare seeking for this vulnerable segment of the population (8).

Health-seeking behavior exhibits variability among many societies and people, influenced by cultural, social, economic, and environmental determinants (9). When examining the health-seeking behavior of FDMNs and the nearest host communities in Bangladesh, it becomes evident that there exist both similarities and differences. They residing in Bangladesh represent a group that has been forcibly relocated, hence giving rise to distinct health-related obstacles associated with their displacement, deprivation of possessions, and psychological distress. In contrast, host communities do not encounter these particular issues (10, 11).

Caregivers of severely wasted children play a crucial role in obtaining appropriate healthcare for their children (12, 13). A significant proportion of female participants from both communities faced the requirement of obtaining permission and financial resources from their male family members to access healthcare services, thereby leading to reduced healthcare accessibility (14). This is even more challenging due to language barriers, cultural differences, and limited access to healthcare services in FDMNs (11). However, language barriers are not as prevalent in the host community, so they do not impede effective communication with healthcare providers like FDMN (15). One of the primary obstacles to accessing healthcare services was the considerable distance between them and the nearest health establishments. The limitation of mobility has been recognized as a hindrance for individuals with disabilities, elderly individuals, and pregnant women due to their advanced age and physical state. Hilly terrain made it difficult for the FDMN population to reach health facilities, which required a 15-min to an hour walk (14).

In addition, FDMN women felt discouraged from obtaining medical assistance from male healthcare providers due to cultural norms that emphasize gender segregation and the need to maintain a modest appearance. Low use of healthcare services among both communities also resulted from several other factors including a lack of trust in the healthcare system and a preference for more traditional forms of treatment (11, 16). This is to be noted that mistrust of FDMNs and host communities about modern medicine is a big challenge for healthcare practitioners. Due to their beliefs in spiritual and supernatural causes of illness, they favor traditional medicine over modern medicine (17). Although the health perspectives of the two communities may be similar, their traditional healing practices are distinct; these cultural distinctions may not have been acknowledged and respected in health care services (11). Furthermore, the COVID-19 pandemic has increased the FDMNs' fear and mistrust of medical professionals, leading them to assume that if they are admitted to the hospital with COVID-19 infection, they will be killed to prevent the virus from spreading (17).

Though key humanitarian assistance programs supported by United Nations (UN) agencies and implemented by non-government organizations (NGO), such as household food rations, ready-to-use therapeutic food (RUTF), fortified blended foods, and micronutrient powders, have expanded greatly (18); the FDMN population remains largely unacquainted with health services (19). In contrast to that, since 2017, approximately 46 NGOs and UN agencies, and the Bangladesh government have been helping host communities with education, food security, gender-based violence, health, shelter, nutrition, protection, and WASH (6). The FDMNs' protracted stay has limited resources for the host population near the camps. Stress on resources causes other host community difficulties (7). The rapid influx of FDMNs into Bangladesh and rising commodity prices have hurt host communities (8). This influx reduced host community income and work prospects and negatively impacted diet diversity, putting children at risk of malnutrition (7).

The convergence of health-seeking behavior among FDMNs and the host community in Bangladesh presents a multitude of advantages. However, it is imperative to acknowledge and tackle potential obstacles, including cultural disparities, linguistic limitations, and the necessity for culturally sensitive healthcare provisions that cater to the distinct requirements of both groups. Therefore, we explored caregivers' sociocultural behavior influence on seeking treatment for their wasted children among Forcibly Displaced Myanmar Nationals and their nearest host communities.

The study findings will provide valuable assistance to the health sector in determining how to effectively deliver appropriate, culturally sensitive, and sufficient resources for severely malnourished children experiencing wasting.

Methods and materials

Study design

We used a qualitative approach to perform the study. The study was exploratory and gave us a better understanding of the healthcare-seeking behavior of the caregivers of the severe wasted children among the FDMN communities and their nearest host communities in Cox's Bazar, Bangladesh. Children of the host community have been treated at different types of healthcare facilities, including government hospitals, private doctors, and nutrition centers; whereas FDMN children get treatment from Integrated Nutrition Facilities or Health Posts situated in every camp (14, 18). Some of these facilities provided free services (only for FDMN), while others charged fees. Few children from FDMN camps were admitted to stabilization centers, and some were referred to hospitals for further examination and testing, such as chest X-rays and skull X-rays.

Study participants

We included caregivers of the children of 6–59 months of the FDMN and their nearest host communities in the Teknaf sub-district of Cox's Bazar district, Bangladesh. Caregivers were described as mothers or other family members who took care of the children most of the time.

We purposively selected the caregivers whose children had recently (within 6 months prior to data collection) received or were getting, inpatient or outpatient treatment for severely wasted children in any healthcare facilities in the study areas. These caregivers were found using records from the integrated nutrition facilities (INFs) in the camps for FDMNs and from any healthcare facilities in Teknaf, Cox's Bazar for host communities. We conducted a total of 17 IDIs (In-Depth Interviews) (8 from the host communities and 9 from the FDMN refugee communities) considering the principles of data saturation.

Study site

The research was conducted in FDMN Camps 25 and 27 and their nearest host communities in the Teknaf sub-district of the Cox's Bazar district. The selection of research areas was determined by the emergency in the aforementioned region. Due to a nutritional emergency, the site was selected where, later on, the intervention of the effectiveness trial of locally produced therapeutic food would be rolled out among the children of the FDMNs suffering from severe wasting without complications.

Camp 25 and Camp 27 collectively contain four health centers. The management and operation of these health centers are divided among many organizations. Specifically, the International Rescue Committee and Terre des Hommes are responsible for the management and operation of health centers in these camps, under the oversight of Save the Children. Additionally, the United Nations Children's Fund (UNICEF) manages the Integrated Nutrition Facility within these camps. In aggregate, these health centers encompass a collective sum of 50 healthcare practitioners. The total population of both camps amounts to 25,964 individuals. As a consequence, there exists a ratio of one health worker for 519 individuals in the population. The mean distance between the residences of participants and the closest health institution is 1.5 kilometers. Utilizing healthcare services incurs no associated expenses, including expenditures related to travel and personal donations. The inhabitants of the camp access the services on foot. There is no expenditure associated with utilizing healthcare services, encompassing travel costs and personal contributions. The residents of the camp receive their services by walking.

The other site of the study was in Hnila Union, a 65,000-person host community. Hnila Union has six health centers. Three community clinics and one Union Health Complex are in the Union. Teknaf Upazila Health Complex and Cox's Bazar District Hospital are the other two hospitals outside the Union. Residents rarely visit the district hospital unless they have a serious illness. In the three community clinics, Union Health Complex, and Teknaf Upazila Health Complex, 119 healthcare providers work. Health workers are 1:2100 to the population. Participants average 4.5 km from their homes to neighborhood clinics and the Union Health & Family Welfare Center (UH&FWC). The average distance to Upazila Health Complex is 20 miles, and Cox's Bazar District Hospital is 66 kilometers. Healthcare costs, including travel and out-of-pocket charges, vary per facility. On average, participants pay 50 Taka to reach a Community Clinic, 120 Taka to the Upazila Health Complex, and 450 Taka to the District Hospital.

Most of the population is Bengali and works as laborers from lower-middle-class backgrounds. Most people speak Bengali and are Muslim.12.8% of the population suffers from global acute malnutrition (Weight-for-height z score < -2.0) and 7.3% from moderate acute malnutrition (Z score < -2.0 & > -3.0). In 5.5% of the population, severe acute malnutrition (Weight-for-height z score < -3.0) is seen.

Data collection

Data collection is a crucial step in qualitative research that involves gathering information from various sources to answer research queries. We gathered both verbal and written informed consent from all the participants before the interviews. Data collection occurred from 15th March to 8th August 2022. Four experienced Field Research Assistants with training in Social Science were engaged in data collection under the supervision of an investigator (MR). Two were female, while the other two were male. They were recruited from the surrounding areas so that they could speak and comprehend the participants' dialect (or local language). Additionally, two investigators (MR and NNN) visited the study sites and received information from the interviewers, and provided necessary feedback for further exploration or clarity of data. Before conducting interviews, the data collectors visited the participants' homes and established rapport with them.

We conducted in-depth interviews (IDIs) with the purposively selected caregivers of the children who had recently received or were currently receiving treatment for SAM in INF and community clinics to gain in-depth insights and understand caregivers' experiences of health-seeking behavior for their wasted children. The roster of children was obtained from the facilities and/or by visiting the homes of the children's primary caregivers. The participants were purposefully selected to maximize variation in terms of education, age, number of offspring, etc. All IDIs were conducted at the level of the household. The interview was conducted using a topic guide (Supplementary Table S2) as a guide. On average, each IDIs lasted 86 min. We conducted a total of eight IDIs from the host communities and nine IDIs from the FDMN communities following the data saturation principle.

Data analysis

In this study, we adopted the definition of a traditional healer from the World Health Organization as a person who does not have formal medical training but is recognized (by the local community) as being qualified to provide health care using animal, plant, and mineral substances and specific alternative methods based on the social, cultural, and religious background that includes the knowledge, attitudes, and beliefs that have been widely accepted in the community regarding physical, mental, and social well-being as well as the underlying causes of sickness and impairment (20). The typology of formal and informal healthcare providers have been conceptualized based on their training (received formally recognized training with a

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TABLE 1 Basic characteristics of the study participants.

Characteristics	Caregivers from FDMN	Caregivers from host communities
Number of participants	9	8
Child's age (average in months)	22.6 (Range 7–52)	23.8 (Range 11–42)
Mother's age (average in years)	26.4 (Range 20–33)	25.8 (Range 19–32)
Mother's years of schooling (average)	3 (Range 0–8)	4 (Range 0–10)
Mother's occupation	Housewife (9)	Housewife (6), Tailor (1)
Father's age (average years)	28.8 (Range 22–35)	29.0 (Range 20–35)
Father's years of schooling (average)	3 (Range 0–10)	5 (Range 0–14)
Father's employment status (Employed in number)	Employed (5), Un-employed (4)	Employed (7), Un-employed (1)
Average number of household members	5 (Range 3–8)	6 (Range 3–12)
Average number of children's below 5 years of age	2 (Range 1–3)	1 (Range 1–2)
Average family income per month (in BDT)	6000.0 (5000–7,000)	14266.6 (6000–30,000)

defined curriculum from a government or academic institution or not), and registration (registered with any government regulatory body or not) (19).

After the interviews were completed, the recordings were transcribed and summarized within 2–3 days (depending on the duration of interviews or discussions) by experienced qualitative researchers. To become familiar with the data, the transcripts and summaries were reviewed very carefully. Peer briefings were held, and field notes were given to the investigators by the data collectors, to gain feedback on what concerns the investigators needed to look into further. The investigator gave timely input on such issues so that the data collectors might study those issues in greater depth during the subsequent interviews or discussions. In this iterative approach, initial analysis was performed while data were still being collected.

In addition, we used a qualitative technique to establish the tenet of credibility in trustworthiness to verify the findings of our research. During the process of qualitative technique, our research team went back to the selected study participants with their transcripts and read aloud the transcripts to the respective participants. They then asked the participants for their comments on whether or not the transcripts were justifiable from their points of view. During the process of member checking, the members of the research team also tried to gain a better understanding of any difficulties (if any) that required additional clarifications.

In the end, we examined the content. Two Research Assistants extracted the condensed meaning units from the raw data, tabulated them, and then finalized the meaning units by checking their work against each other and with each other. After that, data collectors carried out the coding, then the patterns were identified and the findings were interpreted. The results of the study have been compiled and presented in a checklist format that adheres to the consolidated standards for reporting qualitative research (COREQ) (21) (Supplementary Table S3).

Results

The results in this paper have been presented based on thematic areas generated from the study. The themes included different health-seeking behaviors such as home remedies and foods, traditional and informal healthcare seeking, formal healthcare seeking, and the factors triggering the caregivers to seek care from one contact to another contact for healthcare. Until severe wasting was diagnosed or identified in formal healthcare facilities, the caregivers of the children sought care from different contacts (from traditional to informal to formal, or simultaneously from multiple contacts) perceiving the severity of problems or diseases.

Although the participants were from two different communities-FDMN and their host community, their characteristics to some extent varied in terms of their age, education, and number of family members. Some basic characteristics of the interviewees have been given in Table 1.

Home remedies and foods

The majority of caregivers for severely malnourished children from both the FDMN and host communities initially relied on home remedies before their children were formally diagnosed as severely malnourished by healthcare professionals. Home remedies include various food options, including homemade meals consisting of rice, pulses, potatoes, and vegetables, commercially available infant formula, rice powder mixed with sugar or misri, soft rice, suji, khichuri, fruits, eggs, fish, and vegetables. However, these caregivers initially thought their children's weight loss was due to a lack of food, so they fed them alternative foods. We noticed a mother within the FDMN community who resorted to selling her earrings to purchase infant formula for her baby.

> "My boy's father brought 3 annas of gold earrings for me, he says that even it takes to sell the gold to feed the child, he will do that. That's why we sold it. We used to buy lactogen for six hundred and fifty taka. I have fed the child by selling gold."

A mother who perceived that her child was getting thin and sick not for wasting, mentioned:

> "When the child became thin and sick, I fed him blended rice with lactogen. Also, I didn't know that the child needed treatment for undernutrition, though I tried a lot for the treatment of sickness."

Another mother added:

> "… I was giving my child rice flour. I used to mix the rice in the dheki (a traditional manually operated equipment used to prepare powder) before frying and storing it in a bottle. Then I prepared the child's food with misri."

We found two mothers from both communities who tried home remedies for their children before their children were diagnosed as severely wasted. A child in the host community often suffered from common illnesses such as cough and cold, his mother made the child drink warm mustard oil with garlic lemon, and tea.

> *"I used to prepare a solution of mustard oil, lemon juice, and onion powder before feeding it to my child. I forced my child to consume tea. I massaged his entire body with mustard oil before giving him a shower. Then I pour oil on him again and dry him in the sun*."

A mother from the FDMN community tried "*Tula Oushod*" (made of neem leaves and various other leaves and roots) for her *Leda* (severely wasted) child.

Traditional healings

Six mothers of FDMN camp children sought treatment from Vaidya and Moulana healers. Religious leaders are revered in FDMN culture and influence behavior, including child healthcare (22). Their beliefs and respect are shared by the host community. Children in both situations sought treatment early on. They can visit the Moulana anytime without an appointment. Due to their disease treatment inexperience, individuals need recurrent visits. Per visit, 300 to 2000 taka ($18 to $20) are needed to finish the process.

We found two more children with an evil spirit (jinn-chumma dio paise) who were taken to Moulana and given enchanted oil, amulets, and advice to bury a burned egg. Traditional healers Moulana and Vaidya advised three children to drink charmed water and rub mustard oil. One caregiver was advised by a Vaidya to draw an eyeball on paper to escape the bad spirit.

> "I was told in the community that evil spirits possessed my child and they were sucking blood of him and that's why I have gone to the Vaidya 3 times. I drew an eyeball on a paper and then I took a handful of rice on the paper. Then I made a boat with the paper and swept the body of my child with that boat and finally I threw that away."

Some parents read religious holy book verses (Surah) and blew air at the children. These remedies were believed to cure bad spirits-caused sobbing, lack of appetite, and convulsions. Even though symptoms returned, these therapies were questionable. Traditional healing is appropriate and shorter. Mothers find solace in not having to leave domestic duties unfinished.

Three caretakers of wasting children visited Vaidya and one visited Maulana after being informed by neighbors or elderly family members in the host communities. A caregiver's cultural beliefs may lead her to see both a traditional healer and a doctor. A carer who attended a private practitioner also visited Vaidya because the evil spirit (Jinn) was sucking her child's blood and thinning him. One of the three caretakers visited Vaidya numerous times but stopped after her child did not recover. She said:

> "I took him to Vaidya for treatment. He gave nothing but amulets, enchanted water, and mustard oil. He advised me to tie the amulets, wash the body with enchanted water, and then massage the body with enchanted oil. I went there three times in 1-month intervals. Every time he took 200 taka for this. I have to sell some of my food rations to pay the fee. But my child didn't recover after all of this."

Informal and alternative healthcare

In both communities, children were given various informal treatments from pharmacies, including saline and syrup for fever, cough, common cold, and diarrhea. Medicines including vitamin syrups were frequently bought from pharmacies. They need to purchase the required medicines from the pharmacy. In severe instances, the child received an injection and syrup at the pharmacy for diarrhea and was asked to return for another injection the following day. Homeopathy was also used for invasive diarrhea, cough, and cold. Seeking treatment from pharmacies and homeopathist were triggered by family members themselves. Homeopathy is pseudoscientific; the practitioners of homeopathy are called homeopaths and they believe that the drug that causes sickness symptoms in healthy persons can alleviate comparable symptoms in sick people. Sometimes homeopathies and pharmacies were the first contact point for treatments due to the long queues in the primary formal healthcare points in the FDMN community. A caregiver, whose child was suffering from severe wasting and having diarrhea, said:

> "Once my child had severe diarrhoea. At first, his father took him to a hospital. There was a long queue and the child frequently purged; he had to change clothes repeatedly and the child became weak. The child's father got annoyed and left the place and brought the child to a pharmacy for treatment."

The main reason host communities sought care from informal or alternative healthcare providers was their accessibility and availability. Most limitations from spouses and mothers-in-law prevent mothers from seeking formal care outside the home. Many FDMN households have more than 5–6 children. Due to the pressure of caring for other children, mothers typically avoid formal care. They can easily obtain and use informal remedies like pharmacy and homeopathic drugs. Lack of transportation or great distances to official healthcare institutions also hindered treatment. Such caregivers preferred informal or alternative therapies. Peer pressure and neighbors also drove informal healthcare use.

Formal healthcare

INF and community clinics were the first formal contacts for wasting children in FDMN and host communities, respectively. Since community nutrition volunteers screened wasted children in FDMN camps, caregivers were more likely to seek formal healthcare facilities (INFs). A caregiver from the FDMN camp mentioned:

> "The Community Nutrition Volunteer visited my house and took my child's measurements. They said that my child was undernourished and he needed treatment. After that, I took him there (INF) and received lalpushti (RUTF). After taking lalpushti he was doing better than."

Of the nine FDMN camp caretakers interviewed, two initially attended formal healthcare facilities (INFs). One visited INF again after pharmacy services.

None of the eight host community caregivers interviewed visited the clinic first. However, two carers first saw private practitioners.

In wasting treatment, most caretakers in both groups received certified treatment for diarrhea, pneumonia, cold cough, sores, blisters, falls, and fever. Some families visited many hospitals for their children's health. Both groups' parents cannot receive healthcare for their children due to domestic duties and family head consent. A mother said from the host community and FDMN accordingly:

> "I had always taken permission from my mother-in-law' and "We fought for not telling my husband that I am going to take Pushti."

Financial and transportation constraints plagued families seeking child care in both locations. However, FDMN caregivers sometimes encounter language problems when seeking care from non-INF physicians. Some families borrowed money to pay for medical expenditures and traveled far to get care. Families had trouble understanding diagnosis and treatment options because healthcare staff spoke a foreign language.

In both communities, we revealed some triggering factors that eventually led the caregivers to switch to formal treatment options. One of these factors was treatment outcome. When the health condition of children did not improve despite seeking assistance from traditional healers or opting for informal treatments to ensure child wellbeing, concerned family members and neighbors advised the caregivers to seek formal healthcare care.

Challenges of or barriers to utilization of services for wasted children

The provision of care for severe malnourished children faced numerous obstacles and limitations in both FDMN camps and host communities. Within the confines of the camps, there existed a situation where husbands displayed hesitancy in granting permission for their wives to be admitted to Stabilization Centers (SCs) despite the presence of acute malnourishment and associated difficulties in their children. The hesitance stems from the challenges associated with providing care for additional children inside the household in the absence of the primary caregiver. Furthermore, it should be noted that SCs enforced a policy that disallowed males from staying overnight, thus necessitating the presence of female caregivers to remain with the children. This additional need further exacerbated the complexities of the situation. Nevertheless, as a result of domestic responsibilities and insufficient familial assistance, these female caregivers frequently exhibited reluctance to remain at the SCs. In the context of host communities, caregivers originally sought assistance for extremely malnourished children at community clinics (CCs). In cases where a child has been identified with severe malnutrition and associated difficulties, it is customary for them to be referred to Upazila Health Complexes (UHCs). This context presented comparable difficulties, encompassing domestic obligations, insufficient assistance for other offspring, and resistance from spouses concerning overnight visits.

The summary has been displayed in Supplementary Table S1.

Discussion

This qualitative research explored how caregivers of malnourished children among the FDMN and their neighboring host communities in Bangladesh sought healthcare from various providers. The findings of the study revealed a multitude of elements that exerted an effect on the decision-making process of individuals when they were seeking healthcare services.

The FDMN's nearest host community in Cox's Bazar is more conservative in culture and religion than the rest of Bangladesh and shares linguistic, ethnic, and cultural similarities. Nearly 40% of Upazillas near Teknaf and Ukhiya camps are poor, compared to 24% overall. After considerable migration, their health-seeking habits changed (16). In host societies, family members equate filth and impurity with childbirth and segregate the mother and baby to protect them from disease and evil spirits (23). Cultural, religious, and patriarchal views limited FDMN women's reproductive health choices. As part of their traditional medical practices, many FDMNs use herbal medications and spiritual healing (19). In both host communities and FDMN considered informal healthcare providers including neighborhood drug store, Vaidyas, and moulabi is the most accessible. Consistent with the results of another study, it was shown that they visit informal healthcare providers when they become sick (14). In both of these communities, we discovered both beliefs and misconceptions concerning the severe malnutrition of the children. It is important to spread the positive beliefs while working to eradicate harmful misconceptions, as the later may be one of the contributing causes that lead to child wasting (24). Because of this, some people wait longer than necessary to seek medical treatment, which can make their existing health concerns much worse. Various factors, such as cultural differences, financial constraints, and the perception that a disease or its symptoms would naturally resolve, contribute to the decision of certain individuals to forgo official medical intervention (25).

Every day, Bangladeshi FDMNs face malnutrition and a lack of healthcare (26); this phenomenon is not uncommon in other cultures as well (27). Low income (28), illiteracy, and cultural beliefs that prohibit medical treatment exacerbate these issues. This study found that many FDMN and host communities practice spiritual healing and herbal medicine for their children. The Haider et al. study validates our findings, showing that herbal and spiritual treatments, imams, and religious leaders are often sought instead of medical care (11). This dependence on traditional techniques and spiritual healing suggests focused measures to raise knowledge of the benefits of professional medical care and reduce delays in obtaining treatment for severely wasted youngsters.

In both communities, caregivers sought informal treatment for diarrhea, fever, cold, and cough from pharmacies, according to our study that aligns with the research findings that were conducted in African settings, Nigeria (29). This study identified several barriers to seeking formal treatment, including limited accessibility to and availability of formal healthcare facilities, transportation challenges, and long distances. Furthermore, family members and neighbors played a role in influencing the decision to seek care from informal or alternative healthcare providers. Another study also has reinforced our findings in the context of FDMN and host populations in that they seek services from pharmacies, particularly for illnesses like fever, diarrhea, and common cold or cough (28, 30).

Parents, usually women from the host community, know the value of facility-based care but cannot actively seek it due to societal traditions since their community rejects hospital-based delivery (31). Additionally, FDMN camp residents must deal with healthcare facilities. FDMN refugees report a lack of medical facilities and qualified medical staff in several camps (32). Because of this, many FDMNs travel far to get medical care, which can be difficult. Globally, this phenomenon is not infrequent, and prior studies have also demonstrated that transportation expenses play a significant role in accessing formal healthcare services (33).

The findings of this study provide valuable insights into the challenges faced by caregivers in seeking formal healthcare for wasted children among the FDMN communities and their host communities. The initial formal contact for wasted children differed between the two communities, with the integrated nutrition facilities (INF) being the primary point of contact for the FDMN camps and the community clinic serving as the initial point of contact for the host communities. One significant observation was that caregivers in both communities were often unaware that their children required treatment for wasting. This lack of awareness necessitates improved health education and awareness campaigns targeting caregivers to enhance their understanding of wasting and its associated risks. The study highlights a widespread deficiency in health literacy, specifically in relation to the management of common ailments like as diarrhea. This finding is of significant significance within the context of the study's environment (33). Nevertheless, the enhancement of consciousness regarding the significance of health literacy (34) and the acquisition of dietary knowledge among carers may contribute to the attainment of the aforementioned advantage (35). Language barriers were identified by FDMN caregivers seeking medical care outside of INFs. Communication difficulties made healthcare providers' diagnoses and treatment options unclear to caregivers. Research suggests using interpreters and translators in healthcare to help different populations understand medical information (34, 35).

Our investigation identified triggers that lead caregivers to formal therapy. One was the treatment result. When traditional healers or informal remedies failed to improve wasted children's health, concerned family and neighbors recommended caregivers to seek formal healthcare. Social support and community impact decision-making about formal care for wasting children.

As a result of their forced displacement and the cultural beliefs to which they adhere, the FDMNs in Bangladesh have a wide range of difficulties in seeking care for their wasted children. On the other hand, the host communities who are also suffering from resource constraints for hosting the FDMN communities, also need support for seeking timely and appropriate care for their wasted children. Our study suggests that increased engagement of community volunteers to caregivers can be crucial in the early detection of severely wasted children. Therefore, it will reduce the delay in treatment-seeking in both the FDMN and their nearest communities.

Limitations of the study

There are various limitations inherent in our investigation. The study design employed in this research facilitated the identification of primary themes across participant groups. However, it should be noted that our design does not provide a means to quantify the frequency of these themes or establish a hierarchical ranking based on their level of significance. Furthermore, it should be noted that due to resource constraints, our study was unable to recruit a larger number of focus groups representing each demographic stratum, hence limiting our capacity to thoroughly compare responses across subgroups. While our efforts were focused on creating comprehensive interview guidelines that may potentially generate applicable replies in other contexts, it is important to acknowledge that the cultural nuances inherent in this study may not necessarily be transferable to different settings.

Recommendation of the study

The findings obtained from this study will be utilized to inform a further quantitative investigation, which will be done and modified across several contexts to enhance contextual validity.

Conclusion

Findings indicate that in both communities, cultural beliefs, household affordability, and accessibility to healthcare facilities prompt caregivers to seek care from various categories of healthcare providers, as is typically observed in a pluralistic healthcare system. Therefore, it is essential to implement solutions based on the presented findings and recommendations, with the potential for further investigation to mitigate future challenges.

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 humans were approved by the Ethical Research Committee under the Institutional Review Board of icddr,b. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

NN and MR conceptualized the study, drafted the original manuscript, and revised the final version of the manuscript. MR, AA, GK, and IM had contributed to data analyses. MI, MuM, FS, MZM, MS, and TA critically reviewed the manuscripts. 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/fnut.2023.1252657/full#supplementary-material

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Individual and combined association between nutritional trace metals and the risk of preterm birth in a recurrent pregnancy loss cohort

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Background: Recurrent pregnancy loss (RPL) was associated with an elevated risk of pregnancy complications, particularly preterm birth (PTB). However, the risk factors associated with PTB in RPL remained unclear. Emerging evidence indicated that maternal exposure to metals played a crucial role in the development of PTB. The objective of our study was to investigate the individual and combined associations of nutritional trace metals (NTMs) during pregnancy with PTB in RPL.

Methods: Using data from a recurrent pregnancy loss cohort ($n = 459$), propensity score matching (1:3) was performed to control for covariates. Multiple logistic regression and multiple linear regression were employed to identify the individual effects, while elastic-net regularization (ENET) and Bayesian kernel machine regression (BKMR) were used to examine the combined effects on PTB in RPL.

Results: The logistic regression model found that maternal exposure to copper (Cu) (quantile 4 [Q4] vs. quantile 1 [Q1], odds ratio [OR]: 0.21, 95% confidence interval [CI]: 0.05, 0.74) and zinc (Zn) (Q4 vs. Q1, OR: 0.19, 95%CI: 0.04, 0.77) was inversely associated with total PTB risk. We further constructed environmental risk scores (ERSs) using principal components and interaction terms derived from the ENET model to predict PTB accurately ($p < 0.001$). In the BKMR model, we confirmed that Cu was the most significant component (PIP = 0.85). When other metals were fixed at the 25th and 50th percentiles, Cu was inversely associated with PTB. In addition, we demonstrated the non-linear relationships of Zn with PTB and the potential interaction between Cu and other metals, including Zn, Ca, and Fe.

Conclusion: In conclusion, our study highlighted the significance of maternal exposure to NTMs in RPL and its association with PTB risk. Cu and Zn were inversely associated with PTB risk, with Cu identified as a crucial factor. Potential interactions between Cu and other metals (Zn, Ca, and Fe) further contributed to the understanding of PTB etiology in RPL. These findings suggest opportunities for personalized care and preventive interventions to optimize maternal and infant health outcomes.

KEYWORDS

preterm birth, recurrent pregnancy loss, nutritional trace metals, Bayesian kernel machine regression, metal mixture

1 Introduction

Recurrent pregnancy loss (RPL), commonly defined as experiencing two or more consecutive failed clinical pregnancies, has emerged as a critical public health concern (1). Recent evidence suggest the association of RPL with an elevated incidence of adverse pregnancy outcomes, notably preterm birth (PTB) (2). Previous studies have reported that the occurrence of PTB in RPL ranged from 4.9% to 19.6%, significantly higher than the general population (3). However, the precise risk factors for PTB in RPL remained unclear. Growing evidence suggested that prenatal exposure to metals may exert a noteworthy influence on PTB (4, 5). Thus, in our study, we sought to explore whether exposure to nutritional trace metals (NTMs) also played a pivotal role in PTB among women with RPL.

A mounting body of evidence indicated the significant involvement of metal exposure in the development of PTB (6–13). Previous studies have primarily focused on investigating the individual effects of endocrine-disrupting or nutritional trace metals on the subsequent risk of PTB (14–18). However, adopting a "single metal" approach may not fully capture the complexity of interactions among metals. Instead of examining individual metal exposure, assessing the effects of multiple metal exposure, which offered a more comprehensive view of intricate interactions, non-linear associations, and combined effects, maybe more relevant and useful in predicting PTB (19).

Among previous studies that have examined maternal metal exposure in relation to PTB, only a few have evaluated the combined effects, and no study has investigated this association in RPL. Furthermore, these studies have yielded conflicting results. For instance, in a prospective cohort study, Wang et al. reported positive associations between magnesium (Mg), copper (Cu), and titanium (Ti) and PTB, while calcium (Ca), zinc (Zn), strontium (Sr), iron (Fe), and lead (Pb) showed negative associations (12). In a prospective birth cohort in rural Bangladesh, Huang et al. identified titanium (Ti), arsenic (As), and barium (Ba), which were detected in cord serum, as crucial predictors of PTB (7). Moreover, in the PROTECT cohort in Northern Puerto Rico, Ashrap et al. reported that lead (Pb), manganese (Mn), and zinc (Zn) detected in maternal blood were associated with an increased risk of PTB (6). However, Ren et al. indicated that Fe and Zn in hair had the strongest inverse effects on spontaneous PTB (13). In conclusion, the association between metal exposure and preterm birth varied with sample type, sampling time, composition of metal mixture, and statistical models.

Existing studies have mainly focused on the toxic effects of endocrine-disrupting metals. However, the effects of NTMs deserve attention, as they can be influenced by prenatal nutritional supplements and diet (20, 21). Additionally, maternal blood reflected long-term effects more accurately and was less susceptible to external impurities (22, 23). Other limitations from previous studies included the use of the single-metal model, which may not fully capture complicated interactions, non-linear associations, and combined effects (24). Finally, no studies have reported the association between NTMs and PTB in RPL.

To address these research gaps, our study aimed to investigate the association between NTMs in maternal blood and PTB in a RPL cohort in Northeast China. We hypothesized that there would be an inverse association between NTMs and the risk of PTB in RPL.

2 Materials and methods

2.1 Study population

We utilized data from the "Recurrent Pregnancy Loss Cohort Study (RPLCS)", a sub-cohort of China Medical University Birth Cohort (CMUBC). The RPLCS was designed to examine the association between adverse exposure and mother–infant outcomes. In brief, we mainly recruited pregnant women with a history of RPL between May 2018 and January 2023 from Shengjing Hospital of China Medical University, which admitted the largest population of RPL patients in Northeastern China. We enrolled pregnant women who met the following inclusion criteria: women who were planning to conceive or had already conceived; had a history of pregnancy loss ($\geq$2); without any mental disease; and agreed to participate in the project and follow-up. After the screening process, 1,588 women were deemed eligible to participate, out of which 947 agreed to participate. For the current analysis, we excluded non-RPL cases ($n = 55$), those with uterine anatomical abnormalities ($n = 89$), ineffective treatment of immune and endocrine abnormalities during pregnancy ($n = 126$), mother-paired loss to follow-up ($n = 31$), multiple pregnancies ($n = 65$), pregnancy termination (birth defects, abortions, or intrauterine deaths) ($n = 116$), and chronic diseases ($n = 6$). As a result, 459 singleton mother–infant pairs were included in the final analysis.

At the enrollment visit, face-to-face interviews were conducted using structured questionnaires administered by trained doctors to collect information on demographic and socioeconomic status and medical history. Subsequently, we collected the information from medical records and prospectively followed up until delivery, pregnancy termination, or loss of follow-up. Participants were followed up at 19.6 ($\pm$3.58) weeks of gestation for the detection of NTMs in maternal blood, including Cu, Zn, Fe, Mg, and Ca. All participants provided written informed consent, and the ethics committee of China Medical University approved the study.

2.2 Exposure: nutritional trace metals

Nutritional trace metals (Zn, Cu, Fe, Ca, and Mg) were detected in the second trimester (pregnancy weeks: 19.6 $\pm$ 3.58) in maternal blood. Sample collection, preservation, and detection were performed at the Central Laboratory of Shengjing Hospital of China Medical University. Detailed methods including: using atomic absorption spectrometry to measure the concentrations of Zn, Cu, and Fe and the methane-based xylenol blue (MXB) color development method and molybdate direct method to measure the concentrations of Ca and Mg separately (25). The NTMs were measured using the atomic absorption spectrometer system BH5300S (Boya (Beijing), China) and the ARCHITECT automated biochemical analysis system c16000 (Abbott, USA). The protocol was qualified by the China Metrology Accreditation (CMA) system.

The units for Zn, Cu, and Fe were μmol/L, while the units for Ca and Mg were mmol/L. We converted the detection results to units of μg/L by multiplying with the molecular mass, enabling comparison with other studies. In the subsequent analysis, we transformed the continuous concentrations into quantiles.

2.3 Outcomes: preterm birth in RPL

The gestational week was calculated and corrected based on an ultrasound examination. In China, RPL was defined as two or more consecutive abortions (26). PTB was defined as a case group with a live birth within a gestational age between 28 and 36^{+6} weeks. Two subtypes of PTB were further distinguished: spontaneous preterm birth (sPTB) and iatrogenic preterm birth (iPTB) (27). Iatrogenic preterm birth refers to pregnancies that require early termination of pregnancy due to obstetric complications or medical comorbidities. Thus, we considered a successful pregnancy with PTB in RPL as the primary outcome. Conversely, women who delivered at ≥37 weeks in RPL were regarded as controls.

2.4 Covariates

The demographic and socioeconomic status and medical history of participants were collected at the time of recruitment. Pregnant women provided information about their age at enrollment, educational attainment, household income per month, and detailed adverse pregnancy histories through interviewer-administered questionnaires. We treated maternal age, pre-pregnancy BMI, spontaneous abortion frequency, and gestational weeks of detection as continuous variables. We categorized maternal educational attainment into three groups (senior high school or below, university or college, and postgraduate or above); household income per month (Chinese Yuan, ¥) into three groups (≤7,000, 7,000–<10,000, and >10,000); calcium supplement into four groups (600 mg qd, 600 mg bid, 600 mg tid, and unknown); iron supplement into two groups (yes vs. no); gender of infants into two groups (male vs. female); and hypertensive disorders in pregnancy (yes vs. no). We calculated pre-pregnancy body mass index (BMI) by dividing weight (kilograms) by the square of measured height (meters) and treated pre-pregnancy BMI as continuous variables (28).

2.5 Statistical analysis

To reduce heterogeneity in our study, we implemented propensity score matching (PSM) with a 1:3 protocol to minimize selection bias and control for potential covariates. Maternal age, gestational weeks of detection, pre-pregnancy BMI, education attainment, household income per month, calcium supplement usage, iron supplement usage, and number of abortions were used as matching factors. We adopted the nearest neighbor score matching principle and excluded four unmatched cases. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were reported as frequency (percentage). We compared PTB and control groups using the non-parametric test and the chi-square (χ^2) test. Subsequently, we used the multiple logistic regression model to assess the association by calculating crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) for PTB and sPTB in RPL. Furthermore, the multiple linear regression model was also utilized to evaluate the association between concentrations of NTMs and gestational weeks of delivery.

To produce accurate estimates and avoid collinearity, we utilized elastic-net regularization (ENET) to identify significant metals as prediction markers (29). ENET combined the strengths of the Lasso and Ridge models, providing enhanced prediction power. For the ENET regression, we demonstrated the optimal values of α and λ through 10-fold cross-validation, aiming to minimize misclassification error. In this analysis, we only penalized the metal variables, while the covariates (same as the single-metal model) were included in the model. The NTMs with non-zero coefficients from the ENET model represented the key contributors driving the associations with PTB. Subsequently, we extracted the important components and interaction terms to calculate the environmental risk scores (ERSs) (30). We constructed the K–M survival analysis model to assess the association between ERSs and PTB in RPL, using PTB as the survival outcome and gestational week of delivery as the survival time.

Before establishing the BKMR model, we applied ln-transformation to the concentrations of NTMs (22). Bayesian kernel machine regression (BKMR) was utilized to estimate the overall effect, identify key components in the mixture driving the associations with PTB in RPL, capture the potential non-linear relationships, and identify interactions between the NTMs (31). The posterior inclusion probabilities (PIPs) can gauge the importance of each NTM. Variables with PIP values greater than 0.5 were considered statistically significant. We conducted component-wise variable selection for the five metals and evaluated the individual and combined effects with 50,000 iterations of the Markov chain Monte Carlo (MCMC) sampler (8). Furthermore, we validated the stability of our conclusions using the ROC curves. Additionally, we constructed the product of Zn and Cu concentrations and employed logistic regression to assess the combined effect of these two metals on PTB in RPL. All analyses were performed using R 4.2.2 software (R Core Team, Austria) and the following packages: MatchIt (version 4.5.0), glmnet (version 4.1.6), BKMR (version 0.2.2), and pROC (1.18.4).

3 Results

3.1 Characteristics of participants

In our study, 459 singleton mother–infant pairs were included in the final analysis (Figure 1). Moreover, 8.3% of participants experienced preterm birth (38 out of 459 participants). After applying propensity score matching (PSM) in a 1:3 ratio, some participants dropped out due to a lack of appropriate matching. At last, we included 94 controls and 34 PTB patients in the final analyses. Compared with term delivery, those with PTB had a slightly higher BMI (22.8 ± 3.65 vs. 23.9 ± 3.48) and were more likely to have lower levels of educational attainment

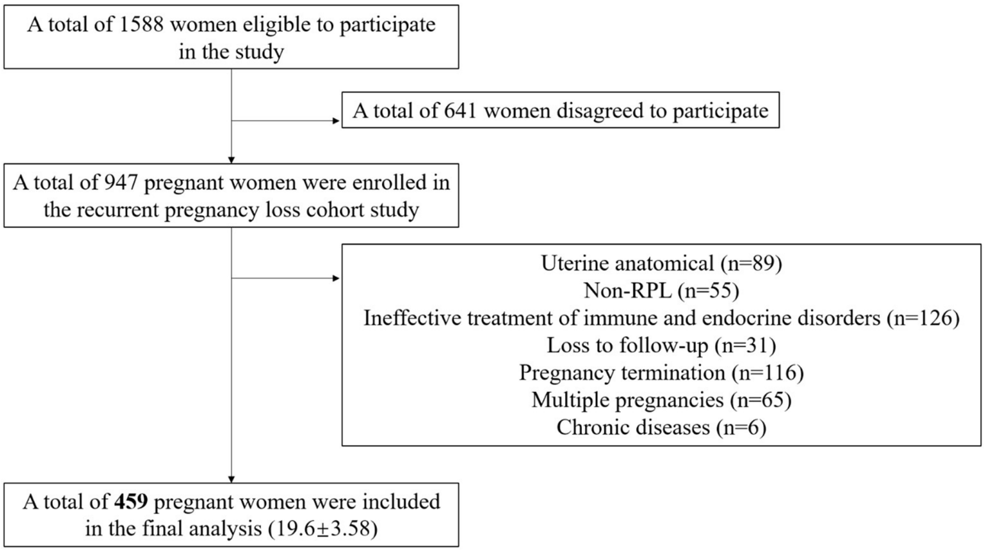

FIGURE 1
Flow chart.

(frequency of senior high school or below: 16.4% vs. 31.6%) and showed a lower likelihood of using iron supplements (11.4% vs. 0) in the total population. In the PTB group, participants tended to have more hypertensive disorders in pregnancy (5.9% vs. 18.4%). However, there were no significant differences in age at enrollment, household income per month, calcium supplement usage, or gestational weeks of detection between the two groups. We used PSM to minimize selection bias and avoid collinearity. In the PSM sets, no significant differences were observed between women with and without PTB in RPL (Table 1). The detailed concentration of NTMs in the included participants is presented in Supplementary Table S1. Additionally, we compared the concentrations of the NTMs with previous studies, as shown in Supplementary Table S2.

3.2 Single NTM and PTB in RPL: multiple logistic and linear regression models

Table 2 shows the associations between individual NTM and PTB risk in RPL, which are assessed using the multiple logistic regression model. The crude model (Model 1) was derived without controlling for covariates. After adjusting for potential covariates (Model 3), we observed that higher concentrations of Cu (quantile 4 [Q4] vs. Q1, odds ratios [OR]: 0.21, 95%CI: 0.05, 0.74; Q3 vs. Q1, OR: 0.23, 95%CI: 0.06, 0.79) and Zn (Q4 vs. Q1, OR: 0.19, 95%CI: 0.04, 0.77) were associated with a lower probability of PTB. However, no significant associations were found for other single exposures (Fe, Ca, and Mg). Similar results were obtained when associations between individual NTM exposure and sPTB in RPL were assessed. The concentration of Cu was associated with a lower risk of sPTB in RPL (Q4 vs. Q1, OR: 0.05, 95%CI: 0.002, 0.40; Q3 vs. Q1, OR: 0.22, 95%CI: 0.04, 0.9). However, consistent results were not observed for Zn in sPTB in RPL.

We further investigated the association between individual NTM and gestational weeks of delivery using the multiple linear regression model (Table 3). In the adjusted model (Model 3), the concentrations of Zn (β: 0.08, 95%CI: 0.06, 0.11, $p < 0.05$) and Cu (β: 0.32, 95%CI: 0.25, 0.38, $p < 0.05$) were positively associated with gestational weeks of delivery.

3.3 Multiple NTMs and PTB in RPL: elastic-net regularization model (ENET)

In the ENET model, we determined the main components and interaction terms using the ln-transformed and scaled values of the nutritional trace metals concentrations while adjusting for the same covariates in the single-metal model. λ and α were determined as 0.03795 and 0.9, respectively, through 10-fold cross-validation (Supplementary Figure S1). As shown in Figure 2A, the ENET model revealed non-zero coefficients ($\beta \neq 0$) for three individual components and three interaction terms after adjustment for covariates. Two metals (Zn and Cu) were inversely associated with PTB in RPL ($\beta < 0$), while Mg exhibited a positive association with PTB in RPL ($\beta > 0$). Notably, Cu showed the largest magnitude of β coefficient ($\beta = -0.382$), signifying the change in log-odds of PTB per increment in standardized ln-transformed and scaled metal concentrations. In addition, Cu demonstrated significant interactions with Ca ($\beta = 0.283$), Zn ($\beta = 0.277$), and Fe ($\beta = 0.066$), all of which were positively associated with PTB in RPL. For further analyses, we constructed environmental risk scores (ERSs) according to the fitted ENET model and categorized individual ERSs into quartiles. As shown in Figure 2B, higher ERSs values were significantly associated with shorter gestational weeks of delivery in the K–M survival analysis.

TABLE 1 Demographic characteristics of participants according to the case and control group in RPL.

Variables	All participants			Propensity score-matched sets		
	Control ($n = 421$)	Preterm birth ($n = 38$)	p value[a]	Control ($n = 94$)	Preterm birth ($n = 34$)	p value[a]
Age (years)	33.0 ± 4.8	32.9 ± 3.6	0.93	32.7 ± 3.75	33.5 ± 3.27	0.30
BMI (kg/m^2)	22.8 ± 3.65	23.9 ± 3.48	0.07	22.9 ± 3.38	23.3 ± 3.33	0.55
Educational level (%)			0.07			0.91
Senior high school or below	69 (16.4)	12 (31.6)		22 (23.4)	7 (21.2)	
University or College	325 (77.2)	25 (65.8)		68 (72.3)	25 (75.8)	
Postgraduate or above	27 (6.4)	1 (2.6)		4 (4.3)	1 (3.0)	
Household income per month (CNY)			0.52			0.75
≤7,000	141 (32.8)	14 (36.8)		33 (35.1)	10 (30.3)	
7,000–<10,000	208 (49.4)	20 (52.6)		47 (50.0)	19 (57.6)	
>10,000	77 (17.8)	4 (10.5)		14 (14.9)	4 (12.1)	
Calcium supplement usage (%)			0.99			NA
600 mg bid	231 (54.9)	14 (55.3)		150 (35.2)	14 (35.9)	
600 mg qd	146 (34.7)	21 (36.8)		232 (54.5)	21 (53.8)	
600 mg tid	42 (10.0)	4 (7.89)		42 (9.9)	4 (10.3)	
Unknown	2 (0.4)	0 (0.0)		2 (0.5)	0 (0)	
Iron supplement usage (%)			<0.05*			NA
Yes	48 (11.4)	0 (0)		49 (11.5)	0 (0)	
No	373 (88.6)	38 (100)		377 (88.5)	39(100)	
Number of abortions	2.29 ± 0.77	2.53 ± 0.89	0.12	2.41 ± 0.932	2.48 ± 0.834	0.69
Gestational weeks of detection	19.6 ± 3.55	19.6 ± 3.63	0.80	19.4 ± 3.35	19.3 ± 3.78	0.85
Gestational hypertension			<0.05*			0.77
Yes	25 (5.9)	7 (18.4)		12 (12.8)	5 (14.7)	
No	396 (94.1)	31 (81.6)		82 (87.2)	29 (85.3)	

[a]Nonparametric test and chi-square (χ^2) test between the control and case groups.
BMI, body mass index.
*$p < 0.05$.

3.4 Multiple NTMs and PTB: Bayesian kernel machine regression

We first identified the significant metal components in the mixture and assessed their individual and combined effects on PTB in RPL in the BKMR model using the ln-transformed concentrations. Supplementary Table S3 shows that two metals, Cu (PIP = 0.84724) and Zn (PIP = 0.81200), were selected as significant variables in the mixture with PIP values >0.5. Figure 3A illustrates the combined effects of the metal mixture (comprised of five metals) on the latent continuous binary outcome of PTB in RPL. The results indicated a decreasing trend in PTB risk as the cumulative level across all metal exposures increased, although the findings were not statistically significant ($p > 0.05$). The independent effect of each metal on the mixed exposure is shown in Figure 3B. Visually, when the concentrations of other metals were constantly fixed at their 25th and 50th percentiles respectively, Cu was still significantly associated with a lower risk of PTB in RPL. Univariate dose–response relationships were estimated to explore potential non-linear correlations. As shown in Figure 3C, when each metal was fixed at its median value, Zn exhibited a non-linear association with PTB. Moreover, Zn had a negative linear relationship with preterm birth at higher levels (the confidence intervals at lower and higher distributions are wide due to sparse data). Additionally, Figure 3D demonstrates the bivariate exposure-response functions for each pair of metals on PTB in RPL. Notably, when Cu was fixed at the 25th quantile, the slope between other metals (Zn, Fe, and Ca) and PTB was different from that when Cu was fixed at the 50th or 75th percentile, indicating the existence of potential interactions between Cu and other metals (Zn, Fe, and Ca). To validate the combined effect of Zn and Cu, we found that their interaction significantly reduced the risk of preterm birth (Q4 vs. Q1, OR: 0.14, 95%CI: 0.03, 0.54), as shown in Supplementary Figure S2. To validate the external applicability and robustness of our results, we conducted the ROC curve analysis (Supplementary Figure S3). The results indicated that total scores

TABLE 2 The association between single nutritional trace metal and preterm birth.

		Preterm birth (*n* = 34), OR (95%CI)			Spontaneous preterm birth (*n* = 19), OR (95%CI)		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Zn	Q1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Q2	1.00 (0.34, 2.90)	0.97 (0.31, 2.95)	0.97 (0.32, 2.96)	1.50 (0.38, 6.57)	1.28 (0.30,5.87)	1.28 (0.30,5.93)
	Q3	1.15 (0.40, 3.32)	1.16 (0.37, 3.72)	1.13 (0.35, 3.64)	1.83 (0.48, 7.86)	1.33 (0.30, 6.39)	1.44 (0.31, 7.23)
	Q4	0.23 (0.05, 0.85)*	0.22 (0.04, 0.85)*	0.19 (0.04, 0.77)*	0.38 (0.05, 2.13)	0.31 (0.04, 1.82)	0.28 (0.02, 1.83)
Cu	Q1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Q2	0.66 (0.23, 1.85)	0.60 (0.19, 1.82)	0.61 (0.19, 1.85)	0.48 (0.13, 1.64)	0.47 (0.11, 1.78)	0.43 (0.10, 1.63)
	Q3	0.34(0.10, 1.02)	0.25 (0.07, 0.84)*	0.23 (0.06, 0.79)*	0.32 (0.08, 1.16)	0.24 (0.05, 0.94)	0.22 (0.04, 0.90)*
	Q4	0.27 (0.08, 0.85)*	0.22 (0.05, 0.75)*	0.21 (0.05, 0.74)*	0.08 (0.00, 0.47)*	0.05 (0.00, 0.38)*	0.05 (0.002, 0.40)*
Fe	Q1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Q2	0.38 (0.11, 1.23)	0.39 (0.10, 1.34)	0.35 (0.09, 1.24)	0.28 (0.04, 1.37)	0.23 (0.03, 1.27)	0.21 (0.03, 1.20)
	Q3	0.67 (0.22, 1.95)	0.65 (0.20, 2.08)	0.63 (0.19, 2.02)	0.61 (0.14, 2.42)	0.55 (0.12, 2.36)	0.53 (0.11, 2.37)
	Q4	0.91 (0.32, 2.58)	0.88 (0.27, 2.82)	0.85 (0.26, 2.78)	1.17 (0.34, 4.16)	1.06 (0.26, 4.40)	1.04 (0.24, 4.61)
Ca	Q1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Q2	1.49 (0.49, 4.71)	1.55 (0.47, 5.34)	1.56 (0.47, 5.41)	1.25 (0.33, 4.86)	1.16 (0.27, 5.04)	1.20 (0.28, 5.17)
	Q3	1.00 (0.30, 3.33)	0.73 (0.20, 2.68)	0.74 (0.20, 2.75)	0.80 (0.18, 3.37)	0.59 (0.11, 2.82)	0.63 (0.12, 3.09)
	Q4	1.79 (0.58, 5.73)	1.62 (0.50, 5.49)	1.60 (0.49, 5.45)	1.00 (0.22, 4.27)	0.86 (0.18, 3.86)	0.84 (0.17, 3.83)
Mg	Q1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Q2	0.84 (0.26, 2.67)	0.81 (0.24, 2.70)	0.84 (0.24, 2.85)	0.39 (0.05, 1.96)	0.38 (0.05, 2.08)	0.47 (0.06, 2.67)
	Q3	1.69 (0.54, 5.30)	1.57 (0.48, 5.25)	1.67 (0.50, 5.67)	1.20 (0.27, 5.14)	0.86 (0.17, 4.00)	1.07 (0.21, 5.26)
	Q4	1.61 (0.54, 4.90)	1.74 (0.55, 5.72)	1.73 (0.53, 5.70)	2.06 (0.60, 7.68)	1.84 (0.48, 7.49)	2.05 (0.53, 8.56)

Table analyzed using multiple logistic regression.
Model 1: crude model.
Model 2: adjusted for age, BMI, educational attainment, household income per month.
Model3: adjusted for Model 2 + number of abortions + hypertensive disorders in pregnancy.
OR, odds ratio; Q1, quantile 1; Q2, quantile 2; Q3, quantile 3; Q4, quantile 4; Zn, zinc; Cu, copper; Mg, magnesium; Ca, calcium; Fe, iron; BMI, body mass index.
*$p < 0.05$.

TABLE 3 The association between single nutritional trace metal and gestational weeks of delivery.

Metal	Gestational weeks of delivery (weeks)		
	Model 1	Model 2	Model 3
Zn	0.14 (0.12, 0.17)*	0.09 (0.07, 0.12)*	0.08 (0.06, 0.11)*
Cu	0.22 (0.16, 0.29)*	0.30 (0.23, 0.36)*	0.32 (0.25, 0.38)*
Fe	0.04 (−0.03, 0.10)	0.00 (−0.06, 0.07)	0.00 (−0.07, 0.06)
Ca	−0.01 (−1.69 1.67)	−0.02 (−1.76, 1.71)	−0.03 (−1.77, 1.72)
Mg	−0.06 (−1.84, 1.73)	−0.05 (−1.89, 1.78)	−0.05 (−1.90, 1.79)

Table analyzed using multiple linear regression.
Model 1: crude model.
Model 2: adjusted for age, BMI, education attainment, household income per month.
Model3: adjusted for Model 2 + number of abortions + hypertensive disorders in pregnancy.
OR, odds ratio; Q1, quantile 1; Q2, quantile 2; Q3, quantile 3; Q4, quantile 4; Zn, zinc; Cu, copper; Mg, magnesium; Ca, calcium; Fe, iron; BMI, body mass index.

calculated by PIPs held predictive value in the overall population, particularly among mothers delivering female infants (AUC: 0.66, 95% CI:0.53, 0.79).

4 Discussion

In our study, we employed multiple logistic regression, multiple linear regression, elastic-net regularization model, and Bayesian kernel machine regression model to investigate the associations between maternal NTMs in the second trimester and PTB in RPL. Across all these methods, Cu was consistently identified as the most significant component among the NTMs and exhibited an inverse association with PTB in RPL. Furthermore, Cu showed a potential interaction with Ca, Zn, and Fe in the ENET and BMKR models. Moreover, the non-linear relationship between Zn and PTB was found in the BKMR model. Finally, we used K–M survival analysis and ROC curve analysis to assess the robustness of our results.

The study identified Cu as the most important factor among NTMs for PTB in RPL, which was similar to the previous findings in non-RPL. For instance, in a case–control study in Iran, Gohari et al. reported that Cu and Zn serum levels in mothers with preterm delivery were significantly lower than in mothers with term delivery (32). However, the sample collection was conducted at delivery, not in the second trimester. Moreover, Li et al. reported that lower Cu levels in the umbilical cord had

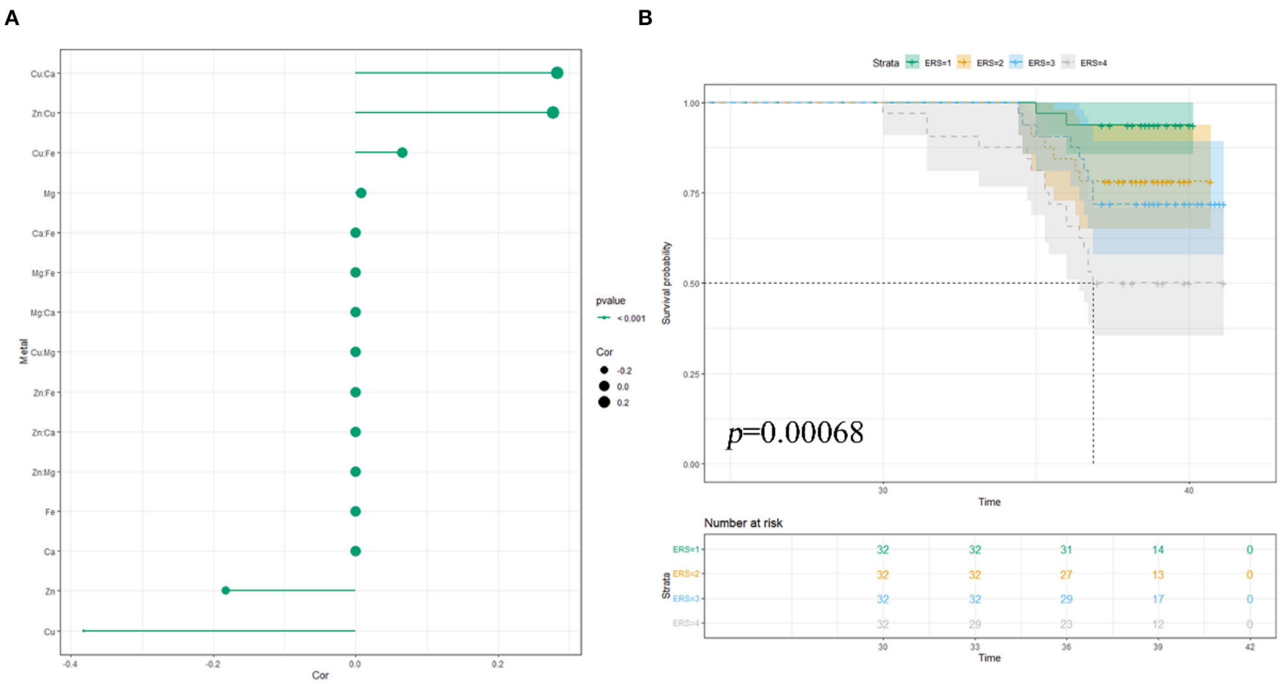

FIGURE 2
Multiple NTMs and preterm birth in RPL: elastic-net regularization model: **(A)** coefficient chart; **(B)** K–M survival analysis; model was adjusted for pre-pregnancy BMI, educational attainment, household income per month, age, number of abortions, and hypertensive disorders in pregnancy.

a significantly higher risk of PTB (OR: 5.06, 95%CI:2.74, 9.34) and early-term birth (OR:1.36, 95%CI:1.10, 1.69) (33). No studies demonstrated the association between lower Cu levels in maternal blood in the second trimester and PTB in RPL. There were some inconsistent findings with our results. For example, Ashrap et al. confirmed no statistically significant association between maternal blood concentrations of Cu in the second trimester and PTB (6). Additionally, Hao et al. reported that serum Cu concentrations in the first trimester were positively associated with spontaneous PTB in a prospective cohort study in China (14). A recent meta-analysis showed that women with pregnancy loss showed significantly lower Cu concentrations than normal pregnant women, which demonstrated that Cu homeostasis was negatively associated with pregnancy loss (SMD = −1.42, 95% CI: −1.97 to −0.87, $p < 0.001$) (34). Furthermore, in the LIFECODES birth cohort, Kim et al. reported that maternal urinary Cu in the third trimester was associated with an increased risk of PTB (10). A possible reason might be attributed to differences in sample types and specific trimesters. Compared with our study in RPL [median (IQR): 1,131.92 (1,123.49, 1,520.66), μg/L], the investigations conducted by Ashrap et al. [mean (SD): 1,622 ± 1.25, μg/L] and Hao et al. [median (IQR): 1,720 (1,360, 1,980), μg/L] exhibited higher Cu (Cu) concentrations in their populations (6, 14). Conversely, Li et al. observed relatively lower Cu concentrations [median (IQR): 298.2 (123.1, 699.6), μg/L] in their study, akin to our findings (33). In other words, there may be a tendency toward an association between Cu and PTB. Low-dose exposure increases the risk of PTB; however, high-dose exposure may also elevate the risk of PTB. Previous studies indicated that increasing urinary Cu levels were associated with higher oxidative stress biomarkers (35). Excessive Cu excretion in urine led to insufficient antioxidant capacity, which might represent an important etiology for PTB. Recent studies have also shown that Cu deficiency is more prevalent in adult women than men in China (36). Therefore, the adverse effects of low Cu levels or even Cu deficiency on pregnancy outcomes deserved significant attention, especially for RPL.

Cu is an essential mineral that plays a crucial role in various physiological processes (37). The mechanisms underlying how lower levels of Cu contributed to PTB were multifaceted. Infection and aseptic inflammation were the main causes of PTB (38). Moreover, Cu was intricately involved in the development of immune cells and the signal transduction of immune responses. Thus, lower levels of Cu can lead to immune cell dysfunction and an increased risk of infection (39, 40). Furthermore, Cu played a significant role in neutralizing harmful free radicals and reducing oxidative stress (41, 42). As a component of enzyme structures, Cu was also essential in the synthesis of elastin and collagen, which contributed to enhancing uterine elasticity (43). Additionally, Cu was involved in the production of nitric oxide (NO) and angiogenesis, which helped regulate blood vessel dilation and blood flow to the uterus (44, 45). Interestingly, PTB and low-birth-weight infants tended to have lower Cu levels at birth, which may be related to maternal exposure to Cu deficiency. Understanding these mechanisms was important for developing effective strategies to prevent and manage PTB in RPL associated with Cu homeostasis (46).

Our findings unveiled a potential non-linear correlation between Zn concentrations and the risk of PTB in RPL. In a similar vein, Ashrap et al. demonstrated a comparable U-shaped pattern in Zn concentration, yet their findings indicated an association of

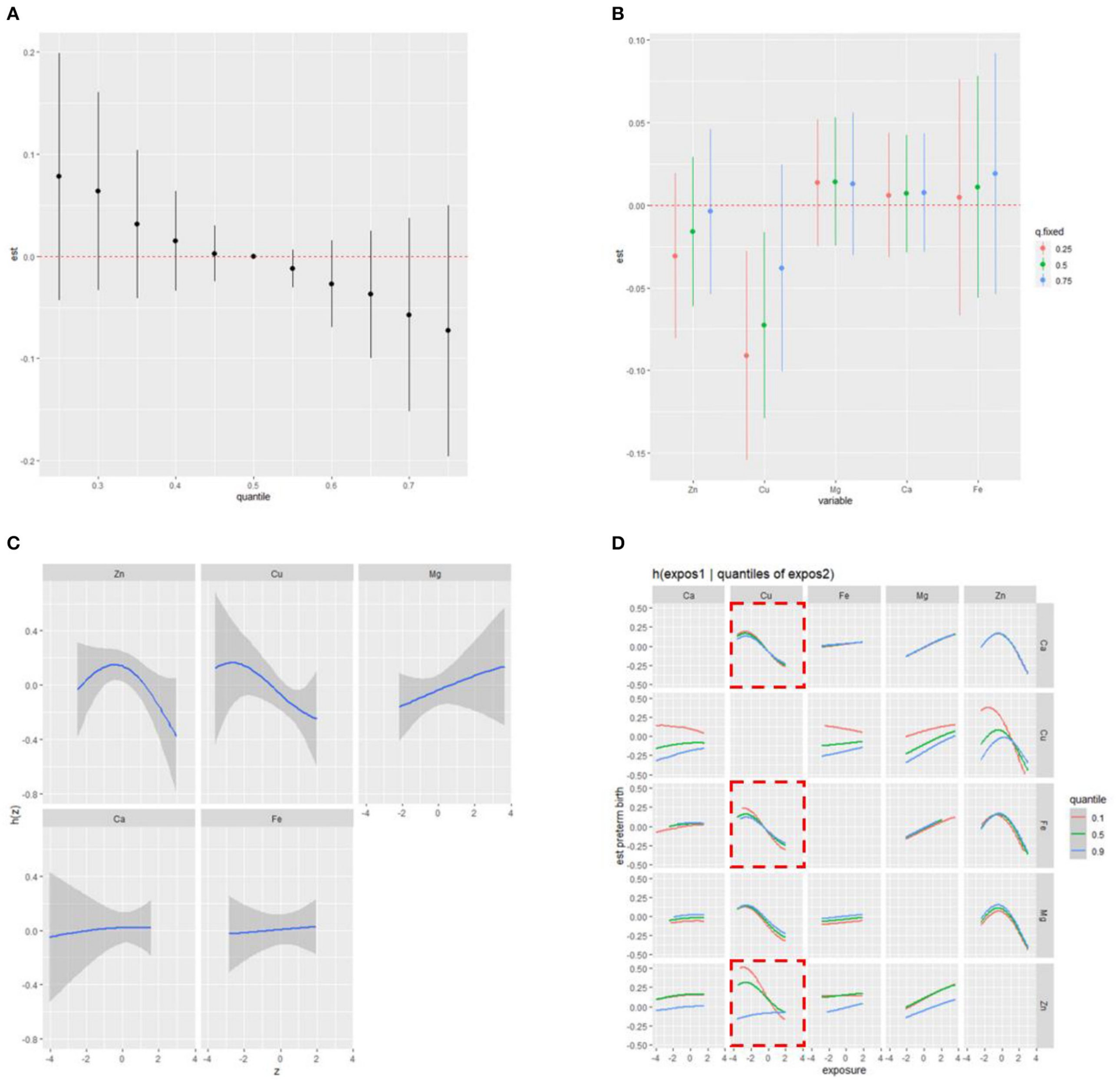

FIGURE 3
Combined effect of the NTMs on preterm birth in RPL estimated by BKMR **(A)** overall effect of NTMs on preterm birth (estimates and 95%CI); **(B)** independent effect of NTMs on preterm birth (estimates and 95%CI); **(C)** univariate cross-section (non-linear relationship); **(D)** bivariate exposure-response functions for each of two metals on preterm birth; model was adjusted for pre-pregnancy BMI, educational attainment, household income per month, age, number of abortions, and hypertensive disorders in pregnancy.

higher concentrations with an increased risk of PTB (6). These non-linear patterns indicated that both excessive and insufficient exposure might have an impact on PTB, which underscored the intricacies of micronutrient interactions and their potential influence on pregnancy outcomes. Another important finding in our study was the potential interactions of Cu with Zn, Fe, and Ca, as revealed by both the ENET and BKMR models in RPL. This was consistent with the study by Liu et al., who reported similar potential interactions between Zn and Cu with PTB in non-RPL (8). The antagonistic relationship between Zn and Cu and PTB has been extensively studied. For example, Baecker et al. observed that Cu supplementation in pregnant female rats led to a significant decrease in brain Zn levels, particularly in the hippocampus (47). Furthermore, Kinnamon reported competition between Cu and Zn in the fetus and placenta, indicating the importance of optimizing the ratio of these elements during pregnancy to enhance reproductive outcomes (48). Interestingly, another case–control study conducted by Priya et al. demonstrated potential interactions between Fe and Cu in the case of polycystic ovary syndrome (49). Andersen et al. proposed that Cu deficiency not only affected the concentration of Fe but also indirectly impacted Fe transporters, which affected the delivery of Fe to the fetus (50). From the perspective of utilization, nutrient metals play a crucial role as signal transduction molecules in the development of the immune system, blood formation, antioxidant stress, cell differentiation, and apoptosis (51). They were involved in a complex regulatory network that controls these physiological processes.

There were several strengths of our study. First, we employed a population-based cohort design in the context of RPL, which allowed us to capture a representative and special sample in northeastern China, enhancing the generalizability of our findings. Second, to ensure the reliability and validity of our results, we employed multiple statistical models. Specifically, we utilized logistic regression, linear regression, the ENET model, and the BKMR model. Each model had its own unique advantages and limitations. This comprehensive approach strengthened the robustness of our conclusions and provided a more comprehensive understanding of the associations between NTMs and PTB in RPL.

Our study had several limitations. First, the sample size of our study was limited due to the difficulty of recruitment, which constrained the assessment of the association between NTM deficiency and PTB. Second, we did not apply the same detection method to various metals, which was distinguished from previous studies; however, it does not affect the accuracy of the results (8). Third, the concentration of NTMs was only detected in the second trimester, which may not reflect the concentration status of the first and third trimesters. However, limited studies investigated the exposure to the second trimester of PTB. Finally, there could still be some potential covariates due to unmeasured factors, such as maternal dietary information.

5 Conclusion

To summarize, we have recognized the individual and combined associations between NTMs and the risk of PTB in RPL. Detailed investigations revealed that maternal blood Cu and Zn levels in the second trimester were inversely associated with PTB in RPL. Additional studies are warranted to confirm these associations in RPL and understand the mechanisms behind the risk of NTMs and PTB in RPL.

Data availability statement

Data presented in this study are available on request from the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of China Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YL contributed to conceptualization, software, formal analysis, writing—original draft, investigation, supervision, project administration, and data curation. TW contributed to writing—original draft, writing—reviewing and editing, and project administration. YG contributed to conceptualization and writing—reviewing and editing. HS contributed to writing—reviewing and editing and project administration. JL contributed to data curation and investigation. CQ contributed to conceptualization, supervision, and funding acquisition. All authors have read and agreed to the published version of 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1205748/full#supplementary-material

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Prevalence of malnutrition and its associated factors among 18,503 Chinese children aged 3–14 years

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Background: Child malnutrition places a major burden on global public health. We aimed to estimate the prevalence of child malnutrition and identify its potential factors among children aged 3–14 years from Beijing and Tangshan.

Methods: We cross-sectionally recruited 18,503 children aged 3–14 years from September 2020 to January 2022, according to a stratified cluster random sampling strategy. Child malnutrition was defined according to the World Health Organization criteria. Data were analyzed by STATA software and R language.

Results: The prevalence of malnutrition among 18,503 children was 10.93%. After multivariable adjustment, seven factors significantly associated with child malnutrition were parental education (adjusted odds ratio, 95% confidence interval, p: 1.52, 1.40 to 1.67, <0.001), family income (1.23, 1.16 to 1.30, <0.001), fast food intake frequency (1.14, 1.06 to 1.21, <0.001), night meals intake frequency (1.09, 1.04 to 1.15, <0.001), eating speed (1.01, 1.01 to 1.02, <0.001), maternal obesity (0.97, 0.95 to 0.99, <0.001), and paternal obesity (0.97, 0.96 to 0.98, <0.001). The seven significant factors had better prediction performance (area under the receiver operating characteristic, 0.956) for child malnutrition.

Conclusion: Approximately 10% of Chinese children aged 3–14 years were in malnutrition status, and seven factors were found to be significant predictors for child malnutrition.

KEYWORDS

malnutrition, children, prevalence, risk factor, association

Introduction

Child malnutrition, including stunting, wasting, and being underweight, is featured by inadequate or unbalanced intake of protein energy or nutrients, and it represents a public health issue, deserving special awareness (1). Statistics from the fund of the United Nations Children (UNICEF) and World Health Organization (WHO) show that 22.0% and 6.7% of children younger than 5 years were separately affected by stunting and wasting worldwide (2). In China, the prevalence of underweight and stunting in children younger than 5 years was estimated to be 3.6 and 9.9%, respectively (3), and the prevalence of malnutrition in 7–18-year-old children was 8.6% (4). The detrimental impact of child malnutrition is manifold because it can not only threaten survival, development, and growth of children but also undermine economic growth and national development (5). The causes of child malnutrition are complex, and no consensus has thus far been reached on its risk profiling.

It is widely accepted that besides factors relating to inheritance and diseases, child malnutrition is mainly caused by inadequate nutrient intake. Over the past decades, dietary patterns and modern lifestyles have undergone profound changes, along with the intensification of industrialization and urbanization in China (6), and we are experiencing significant public health challenges (7). Due to inadequate intake of vegetables and fruits, as well as excessive intake of red meat, oil, and salt, nutrition deficiency and nutrition imbalance have aroused extensive concerns (8, 9). There is evidence for the significant influence of parental dieting behavior affected by rhythm of life, family income and education on child dieting behavior, and weight status (10). Hence, identifying potential factors underlying child malnutrition to facilitate the development of personalized intervention and follow-up care is urgently needed. Some factors, such as parental obesity and eating habits, were reported to be associated with child malnutrition (11–13), whereas the majority of these association studies focused on only a few factors and were largely underpowered to provide reliable estimates.

To fill this gap in knowledge, a large cross-sectional survey of children of 3–14 years of age from Beijing and Tangshan estimated the prevalence of child malnutrition and identified factors that are independently associated with the risk of child malnutrition.

Methods

Study design

We conducted two cross-sectional surveys from September 2020 to January 2022. The first survey was performed in Beijing and Tangshan (in Hebei province) from September to December 2020, and the second in January 2022 in Pinggu district, Beijing.

According to the 2022 census data, there are approximately 21.8 million persons in Beijing and 7.7 million persons in Tangshan. There are 16 districts in Beijing and 7 districts in Tangshan. Beijing covers an area of 16,410 km^2, and Tangshan covers an area of 13,472 km^2. *Per capita* disposable income was 77,400 RMB in Beijing and 39,600 RMB in Tangshan.

Study participants

The selection process of study participants was reported previously (14, 15). Specifically, in the first survey, study participants were consisted of preschool-aged children attending junior to senior kindergarten classes. We randomly selected 4 out of 16 districts in Beijing and 2 out of 7 districts in Tangshan by using the stratified and cluster sampling methods. In total, 5 kindergartens were selected from each district, and 30 kindergartens were included finally. In the second survey, study participants included children attending primary school or junior high school. We randomly selected 26 schools, including 8 primary schools and 18 junior high schools, in Pinggu district, Beijing. In this study, data were collected from children aged 3–14 years in 30 kindergartens and 26 schools in Beijing and Tangshan.

Data collection

We collected data by self-designed questionnaires. To ensure reliability and validity, both questionnaires were separately distributed in 200 samples before formal circulation, and the reliability coefficient (alpha) was over 0.85.

We integrated the items from both questionnaires, covering four main areas as follows: (i) demographic area: age, sex, nationality, date of birth, height, weight, and food and drug allergy; (ii) fetal and neonatal area: birth body length, gestational age, delivery mode, pregnancy order, delivery order, assisted reproduction, twin birth, infancy feeding, breastfeeding duration, and time of adding solid food; (iii) lifestyle-related area: sitting time, screen time, outdoor activity time, sleep duration, fall asleep time, eating speed, number of dental caries, and weekly intake frequencies of sweet food, night meals, and fast food; (iv) family-related area: parental age, parental weight, parental height, parental education, and family income. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

The questionnaires were generated by the "Wenjuanxing" website.[1] As an online platform in China, the "Wenjuanxing" can yield a unique QR code for each questionnaire. The QR code can be recognized by smartphones and was sent to the parents or guardians by teachers-in-charge via the "WeChat" social media application. The "Wenjuanxing" platform automatically integrated data from individual questionnaires as an Excel spreadsheet, which can be downloaded for analysis.

Quality control

Before the distribution of questionnaires, healthcare physicians and teachers-in-charge selected in this survey from all schools and kindergartens were trained to be familiar with the survey procedures and each item in the questionnaires. During the survey, healthcare physicians and teachers-in-charge can help parents or guardians of participating children to fill out questionnaires. At the end of the survey, data were downloaded into a Microsoft Office Excel™ spreadsheet from the "Wenjuanxing" platform and were strictly checked by our trained staff. Healthcare physicians and teachers-in-charge were requested to contact the parents or guardians of participating children to resupply or confirm information that was obviously abnormal in the questionnaires. Body weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) were measured by healthcare physicians.

Definitions of stunting, underweight, wasting, and malnutrition

Child malnutrition included stunting, underweight, and wasting. In this study, we adopted the WHO criteria to define child malnutrition. Specifically, the 2006 WHO Child Growth Standard (16) defined stunting, underweight, and wasting for children aged 0–5 years (0–60 months), and the 2007 WHO growth reference for

1 https://www.wenjuan.com/

school-aged children and adolescents (17) defined stunting and wasting for children aged 5–19 years (61–228 months). The nutritional status of a child was evaluated by the Z-score, which was calculated using the deviation of the value of a child from the median of the reference population, divided by the standard deviation of the reference population. According to the WHO criteria, we defined stunting, underweight, and wasting based on two age stages: (i) children aged 36–60 months: stunting was defined as a height-for-age Z-score (HAZ) less than −2 standard deviations (SDs), underweight as weight-for-age Z-score (WAZ) of less than −2 SDs, and wasting as weight-for-height Z-score (WHZ) less than −2 SDs; (ii) children aged 61–180 months: stunting was defined as a height-for-age Z-score (HAZ) less than −2 standard deviations (SDs) and BMI for age Z-score (BMIZ) less than −2 SDs.

Definitions of other items

Delivery modes included vaginal delivery and cesarean section. Gestational age was recorded in months, and birth between 37 and 42 gestational weeks was regarded as full-term birth. Birth body length (to the nearest 0.1 cm) was reported by the parents or guardians of participating children. Pregnancy order and delivery order meant the times of pregnancy and bearing birth, respectively.

Infancy feeding included pure breastfeeding, partial breastfeeding, and non-breastfeeding. Breastfeeding duration and time of adding solid food were recorded in months. Some lifestyle-related factors, including sitting time, screen time, and outdoor activity time recorded in hours, were calculated as the sum of time spent on workdays × 5 and weekends × 2 divided by 7. In this survey, sitting time included screen time, and screen time referred to the amount of time spent on screen-related behaviors such as watching TV and playing computer games (18). Sleep duration included time for a lunch break. Eating speed was calculated as the average of breakfast, lunch, and dinner. Sweet food refers to food with sweet taste (such as bread cakes and desserts), and fast food is defined as food with high energy and low nutrition, such as hamburger and pizza. Night meal refers to food eaten within 2 h before bedding. We investigated the weekly intake frequency, which was classified as every day, often (3–5 times), occasional (1–2 times), and none, of sweet food, fast food, and night meals.

Parental BMI was calculated from self-reported weight and height. Family education referred to the highest educational level of parents and was categorized as master's degree or above, bachelor's degree, and high school degree or below. Family income (RMB per year) was categorized as ≥300,000, 100,000–300,000, and < 100,000.

Statistical analyses

Data were analyzed using STATA software version 16.0 (Stata Corp, College Station, TX, United States) and R programming environment (version 3.5.2). Study power was calculated using PS (Power and Sample Size Calculations) software version 3.0.

We assign values to categorical variables, as shown in Supplementary Table S1. The possible biases arising from different kindergartens and schools were assessed by the intraclass correlation coefficient (ICC). In theory, ICC can be used to quantify observed differences within and between clusters (19).

To reduce the influence of potential bias and confounding, we adopted 1:4 propensity score matching (PSM) between the malnutrition and control groups. Continuous variables are expressed as mean (standard deviation), in the case of no deviation from normal distribution based on the Skewness and Kurtosis tests, and as median (interquartile range). Categorical variables are expressed as count (percent). Between-group comparisons of variables were performed using the t-test, χ^2 test, or rank-sum test, where appropriate. The variance inflation factor (VIF) was calculated to assess multiple collinearities.

To identify statistically significant risk factors for child malnutrition, logistic regression analyses were conducted before and after considering age, sex, twins and infancy feeding, birth length, pregnancy order, and delivery order. Effect-size estimates are expressed as odds ratio (OR) and 95% confidence interval (CI).

After adding significant factors associated with child malnutrition to the basic model, prediction performance was appraised from both calibration and discrimination aspects. From the calibration aspect, Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to observe how closely the prediction probability, by adding significant factors, reflected the actual observed risk and global fit of the modified risk model, and the calibration curves for different models provide another form of visualization. From the discrimination aspect, the receiver operating characteristic (ROC) curve of both models was also presented to observe the discrimination capability of identified significant factors. The net benefits of this addition were also inspected by decision curve analysis (DCA).

Results

Baseline characteristics

In the first survey from September to December 2020, questionnaires were distributed to the parents or guardians of 10,441 children. In the second survey in January 2022, 11,633 questionnaires were sent. We pooled data from both surveys and strictly reviewed the validity of the survey data. Finally, 18,503 questionnaires were deemed eligible for inclusion. In this study, the prevalence of child malnutrition was 10.93% ($n = 2022$), and stunting, underweight, and wasting were 1.34% ($n = 248$), 11.22% ($n = 563$), and 9.77% ($n = 1808$), respectively.

The baseline characteristics of participating children are shown in Table 1 and Supplementary Table S2. The ICCs for all factors under the study were all relatively low (<0.01), indicating a low probability of clustering within kindergartens or schools and a lower likelihood of differences in surveyed items (Supplementary Table S3).

Identification of potential factors for child malnutrition

Multiple collinearities revealed by variance inflation factor (VIF) indicated that no multiple collinearities existed between different variables (Supplementary Table S4).

TABLE 1 Baseline characteristics of study children.

Characteristics	Unmatched population			1:4 matched population		
	Children without malnutrition	Children with malnutrition		Children without malnutrition	Children with malnutrition	
	(n = 16,481)	(n = 2022)	p	(n = 8,088)	(n = 2022)	p
Demographic information						
Age (years)	7.92 (4.91, 11.17)	5.5 (4.33, 7.58)	<0.001	5.5 (4.33, 7.5)	5.5 (4.33, 7.58)	0.771
Boys	8,486 (51.5)	1,036 (51.2)	0.848	4,234 (52.3)	1,036 (51.2)	0.370
Nationality			<0.001			0.093
Han	15,368 (93.2)	1828 (93.4)		7,407 (91.6)	1828 (90.4)	
Others	1,113 (6.8)	194 (9.6)		681 (8.4)	194 (9.6)	
Height (cm)	132 (111, 153)	115 (105, 125)	<0.001	115 (106, 130)	115 (105, 125)	<0.001
Weight (kg)	29 (20, 46.5)	14 (10.5, 20)	<0.001	20.5 (17.5, 29)	14 (10.5, 20)	<0.001
BMI (kg/m^2)	16.91 (15.18, 20.2)	10.68 (8.5, 12.86)	<0.001	16 (14.83, 18.01)	10.68 (8.5, 12.86)	<0.001
Food allergy	1,658 (10.1)	239 (11.8)	0.015	848 (10.5)	239 (11.8)	0.083
Drug allergy	694 (4.2)	81 (4.0)	0.707	312 (3.9)	81 (4.0)	0.758
Stunting	0 (0.0)	248 (12.3)	<0.001	0 (0)	248 (12.3)	<0.001
Underweight	0 (0, 0)	563 (67.7)	<0.001	0 (0)	563 (67.7)	<0.001
Wasting	0 (0.0)	1808 (89.4)	<0.001	0 (0)	1808 (89.4)	<0.001
Fetal and neonatal factors						
Birth length (cm)	50 (50, 52)	50 (50, 52)	0.174	50 (50, 52)	50 (50, 52)	0.013
Full-term birth (weeks)	13, 652 (90.10)	1729 (89.4)	0.346	767 (10)	205 (10.6)	0.411
Delivery mode			0.081			0.360
Vaginal delivery	8,125 (49.3)	1,049 (51.9)		4,080 (50.4)	1,043 (51.6)	
Cesarean section	8,356 (50.7)	973 (48.1)		4,008 (49.6)	979 (48.4)	
Pregnancy order	1 (1, 2)	2 (1, 2)	<0.001	1 (1, 2)	2 (1, 2)	0.005
Delivery order	1 (1, 2)	1 (1, 2)	<0.001	1 (1, 2)	1 (1, 2)	<0.001
Assisted reproduction	288 (1.7)	51 (2.5)	0.018	158 (2)	51 (2.5)	0.108
Twins	402 (2.4)	43 (2.1)	0.430	203 (2.5)	43 (2.1)	0.317
Infancy feeding			0.069			0.006
Pure breastfeeding	9,307 (56.5)	1,194 (59.1)		4,526 (56.0)	1,194 (59.1)	
Partial breastfeeding	5,688 (34.5)	665 (32.9)		2,968 (36.7)	665 (32.9)	
Non-breastfeeding	1,486 (9.0)	163 (8.1)		594 (7.3)	163 (8.1)	
Breastfeeding duration (months)	12 (0, 15)	12 (6, 18)	<0.001	12 (6, 18)	12 (6, 18)	0.906
Solid food introduction (months)	6 (6, 7)	6 (6, 7)	0.140	6 (6, 7)	6 (6, 7)	0.453
Lifestyle-related factors						
Outdoor activities (hours per day)	1.29 (1, 2)	1.29 (1, 2.29)	<0.001	1.43 (1, 2.29)	1.29 (1, 2.29)	0.412
Screen time (hours per day)	1.14 (0.64, 1.57)	1 (0.64, 1.57)	<0.001	1 (0.64, 1.57)	1 (0.64, 1.57)	0.014
Fall asleep time (hours per day)	9.5 (9, 10)	9 (9, 10)	<0.001	9 (9, 10)	9 (9, 10)	0.449
Sleep duration (hours per day)	9.29 (8.29, 10)	9.36 (8.64, 10.29)	<0.001	9.43 (8.57, 10.29)	9.36 (8.64, 10.29)	0.859
Eating speed (minutes)	16.67 (13.33, 21.67)	18.33 (15, 25)	<0.001	18.33 (13.33, 23.33)	18.33 (15, 25)	<0.001
Fast food intake frequency			<0.001			0.001
Every day	4,362 (26.5)	237 (11.7)		1,006 (12.4)	237 (11.7)	
3–5 times weekly	4,801 (29.1)	237 (11.7)		1,205 (14.9)	237 (11.7)	
1–2 times weekly	2,694 (16.3)	536 (26.5)		2021 (25.0)	536 (26.5)	
None or once in a while	4,624 (28.1)	1,012 (50.1)		3,856 (47.7)	1,012 (50.1)	

(Continued)

TABLE 1 (Continued)

Characteristics	Unmatched population			1:4 matched population		
	Children without malnutrition	Children with malnutrition		Children without malnutrition	Children with malnutrition	
	(n = 16,481)	(n = 2022)	p	(n = 8,088)	(n = 2022)	p
Sweet food intake frequency			<0.001			0.045
Every day	2,348 (14.2)	202 (10.0)		817 (10.1)	202 (10.0)	
3–5 times weekly	7,314 (44.4)	627 (31.0)		2,742 (33.9)	627 (31.0)	
1–2 times weekly	5,356 (32.5)	957 (47.3)		3,564 (44.1)	957 (47.3)	
None or once in a while	1,463 (8.9)	236 (11.7)		965 (11.9)	236 (11.7)	
Night meals intake frequency			<0.001			0.012
Every day	5,691 (34.5)	356 (17.6)		1,682 (20.8)	356 (17.6)	
3–5 times weekly	3,417 (20.7)	285 (14.1)		1,152 (14.2)	285 (14.1)	
1–2 times weekly	2,540 (15.4)	412 (20.4)		1,582 (19.6)	412 (20.4)	
None or once in a while	4,833 (29.4)	969 (47.9)		3,672 (45.4)	969 (47.9)	
Dental caries	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.318	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.343
Family-related factors						
Maternal age (years)	36 (33, 39)	35 (32, 38)	<0.001	35 (32, 38)	35 (32, 38)	<0.001
Paternal age (years)	37 (34, 40)	37 (33, 40)	<0.001	36 (33, 39)	37 (33, 40)	<0.001
Family education			<0.001			<0.001
High school degree or below	6,677 (40.5)	689 (34.1)		3,143 (38.9)	689 (34.1)	
Bachelor's degree	9,039 (54.8)	1,019 (50.4)		4,399 (54.4)	1,019 (50.4)	
Master's degree or above	765 (4.7)	314 (15.5)		546 (6.7)	314 (15.5)	
Family income (RMB per year)			<0.001			<0.001
<100, 000	6,964 (42.3)	731 (36.2)		3,273 (40.5)	731 (36.2)	
100, 000–300, 000	7,161 (43.5)	748 (37.0)		3,325 (41.1)	748 (37.0)	
>300, 000	2,356 (14.2)	543 (26.8)		1,490 (18.4)	543 (26.8)	
Maternal BMI	22.89 (20.76, 25.71)	22.04 (20.20, 24.51)	<0.001	22.60 (20.57, 25.22)	22.04 (20.20, 24.51)	<0.001
Paternal BMI	25.83 (23.46, 28.41)	25.06 (22.64, 27.76)	<0.001	25.57 (23.32, 28.34)	25.06 (22.64, 27.76)	<0.001

Data are expressed as median (interquartile range) or count (percent). p-value was calculated by the rank-sum test or the χ^2 test, where appropriate. BMI, body mass index.

As shown in Table 1, baseline variables were selected based on clinical relevance or with a p-value of less than 0.05 on univariate analyses. After adjusting for age, gender, twins and infancy feeding, birth length, pregnancy order, and delivery order, seven factors, namely, family education (OR, 95% CI, p: 1.52, 1.40 to 1.67, <0.001), family income (1.23, 1.16 to 1.30, <0.001), fast food intake frequency (1.14, 1.06 to 1.21, <0.001), night meals intake frequency (1.09, 1.04 to 1.15, <0.001), eating speed (1.01, 1.01 to 1.02, <0.001), maternal BMI (0.97, 0.95 to 0.99, <0.001), and paternal BMI (0.97, 0.96 to 0.98, <0.001) were found to be associated with the significant risk of child malnutrition, as shown in Table 2.

The power to detect significance when estimating the risk for child malnutrition was over 80% for the above comparisons.

Prediction performance assessment

We constructed both the basic model and full models to assess the prediction performance of seven significant factors identified above. The full model included all variables, and the basic model included all variables with the exception of seven significant factors. The prediction performance of both models was assessed from calibration and discrimination aspects, and the difference between the basic model and full model was compared. Significant improvement was observed in the prediction accuracy of the full model relative to that of the basic model (Table 3). In addition, the DCA plot showed that the net benefits gained by adding seven significant factors to the basic model were obvious (Figure 1).

The ROC curves are shown in Figure 2, and calibration curves are shown in Supplementary Figure S1. As revealed by the area under the receiver operating characteristic (AUROC) curve, both models differed significantly in discrimination ($p < 0.001$).

Discussion

In this study, we aimed to estimate the prevalence of child malnutrition and identify its potential factors among 18,503 Chinese

TABLE 2 Identification of potential factors for child malnutrition.

Significant variables	Univariate model (unadjusted)			Multivariable adjusted model*		
	OR	95% CI	*p*	OR	95% CI	*p*
Family education	1.43	1.32 to 1.54	<0.001	1.52	1.40 to 1.67	<0.001
Family income	1.23	1.17 to 1.30	<0.001	1.23	1.16 to 1.30	<0.001
Fast food intake frequency	1.07	1.02 to 1.12	0.008	1.14	1.06 to 1.21	<0.001
Night meals intake frequency	1.07	1.02 to 1.11	0.002	1.09	1.04 to 1.15	<0.001
Eating speed	1.01	1.01 to 1.02	<0.001	1.01	1.01 to 1.02	<0.001
Maternal BMI	0.98	0.97 to 0.99	<0.001	0.97	0.95 to 0.99	<0.001
Paternal BMI	0.97	0.96 to 0.98	<0.001	0.97	0.96 to 0.98	<0.001

BMI, body mass index; OR, odds ratio; 95% CI, 95% confidence interval. *The *p*-value was calculated after adjusting for age, gender, twins and infancy feeding, birth length, pregnancy order, and delivery order.

TABLE 3 Prediction performance before and after adding seven significant factors identified for child malnutrition.

Statistics	Basic model	Full model
Calibration		
AIC	10050.156	3860.350
BIC	10215.485	4125.173
Discrimination		
AUROC	0.564	0.907
p value for AUROC	<0.001	

AIC, Akaike information criterion; BIC, Bayesian information criterion; AUROC, area under the receiver operating characteristic. Basic model included all variables under the study with the exception of seven significant factors is presented in Table 2, and full model included all variables under the study.

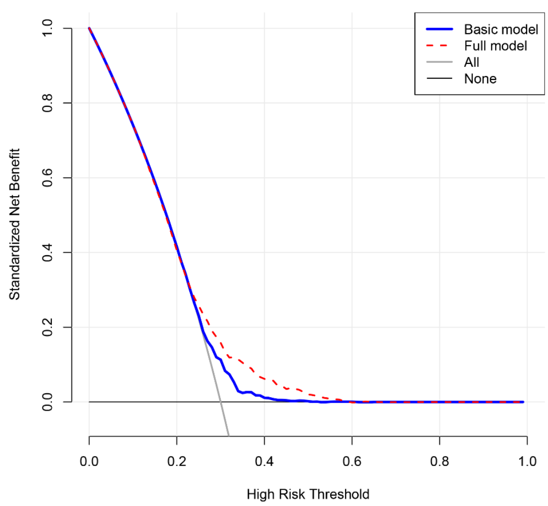

FIGURE 1
Decision curve analysis on the net benefits gained by adding seven significant factors associated with child malnutrition. Basic model included all variables under study with the exception of seven significant factors is presented in Table 2, and full model included all variables under the study.

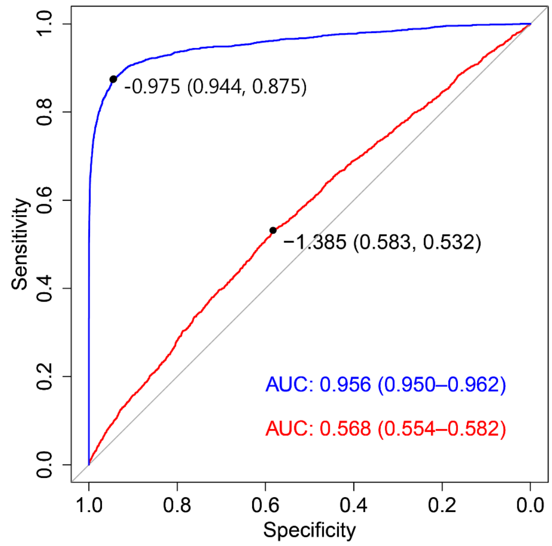

FIGURE 2
Receiver operating characteristic (ROC) curve for both basic and full models. AUC: area under curve. The red solid line corresponds to basic model, and the blue solid line corresponds to full model. Basic model included all variables with the exception of seven significant factors is presented in Table 2, and full model included all variables under the study.

children aged 3–14 years from Beijing and Tangshan. The key finding of this study was that approximately one in ten children suffered from malnutrition in North China. Moreover, parental education, family income, fast food intake frequency, night meals intake frequency, eating speed, and parental obesity were significantly and independently associated with child malnutrition under the WHO criteria. Thus far, to the best of our knowledge, this is the first study that has explored the risk profiling of child malnutrition among Chinese preschool and school-age children.

Recently, the overall detection rate of malnutrition has shown a downward trend (4, 20, 21). As reflected in this study, approximately 10% of Chinese children aged 3–14 years was in malnutrition status (stunting: 1.34%, underweight: 11.22%, and wasting: 9.77%), which was higher than that released in 2019 among Chinese children aged 7–18 years at 8.64% (4). The difference in the prevalence can be attributable to the differences in diagnostic criteria and participant characteristics. In this study, for the sake of extrapolation and comparisons, we adopted the WHO criteria, instead of the China criteria (22). In addition to malnutrition prevalence, we also attempted to identify factors that can predict the significant risk of child malnutrition based on the survey data.

In this study, parental nutrition status (indexed by BMI) was found to be associated with child malnutrition, which was consistent with the results of several previous studies (23, 24). The connection between parental nutrition status and child malnutrition may be due to inherited factors, lifestyle habits, and cultural and social backgrounds. For example, the prevalence of child malnutrition was higher among mothers with lower BMI (25, 26). In light of this significant association, it is of added interest to examine the association of pregnancy BMI, which is not collected in this study, with child malnutrition, as pregnancy BMI can reflect the development of the fetus *in utero* (27).

The findings of this study underscored the importance of parental socioeconomic status, including education and family income, for child malnutrition. Some studies have reported that high family education and high family income are protective factors against child malnutrition (28, 29). By contrast, our findings indicated that high family education and income were significant risk factors in this study. This conflicting observation is explainable. On one hand, with higher family education and income and heavier work pressure, meal time spent with children becomes fewer, which might serve as a possible reason for child malnutrition. On the other hand, the transition from traditional diets to modern diets is characterized by "high sugar, high oil, and less nutrition" which provides a more convenient choice for parents to please their children, especially in high-income households, while commercial foods available on the market do not always deserve the "healthy halo" (30). Moreover, pocket money given by parents is often used to buy unhealthy snacks (31). Therefore, parents are encouraged to accompany their children to eat and to focus on a healthy and balanced diet for their children.

In addition to inherited and environmental factors, dietary factors were also attributable to the occurrence of malnutrition. In this study, we found that dietary habits such as fast food intake frequency, night meals intake frequency, and eating speed were associated with the occurrence of children's malnutrition. Generally, fast food, which belongs to ultra-processed foods and is devoid of nutrients, can increase the risk of malnutrition, consistent with the results of Khan et al. (32). In addition, frequent night meals and fast eating speed were associated with child malnutrition, and this association was rarely reported in the literature. There is evidence that late dinner eating was linked to low cortisol concentrations and then low appetite during meals (33, 34), and a lower appetite infecting the speed of eating and alimentation could result in childhood undernutrition. Moreover, slow eating may be a symptom of anorexia, a disorder of nutrient absorption. Nevertheless, we cannot exclude the possible impact of different timelines for measurement on the results of this association study. There is no doubt that such poor dietary habits are considered preliminary, and further large, well-designed studies are needed to confirm or refute this finding.

Limitations

Some limitations should be acknowledged for this study. First, in this study, all participating children were enrolled from Beijing and Tangshan, which are two economically developed cities; hence, extrapolation of our findings to the other areas should be made with caution. Second, data derived from questionnaires filled by parents or caregivers cannot exclude the possibility of recall bias. Third, some socioeconomic data were unavailable for us, such as parental employment. Fourth, the causality of potential risk factors with child malnutrition cannot be addressed due to the cross-sectional design.

Conclusion

To sum up, we found that approximately 10% of Chinese children aged 3–14 years were in malnutrition status, and seven factors, namely, parental education, family income, fast food intake frequency, night meals intake frequency, eating speed, maternal obesity, and parental obesity, were found to be significant predictors for child malnutrition. For practical reasons, our findings provide an opportunity to understand the risk profiles of child malnutrition and address the utility of screening these factors for primary prevention by changing diets and lifestyles, eventually, preventing the occurrence of child malnutrition.

Data availability statement

The datasets presented in this article are not readily available because the data includes identifiable data of minors and privacy. Requests to access the de-identified datasets should be directed to zhangzhixin032@163.com.

Ethics statement

The studies involving humans were approved by The Ethics Committee of China-Japan Friendship Hospital and Beijing University of Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

XZ, ZhZ, and WN designed the study. XZ, QW, and ZiZ obtained statutory and ethics approvals. QW and ZhZ contributed to data acquisition. ZG, JW, and WN performed the statistical analysis. XZ and QW wrote the first draft. ZhZ and WN are the study guarantors. 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/fnut.2023.1228799/full#supplementary-material

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Unfavorable nutrient intakes in children up to school entry age: results from the nationwide German KiESEL study

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Background: Nutrition in the first years of life is a cornerstone for child development and long-term health, yet there is a lack of current data on energy and nutrient intake among toddlers and preschoolers in Germany.

Objective: To analyze energy and nutrient intake in toddlers (1- to 2-year-olds) and preschoolers (3- to 5-year-olds) in Germany and compare the results with the Dietary Reference Values (DRVs) by the European Food Safety Authority.

Design: Dietary intake was assessed by weighed food record data (3 + 1 day) of 890 children from the representative cross-sectional Children's Nutrition Survey to Record Food Consumption (KiESEL), carried out in 2014–2017 as a module of the German Health Interview and Examination Survey for Children and Adolescents Wave 2. For the calculation of energy and nutrient intake, the German Nutrient Database BLS 3.02, LEBTAB, and a supplement database were used.

Results: Median intakes of energy and most nutrients met or exceeded the DRVs in both toddlers and preschoolers. However, low intakes relative to DRVs were found for vitamin D (6–9% of DRV, including supplements) and iodine (57–65% of DRV). Age specific downward deviations were observed for iron intake in toddlers (75% of DRV) and for calcium intake in preschoolers (67–77% of DRV). In contrast, intakes were high for saturated fatty acids (SFA) (14–16 E%), mono-/disaccharides (60–87 g/day), and protein [2.1–2.6 g/(kg body weight*day)].

Conclusion: Nutrient imbalances in toddlers and preschoolers in Germany, which are partly age-related, give rise to concern. Research is needed to determine if routine vitamin D supplementation should be extended beyond infancy. Public health efforts to increase the rate of use of iodized salt and to reduce the intake of SFA and mono-/disaccharides in children's diets are to be strengthened.

KEYWORDS

energy intake, nutrient intake, toddlers, preschoolers, nutrition survey, Germany

1 Introduction

Nutrition is a key factor in child development (1), substantially influencing not only physical but also mental and cognitive health (2). Moreover, early life nutrition has been found to have long-term effects on health, which include modulating the risk for non-communicable diseases such as obesity, diabetes mellitus, and cardiovascular disease (3, 4). At the same time, young children are particularly vulnerable to nutrient deficiencies, as nutrient requirements per kg body weight are high (5). In the midst of the overweight and obesity pandemic in the European Region, affecting an estimated 7.9% of children under the age of 5 and 29.5% of children aged 5 to 9 years (6), excessive energy and macronutrient intake appears to be accompanied with micronutrient deficiencies (7).

While the European Food Safety Authority (EFSA) has identified vitamin D, iron, and – in some countries – iodine as critical micronutrients among infants and young children below the age of 3 years (8), there is no such scientific opinion referring to critical nutrients in preschoolers. However, vitamin D and iodine are likely to be critical nutrients in older children as well, as an evaluation of the German *food-based* dietary guidelines for children and adolescents demonstrated that even adherence to the recommendations does not ensure adequate vitamin D and iodine intake (9).

Considering the long-term nature of nutrition-associated health consequences, the promotion of optimal nutrient intake in the earliest stages of life is pivotal. This in turn requires a comprehensive understanding of the various phases of child nutrition throughout early development and of potential levers for improvement. Yet, the last national dietary survey analyzing food consumption and nutrient intake in toddlers and preschoolers in Germany was the VELS study, carried out in children aged 1–4 years from 2001 to 2002 (10).

The Children's Nutrition Survey to Record Food Consumption (*Kinder-Ernährungsstudie zur Erfassung des Lebensmittelverzehrs*, KiESEL), conducted between 2014 and 2017, offers the most recent representative data on food consumption for children aged 6 months to 5 years in Germany (11). Based on the KiESEL data, this study's objective is to assess whether energy and nutrient intake in children aged 1–5 years in Germany comply with the Dietary Reference Values (DRVs) by EFSA (12). Furthermore, the study seeks to explore differences in nutrient intake specific to sex and age group, i.e., toddlers and preschoolers.

2 Materials and methods

KiESEL is a representative cross-sectional study performed by the German Federal Institute for Risk Assessment (*Bundesinstitut für Risikobewertung*, BfR) from 2014 to 2017. Originally, the study was designed to obtain current data on children's food consumption for exposure assessment (11). Subsequent analysis of data on nutrient intake was performed by the Max Rubner-Institut (MRI). The study is a module of the German Health Interview and Examination Survey for Children and Adolescents Wave 2 (*Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland Welle 2*, KiGGS Wave 2), which is part of the national health monitoring by the Robert Koch Institute (11). KiESEL was approved by the ethics committee of the Berlin Chamber of Physicians (Eth–28/13). Written informed consent was obtained from the primary caregiver of each child enrolled in the study. KiESEL was further approved by the German Federal Commissioner for Data Protection and Freedom of Information. To ensure adherence to the quality standards in nutritional epidemiology, the STROBE-nut reporting guidelines were used during manuscript preparation (13) (**Supplementary Table 1**).

The KiESEL sample was randomly selected from the gross sample of KiGGS Wave 2 (11). The sample of KiGGS Wave 2 was drawn from official residency registries of 167 representative German cities and municipalities originally chosen for the KiGGS baseline study (14). The total KiESEL sample includes n = 1104 children aged 0.5–5 years (11). The present analyses refer to a subsample of children aged ≥1 to ≤5 years (n = 890), after excluding children with missing food record data (n = 96) and infants aged ≥6 to ≤11 months (n = 118), as this age group is subject to a separate analysis. A participant flow chart is provided in **Supplementary Figure 1**. Children were assigned to two age groups based on their age at the beginning of data collection, namely toddlers (≥1 to ≤2 years) and preschoolers (≥3 to ≤5 years). Owing to the time lag between recruitment and data collection, the group of preschoolers additionally included n = 62 (6.2%) children aged 6 years. Note that all age specifications refer to completed years of life, e.g., the age group "1 year" refers to children aged

Abbreviations: AI, Adequate Intake; AR, Average Requirement; BfR, German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung); BLS, German Nutrient Database (Bundeslebensmittelschlüssel); CI, Confidence Interval; DRV, Dietary Reference Value; EFSA, European Food Safety Authority; E%, percentage of energy intake; KiESEL, Children's Nutrition Survey to Record Food Consumption (Kinder-Ernährungsstudie zur Erfassung des Lebensmittelverzehrs); KiGGS, German Health Interview and Examination Survey for Children and Adolescents (Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland); MRI, Max Rubner-Institut; P, Percentile; PAL, Physical Activity Level; PRI, Population Reference Intake; RI, Reference Intake Range for Macronutrients; SES, socioeconomic status.

1.0–1.9 years. The KiESEL study design and survey protocol are reported elsewhere (11, 14).

Dietary assessment included a parent-administered food record, which was conducted on three consecutive days plus one independent day, scheduled 2–16 weeks later (3 + 1 design). To facilitate data collection, parents received face-to-face instructions during an initial home visit. They were provided with digital kitchen scales and a journal with pre-printed log pages explicitly inquiring about specific details of the foods and beverages consumed (e.g., preparation method, brand) and the place and time of the respective eating occasion. In cases where weighing was unfeasible, consumed amounts were estimated using package labels, household measures, or the KiESEL picture book visualizing different portion sizes. In child day-care facilities, a simplified food record was completed. If ambiguities were found in the protocol entries, the parents were contacted for clarification (11).

Data collection in KiESEL also included anthropometric measurements and a standardized questionnaire on nutritional behavior including a food propensity questionnaire, e.g., on seldomly eaten foods, which were performed by trained nutritionists during the home visit (11). To characterize the study population, data on socioeconomic status (SES) collected in KiGGS Wave 2 were used. The categories low, medium, and high SES reflect parental level of education, employment status, and income (equally weighted).

Amounts of human milk were estimated based on the age of the child and the frequency of feeding. Following the approach by Briefel et al. (15), the amount of human milk per feed was set at 89 ml for children aged 12–17 months and at 59 ml for children aged ≥18 months. The maximum daily human milk consumption observed in this KiESEL sub-sample was considered plausible, hence no upper daily limits were applied.

For the calculation of energy and nutrient intake, the food record data were either linked to the German Food Composition Database (*Bundeslebensmittelschlüssel*, BLS), version 3.02 (16), or to LEBTAB (17), considering all details of a food item as specified in the protocols (e.g., preparation method, brand). LEBTAB is a food composition database that contains a wide range of foods intended for infants and young children, such as follow-on formula or fortified toddler cereals. As far as included in the BLS, fortification of other foods, e.g., fruit juices and cereals, was also accounted for. Data on vitamin A are provided as retinol equivalents, vitamin E as α-tocopherol equivalents, vitamin K as phylloquinone, niacin as niacin equivalents, and folate/folic acid as folate equivalents.

The use of supplements was recorded using a free-text box within the food record (14). When the quantity and/or dosage of a supplement was not specified, amounts were derived as median from comprehensive protocol entries, referring to similar products in children of the same age. Protocol entries were linked to a supplement database (18), which was developed by the BfR and complemented by the MRI. To incorporate both dietary supplements and medicinal products such as vitamin D preparations for the prevention of rickets, the generic term "supplements" is used. The term "vitamin D-containing supplements" refers to all supplement preparations in which vitamin D has been specified as a component, i.e., mono and combination preparations with vitamin D. With the exception of vitamin D, nutrient intake from supplements was not considered in the analyses.

Following the EFSA protocol (19), misreporting of energy intake was identified using the Goldberg cut-off method updated by Black. Children aged ≥1 to ≤3 years were assigned a Physical Activity Level (PAL) of 1.4 and those ≥4 years a PAL of 1.6. Basal metabolic rate was calculated with the Schofield equations as a function of the child's age, sex, height, and body weight (19). The ratio of reported energy intake to estimated basal metabolic rate was compared to calculated cut-off values (**Supplementary Table 2**). In line with the EFSA recommendation, under- and over-reporters were not excluded as this would introduce unknown bias (19).

A weighting factor was applied to approximate the sample's sociodemographic structure to that of the German population. The weighting factor was developed by the Robert Koch Institute for the total KiESEL sample based on the factors sex, age, region, regional structure (e.g., rural area, large city), and household education level, fitted to data from official statistics (Microcensus 2015, except for household educational level Microcensus 2013 (20)).

For statistical analyses, the software SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA), was used. Statistical measures of energy and nutrient intake of the sample [median, 95% confidence interval (CI) of the median, and the 5th and 95th percentiles (hereafter P5 and P95, respectively)] were calculated from individual values derived as the mean of all protocol days per child. As nutrient intake distributions are frequently skewed, medians were calculated for each age group instead of means. Significant differences were identified by non-overlapping 95% CIs of medians for metric data and by chi-square tests ($\alpha = 0.05$) for categorical data.

The DRVs by EFSA were used as measures for comparison (**Supplementary Tables 3, 4**). Intakes were additionally displayed as % of DRVs (median, interquartile range, minimum, maximum), derived from the individual intakes as % of sex- and age-specific DRV. In some cases, more than one DRV was applied for one KiESEL age group. For example, this was necessary for calcium, as the DRVs for calcium refer to 1- to 3-year-olds and to 4- to 10-year-olds, while the KiESEL age groups refer to 1- to 2-year-olds and to 3- to 5-year-olds.

Wherever possible, this report refers to the Population Reference Intake (PRI). In cases where PRIs have not yet been established, the Adequate Intake (AI) was used. Both are designed to cover the requirements of nearly all healthy individuals in a given reference population (12). Thus, an individual intake below a given reference value does not necessarily indicate an actual deficit but rather an increased probability of inadequate intake. Moreover, it should be noted that DRVs for young children are often derived from extrapolations from other age groups due to lacking data (21). DRVs for energy are provided as Average Requirements (ARs), whereas those for fat and carbohydrates are set as Reference Intake Ranges for Macronutrients (RIs) (12).

3 Results

3.1 Sample characteristics

The characteristics of the sample are described in **Table 1**. Compared to medium and high SES, the lowest proportion of

TABLE 1 Characteristics of KiESEL toddlers and preschoolers[1].

	Toddlers (1–2 years; *n* = 354)	Preschoolers (3–5 years; *n* = 536)
Sex (n, %)		
Male	175 (51.6)	279 (51.4)
Female	179 (48.4)	257 (48.6)
Anthropometric measurements (mean ± SD)		
Body weight (kg)	12.2 ± 2.1	18.6 ± 3.6
Body height (cm)	85.7 ± 7.0	107.9 ± 8.8
BMI (kg/m^2)	16.5 ± 1.6	15.8 ± 1.6
Socioeconomic status (n, %)[2]		
Low	19 (14.3)	34 (12.4)
Medium	205 (61.0)	330 (65.7)
High	130 (24.6)	169 (21.9)
Region (n, %)[3]		
North	50 (16.1)	61 (16.2)
East	129 (19.2)	171 (19.2)
South	93 (29.3)	164 (29.2)
West	82 (35.4)	140 (35.4)

[1]Weighted data (*n* unweighted). The age group toddlers refers to children aged ≥1 to ≤2 years and the age group preschoolers refers to children aged ≥3 to ≤5 years, but also includes 62 children of 6 years of age. [2]Data on SES were missing for *n* = 3 children. [3]Federal states were assigned as follows. North: Schleswig-Holstein, Hamburg, Lower Saxony, Bremen; East: Berlin, Brandenburg, Mecklenburg-Western Pomerania, Saxony, Saxony-Anhalt, Thuringia; South: Baden-Wuerttemberg, Bavaria; West: North Rhine-Westphalia, Hessia, Rhineland-Palatinate, Saarland.

children came from families with a low SES (<15%). Regarding misreporting of energy intake, 5.6% of parents were identified as under-reporters and 1.1% as over-reporters of their children's food consumption. Supplement use was frequent only in 1-year-olds, with supplement use being reported for one in three at least once during the protocol period (Table 2). Among those, vitamin D-containing supplements were most commonly administered.

TABLE 2 Supplement use in KiESEL toddlers and preschoolers[1].

Age	Total participants (*n* = 890)	Supplement use (*n*, %)	Vitamin D-containing supplement[2] use (*n*, %)
Toddlers	354	74 (21.7)*	63 (19.5)*
1 year	190	58 (32.5)	54 (31.1)
2 years	164	16 (10.3)	9 (7.2)
Preschoolers	536	41 (5.0)*	30 (3.8)*
3 years	147	10 (7.3)	8 (5.8)
4 years	163	19 (3.9)	13 (2.3)
5 years[3]	226	12 (4.0)	9 (3.4)

[1]Weighted data (n unweighted). Note that all age specifications refer to completed years of life, e.g., the age group "1 year" refers to children aged 1.0–1.9 years. [2]Referring to mono and combination preparations with vitamin D. [3]Incl. A total of 62 children of 6 years of age. *Significant difference between toddlers and preschoolers.

3.2 Energy and macronutrient intake

Daily energy and nutrient intakes in toddlers and preschoolers are depicted in Tables 3, 4. Median daily energy intakes were in the range of the respective sex- and age-specific ARs for both toddlers and preschoolers (Supplementary Table 3 and Table 3). With regard to intakes expressed as % of DRVs (Supplementary Table 4 and Figures 1, 2), protein intakes per kg body weight corresponded to about 2.5 times the PRIs in both toddlers and preschoolers, while carbohydrate intakes were within the RIs (Supplementary Table 4 and Table 3). Fat intakes were below the RI in toddlers but not in preschoolers. Also, median fiber intakes in toddler girls (but not in toddler boys) and preschoolers fell short of the DRVs and corresponded to 85 and 90% of the AIs, respectively. Mono-/disaccharides accounted for about half the total carbohydrate intake and made up approximately a quarter of the total energy intake (Table 3). Regarding fatty acids, SFA contributed to about 15 percent of energy intake (E%).

The difference in energy intake between boys and girls was more pronounced in preschoolers (median Δ 109 kcal) than in toddlers (median Δ 63 kcal). Consequently, sex-specific differences in daily median macronutrient intakes were predominantly observed in preschoolers (protein, fat, SFA, polyunsaturated fatty acids, cholesterol, carbohydrates, mono-/disaccharides) and less in toddlers (SFA, monounsaturated fatty acids, fiber). Differences in the contribution to energy intake (E%) were only found for mono-/disaccharides in preschoolers. For all differences, intake was consistently higher amongst boys than girls.

3.3 Micronutrient intake

Except for vitamin D, α-tocopherol equivalents, and pantothenic acid, median vitamin intakes met or exceeded the applicable DRVs in both toddlers and preschoolers (Figures 1, 2). The largest shortfall relative to the DRVs was found for vitamin D, with median intakes corresponding to less than 10% of the AI for both age groups and sexes, regardless of individual supplement use. Depending on age group and sex, median intakes of α-tocopherol equivalents corresponded to 61–77% and median intakes of pantothenic acid to 60–67% of the AIs, respectively. Total vitamin intakes were largely higher in preschoolers than in toddlers or showed no differences between age groups, except that girls' vitamin D intakes and boys' vitamin K intakes were higher in toddlers than in preschoolers. Sex-specific differences in vitamin intake were found more frequently in preschoolers (vitamin D without supplements, thiamin, biotin, vitamin B12) than in toddlers (pyridoxine), with consistently higher intakes in boys than in girls (Table 4).

Among the minerals, median intakes below the DRVs were found for iodine, iron, calcium (preschoolers only), magnesium, and copper. The largest gap in intake relative to the DRVs was found for iodine, with median intakes corresponding to 57–65% of the AI. Median iron intakes corresponded to around 75% of the PRI in toddlers. In preschoolers, median iron intakes were higher, at 92% of the PRI in boys and 85% of the PRI in girls. While median calcium intakes in toddlers met the DRV, the intakes in preschooler boys and girls corresponded to 77 and 67% of the

TABLE 3 Daily energy and macronutrient intake from food and beverages in KiESEL toddlers and preschoolers stratified by sex[1].

	Toddlers (1–2 years; *n* = 354)						Preschoolers (3–5 years; *n* = 536)					
	Boys (*n* = 175)			Girls (*n* = 179)			Boys (*n* = 279)			Girls (*n* = 257)		
	Median	CI Median	P5, P95	Median	CI Median	P5, P95	Median	CI Median	P5, P95	Median	CI Median	P5, P95
Energy (kcal)*	979	937–1027[a]	689, 1410	916	868–922[a]	576, 1300	1297	1283–1334[a]	876, 1670	1188	1156–1215[a]	831, 1570
Protein (g)*	32.2	28.8–33.6	19.0, 45.1	30.0	28.4–32.8	16.1, 43.7	41.9	40.9–43.1[a]	26.5, 59.6	39.0	37.5–39.7[a]	26.3, 53.4
Protein (E%)	12.7	12.4–13.3	9.6, 16.4	13.0	12.2–13.3	9.5, 17.1	13.1	12.9–13.4	9.9, 15.8	13.0	12.7–13.3	10.4, 17.2
Protein (g/kg body weight)[2]*	2.6	2.4–2.7	1.5, 4.0	2.5	2.4–2.7	1.4, 3.9	2.3	2.2–2.4	1.6, 3.2	2.1	2.0–2.2	1.5, 3.5
Fat (g)*	36.1	33.3–38.0	22.5, 56.9	31.5	29.8–34.2	16.1, 50.2	47.7	45.7–49.8[a]	27.0, 73.0	42.7	39.6–44.2[a]	23.7, 65.4
Fat (E%)	32.7	32.0–33.7	24.8, 40.3	32.4	31.2–32.7	23.0, 41.2	33.3	32.4–34.1	23.6, 40.5	32.0	31.7–33.8	22.2, 42.0
Saturated fatty acids (g)*	17.3	16.1–18.2[a]	9.1, 27.9	15.1	13.3–15.8[a]	7.2, 26.6	22.1	21.2–23.1[a]	12.1, 34.3	19.8	18.9–20.9[a]	10.4, 31.2
Saturated fatty acids (E%)	15.9	14.7–16.7	10.3, 22.0	14.2	13.9–15.2	9.8, 20.8	15.5	14.6–16.0	9.8, 20.4	15.3	14.9–15.7	8.3, 20.8
Monounsaturated fatty acids (g)*	11.3	10.9–11.9[a]	6.8, 18.7	9.8	9.4–10.8[a]	4.5, 17.7	15.1	14.4–16.3	8.8, 24.0	13.8	13.4–14.5	7.0, 23.5
Monounsaturated fatty acids (E%)	10.3	10.1–10.8	7.9, 14.2	10.1	9.8–10.8	7.0, 15.3	10.7	10.5–11.1	7.5, 14.5	11.0	10.2–11.2	6.2, 15.9
Polyunsaturated fatty acids (g)*	4.1	3.9–4.5	2.5, 8.1	4.0	3.7–4.2	2.1, 9.1	6.1	5.8–6.3[a]	3.0, 11.1	5.1	4.9–5.6[a]	2.5, 10.2
Polyunsaturated fatty acids (E%)	4.1	3.9–4.4	2.4, 7.4	4.2	3.7–4.4	2.6, 7.0	4.1	3.9–4.3	2.5, 6.7	4.0	3.8–4.2	2.4, 7.1
Cholesterol (mg)*	128.8	120.2–138.9	42.9, 212.1	112.9	100.2–123.2	25.7, 205.8	169.3	162.8–176.7[a]	77.5, 299.9	145.8	138.8–159.1[a]	61.1, 332.2
Carbohydrates (g)*	127.6	125.1–132.0	91.5, 188.9	122.1	112.5–125.6	79.7, 177.3	170.5	166.1–177.0[a]	123.7, 229.5	156.8	150.9–162.9[a]	104.9, 214.2
Carbohydrates (E%)	53.1	52.5–53.4	44.4, 60.4	53.3	52.2–55.1	42.2, 64.3	52.5	51.5–53.9	44.3, 62.6	53.5	52.6–54.3	42.0, 63.3
Mono-/disaccharides (g)*	63.4	59.6–67.1	40.9, 108.8	59.9	54.4–62.2	27.5, 99.9	86.7	83.2–89.5[a]	44.4, 136.3	74.5	69.8–77.7[a]	43.5, 131.3
Mono-/disaccharides (E%)	25.3	24.4–27.2	17.4, 38.9	26.5	25.2–27.4	17.4, 38.4	27.1	26.4–28.6[a]	15.4, 40.1	24.4	24.2–26.4[a]	16.4, 38.0
Fiber (g)*girls only	10.6	10.1–11.1[a]	6.0, 17.2	8.6	8.2–9.3[a]	4.3, 16.9	11.3	10.8–12.0	6.9, 21.4	10.7	10.6–11.2	6.0, 17.8

[1]Weighted data (n unweighted). The age group toddlers refers to children aged ≥1 to ≤2 years and the age group preschoolers refers to children aged ≥3 to ≤5 years, but also includes 62 children of 6 years of age. Energy and nutrient intake was calculated using BLS 3.02 (for ordinary foods/beverages) and LEBTAB (for foods/beverages intended for infants/young children). CI Median, 95% confidence interval of the median; P, percentile. Due to the display of median values, the sum of protein, fat, and carbohydrate E% does not equal 100%. [2]The EFSA DRVs are given in g per kg body weight. *Significant difference between age groups (95% confidence intervals of the medians do not overlap). [a]Significant difference between sexes (95% confidence intervals of the medians do not overlap).

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TABLE 4 Daily micronutrient intake from food and beverages in KiESEL toddlers and preschoolers stratified by sex[1].

		Toddlers (1–2 years; *n* = 354)						Preschoolers (3–5 years; *n* = 536)					
		Boys (*n* = 175)			Girls (*n* = 179)			Boys (*n* = 279)			Girls (*n* = 257)		
		Median	CI Median	P5, P95	Median	CI Median	P5, P95	Median	CI Median	P5, P95	Median	CI Median	P5, P95
Vitamins	Retinol equiv. (µg)	649	602–700	273, 1631	484	428–652	217, 1357	616	573–666	240, 2233	592	561–691	235, 1819
	Vit. D excl. suppl. (µg)*girls only	1.1	1.0–1.2	0.5, 6.0	1.1	1.0–1.3	0.3, 6.1	1.0	1.0–1.1[a]	0.4, 3.1	0.9	0.9–1.0[a]	0.3, 2.7
	Vit. D incl. suppl. (µg)*girls only	1.3	1.1–1.5	0.5, 14.8	1.3	1.1–1.7	0.3, 14.4	1.0	1.0–1.1	0.4, 5.4	0.9	0.9–1.0	0.3, 2.7
	α-TE equiv. (mg)*boys only	4.6	4.4–5.1	2.6, 11.2	4.6	4.3–5.2	2.1, 11.2	6.1	5.8–6.4	2.7, 14.9	5.5	5.2–6.0	2.8, 12.1
	Vit. K (µg)*boys only	42.0	37.6–45.9	16.1, 129.5	34.3	29.8–38.1	10.9, 119.0	34.3	31.9–36.4	15.9, 115.4	33.6	30.6–37.4	11.6, 105.8
	Thiamin (mg)*	0.60	0.56–0.64	0.35, 1.14	0.56	0.52–0.60	0.27, 1.22	0.74	0.73–0.79[a]	0.42, 1.74	0.69	0.67–0.72[a]	0.40, 1.83
	Thiamin (mg/MJ)[2]	0.14	0.14–0.15	0.09, 0.29	0.15	0.14–0.16	0.10, 0.31	0.14	0.13–0.15	0.09, 0.30	0.14	0.13–0.15	0.09, 0.35
	Riboflavin (mg)	0.79	0.74–0.88	0.46, 1.41	0.76	0.71–0.82	0.33, 1.51	0.91	0.87–0.98	0.50, 2.04	0.83	0.81–0.88	0.47, 1.70
	Niacin equiv. (mg)*	11.7	11.0–12.4	7.5, 19.8	11.6	10.7–12.9	6.7, 17.6	16.3	15.6–16.6	10.1, 28.7	15.0	13.8–15.9	9.6, 23.9
	Niacin equiv. (mg/MJ)[2]	2.93	2.77–3.02	2.20, 4.02	2.92	2.72–3.12	2.22, 4.23	2.89	2.82–2.93	2.23, 4.47	2.94	2.86–3.04	2.22, 4.65
	Pantothenic acid (mg)*	2.5	2.3–2.7	1.4, 5.2	2.4	2.2–2.5	1.0, 4.5	2.8	2.7–2.9	1.6, 6.6	2.7	2.6–2.7	1.4, 5.9
	Pyridoxine (mg)*	0.81	0.78–0.87[a]	0.48, 1.36	0.74	0.71–0.77[a]	0.33, 1.34	0.92	0.90–0.98	0.58, 2.17	0.89	0.87–0.96	0.50, 2.10
	Biotin (µg)*	26.0	24.3–27.8	16.0, 62.8	22.3	21.2–24.9	10.6, 64.4	31.4	30.2–33.3[a]	16.2, 119.1	29.3	27.8–30.1[a]	15.2, 119.9
	Folate equiv. (µg)	130	123–142	70, 227	122	116–128	57, 224	140	133–151	76, 328	141	127–149	71, 320
	Vit. B12 (µg)*	2.0	1.8–2.1	0.9, 3.6	1.8	1.5–2.0	0.6, 3.3	2.5	2.4–2.6[a]	1.1, 4.8	2.2	2.1–2.3[a]	1.0, 4.2
	Vit. C (mg)	65.7	58.7–73.7	23.2, 129.5	64.3	60.7–68.5	15.1, 128.4	66.5	63.8–71.7	21.6, 165.3	59.6	57.3–65.4	23.5, 160.7
Minerals	Sodium (g)*	1.00	0.93–1.09	0.40, 1.91	1.00	0.96–1.09	0.49, 1.88	1.44	1.42–1.50	0.81, 2.51	1.45	1.41–1.50	0.86, 2.21
	Potassium (mg)*	1418	1347–1494	913, 2139	1284	1239–1356	593, 2012	1597	1573–1624	964, 2410	1545	1511–1577	919, 2293
	Calcium (mg)	473	449–503	221, 793	454	391–518	210, 791	519	495–558	269, 952	485	467–519	276, 788
	Magnesium (mg)*	150	139–158[a]	87, 226	128	121–138[a]	75, 233	172	167–177	105, 265	170	158–178	110, 232
	Phosphorus (mg)*	600	541–626	390, 902	537	505–584	318, 849	741	716–757[a]	468, 1066	676	658–702[a]	436, 934
	Iron (mg)*	5.3	5.0–5.5	3.3, 9.1	5.3	5.0–5.5	2.4, 8.5	6.4	6.3–6.8	3.9, 11.7	6.0	5.9–6.3	3.4, 9.7
	Zinc (mg)*	4.6	4.5–4.9	3.1, 7.8	4.3	4.1–4.7	2.3, 6.4	5.4	5.2–5.6	3.5, 8.0	5.1	4.9–5.3	3.4, 7.3
	Copper (mg)*	0.66	0.64–0.73[a]	0.45, 1.04	0.59	0.55–0.62[a]	0.37, 1.16	0.83	0.81–0.88	0.52, 1.29	0.79	0.76–0.82	0.51, 1.18
	Manganese (mg)*girls only	2.0	1.8–2.1[a]	1.0, 3.3	1.6	1.5–1.7[a]	0.7, 3.9	2.2	2.0–2.3	1.2, 4.3	2.1	1.9–2.3	1.2, 3.6
	Iodine (µg)[3]	54.0	48.0–56.0	23.8, 111.8	58.2	51.4–63.0	19.4, 102.4	52.1	48.2–55.4	24.1, 120.2	51.7	50.9–55.0	28.6, 135.7

[1]Weighted data (n unweighted). The age group toddlers refers to children aged ≥1 to ≤2 years and the age group preschoolers refers to children aged ≥3 to ≤5 years, but also includes 62 children of 6 years of age. Nutrient intake was calculated using BLS 3.02 (for ordinary foods/beverages) and LEBTAB (for foods/beverages intended for infants/young children). CI Median, 95% confidence interval of the median; Equiv., equivalents; P, percentile; Vit., vitamin; α-TE, α -tocopherol. [2]The EFSA DRVs are given in mg per MJ. [3]Possibly underestimated, as iodized salt in family foods is not fully accounted for. *Significant difference between age groups (95% confidence intervals of the medians do not overlap). [a]Significant difference between sexes (95% confidence intervals of the medians do not overlap).

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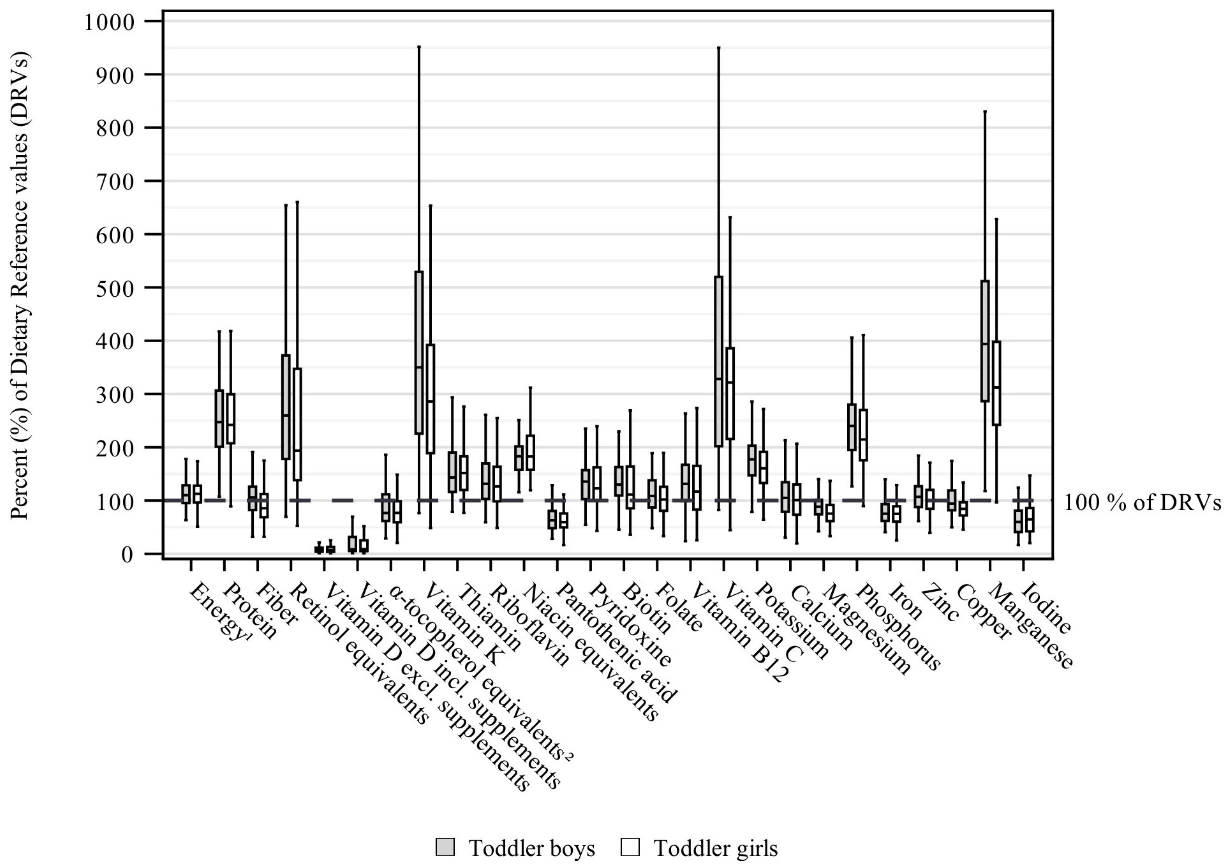

FIGURE 1
Daily energy and nutrient intake from food and beverages in toddlers (aged ≥1 to ≤2 years) stratified by sex and expressed as % of the EFSA DRVs (12) (weighted data; box and whisker plots with median, interquartile range, and minimum-maximum; whisker length limited to 1.5 times the interquartile range, outliers excluded). [1]Assuming a PAL of 1.4.[2]The EFSA DRVs include α-tocopherol only, while KiESEL intakes are given as α-tocopherol equivalents.

PRIs, respectively, and did not meet the ARs either [390 mg/day for 3-year-olds and 680 mg/day for 4- to 6-year-olds (12)]. Relating to both age groups, median magnesium intakes were equivalent to 74–89% of the AI. For copper, median intakes reached 79–94% of the AI. Overall, mineral intake was higher in preschoolers than in toddlers. However, for calcium and manganese (in boys), the difference between age groups was not significant. Sex-specific differences were found for magnesium, copper and manganese in toddlers, and for phosphorus in preschoolers, all showing higher intakes in boys (**Table 4**).

4 Discussion

This representative study identified nutrient imbalances in young children in Germany up to school entry age, showing vitamin D and iodine intakes well below DRVs, irrespective of age and sex, as well as age-specific non-attainment of DRVs for iron in toddlers and calcium in preschoolers. In contrast, high intakes were found for SFA, mono-/disaccharides, and protein in both age groups.

For vitamin D, the majority of requirement is usually covered by endogenous synthesis in the skin. However, the EFSA AI is based on the premise of minimal cutaneous vitamin D synthesis (12) and may overestimate dietary requirements in case of sufficient sun exposure. According to the European Academy of Paediatrics (EAP), vitamin D deficiency is likely to affect a considerable proportion of healthy European children (22). For Germany, KiGGS data showed a prevalence of vitamin D deficiency (25-hydroxyvitamin D <30 nmol/L) of 5.7% (girls) and 4.9% (boys) in 1- to 2-year-olds and 9.1% (girls) and 11.5% (boys) in 3- to 6-year-olds (23). All European countries recommend vitamin D supplementation in infants (22). In some countries, this recommendation is extended to older children (24), but not in Germany (25). This is reflected by the higher proportion of vitamin D supplement users in KiESEL children of 1 year of age compared to children aged ≥2 years. Given the overall low percentage of supplement users in both age groups, vitamin D intake was likely inadequate with insufficient sun exposure. Vitamin D intakes reported for other European countries, seemed to be higher than in KiESEL, though still below the AI (26–34). In contrast to Germany, some of these countries have mandatory vitamin D fortification policies and/or a broader range of products to which vitamin D may be added voluntarily (35).

Iodine was confirmed as being another critical nutrient in both age groups. While iodine in fortified infant and toddler

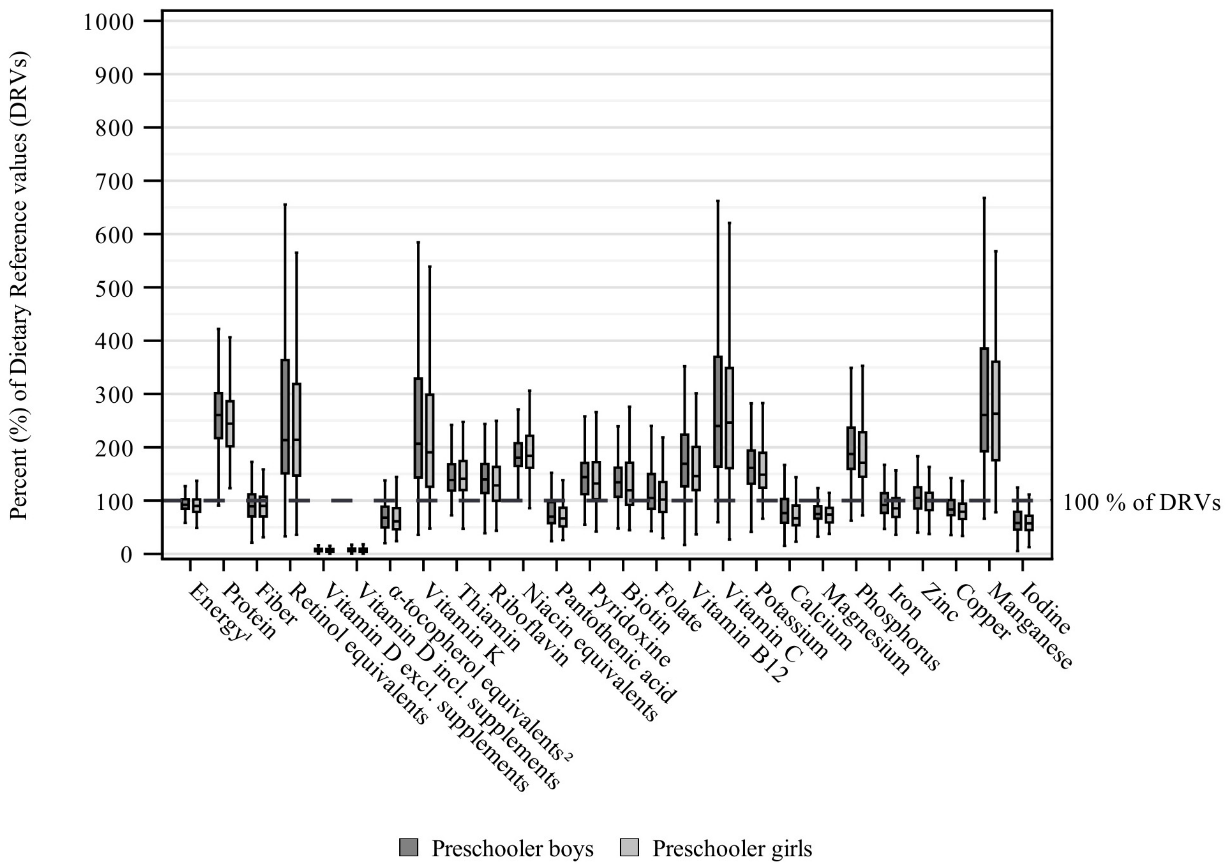

FIGURE 2
Daily energy and nutrient intake from food and beverages in preschoolers (aged ≥3 to ≤5 years) stratified by sex and expressed as % of the EFSA DRVs (12) (weighted data; box and whisker plots with median, interquartile range, and minimum-maximum; whisker length limited to 1.5 times the interquartile range, outliers excluded). The age group preschoolers refers to children aged ≥3 to ≤5 years, but also includes 62 children of 6 years of age. [1]Assuming a PAL of 1.4 for preschoolers 3 years of age and a PAL of 1.6 for preschoolers ≥4 years of age. [2]The EFSA DRVs include α-tocopherol only, while KiESEL intakes are given as α-tocopherol equivalents.

foods was considered, iodine from iodized salt could only be accounted for if explicitly reported for homemade dishes, as the preset recipes of the BLS contain non-iodized salt by default. However, according to an analysis of iodine exposure levels within the total diet BfR-MEAL-study, 1- to 6-year-olds in Germany have a high risk of inadequate intake, even under the premise of household use of iodized salt (36). A German regional cohort study (DONALD) found that the median 24-h urine iodine excretion in children aged 6–12 years decreased from 2012 onward and reached a minimum of 58.9 μg/d in 2018 (37), classified as mild iodine deficiency (38). This is thought to be due to a decrease in the use of iodized salt (37), described as a key iodine source in German preschoolers (39). Other European surveys showed iodine intakes twice as high (26, 27, 30, 31, 34), and in Danish preschoolers even three times as high as in KiESEL (32), likely explained by the mandatory iodine fortification of household salt and salt for commercial bread production in Denmark (40). In contrast, the use of fortified salt is voluntary in Germany (36). The German food-based dietary guidelines for children and adolescents recommend that households use iodized salt and choose foods with iodized salt over foods with unfortified salt for intakes to meet DRVs (9). In KiESEL, around 74% of parents stated using mainly iodized salt (36). However, the rate of use in the German food industry is estimated at 29% (41), which makes it challenging for households to choose foods with iodized salt. The apparently lower iodine intake in KiESEL in a European comparison may also be explained by mean consumption of milk and milk products (26, 30, 32, 34) and fish being lower (27, 30, 32, 34), which are important sources of iodine.

The present analysis also suggests age-specific deficits in intake for iron in toddlers and calcium in preschoolers. Though reaching only two-thirds of the PRI, toddlers' iron intake seemed to be lower midfield in a European comparison (26–31) and met the AR of 5 mg/day (12). Worth noting, KiESEL infants (≥6 to ≤11 months) even had iron intakes less than the AR (own unpublished data, 2022). Thus, both infancy and toddlerhood appear to be associated with a higher likelihood of low iron intake than preschool age. One possible explanatory factor might be a higher consumption of meat and meat products at older ages [e.g., 5-year-olds showed an over 1.5 times higher meat consumption per kcal energy intake than 1-year-olds in KiESEL (own unpublished data, 2023)].

Calcium intake, on the other hand, appeared to be potentially critical in preschoolers only, which could be related to the PRI being considerably higher in preschoolers than in toddlers [800 vs. 450 mg/day (12)]. According to EFSA, a median intake equal to the AR reflects a risk of inadequate intake in 50% of individuals

(42). Consequently, more than half of KiESEL preschoolers were at risk of insufficient calcium intake. Calcium intake in KiESEL preschoolers seemed lower than in other European surveys (27, 28, 32–34), which may too be related to mean consumption of milk and milk products being lower (28, 32, 34, 43).

In contrast, protein intakes in KiESEL toddlers and preschoolers might be too high. There is emerging evidence supporting a link between high protein intake in early life and later risk of obesity (44). However, in the absence of applicable upper intake levels for the period beyond complementary feeding, a final conclusion on protein intake is not possible. Though intakes in KiESEL exceeded DRVs, available data on protein intake (E%) from other European studies suggest them being at the lower end of the spectrum (26, 28–32, 34).

In the absence of an intake threshold below which no adverse effects exist, the EFSA recommends SFA intake to be as low as possible (12). The WHO set a recommended limit of 10 E% (45), which was clearly exceeded in both KiESEL toddlers and preschoolers, pointing to an unfavorable fatty acid pattern with regard to the risk of cardiovascular disease in later life (46). This observation is in line with a review concluding that the intake of SFA in children aged 1–7 years worldwide was mostly above recommended maximum thresholds, especially in Europe (47). In a European comparison, SFA intakes in KiESEL appeared to be mid-range (26, 28–30, 32, 34).

Similarly, the WHO recommends reducing free sugar intake to <10 E% (48), while EFSA could not identify a level of intake without adverse effects (49). A high intake is likely to facilitate adverse food preferences in early life, e.g., for sweet taste (5), and promote weight gain (48). In KIESEL, free sugars from soft drinks, sweets, fruit juices, cakes, milk and milk products, breakfast cereals, and spices/seasoning sauces corresponded to an estimated 12 E% in toddlers (in boys and girls) and 18 and 17 E% in preschooler boys and girls, respectively (own unpublished data, 2023), estimates derived as in Heuer (50). Intakes were thus too high, particularly in preschoolers. Based on an EFSA analysis, the mean free sugar intake in Europe ranged between 4 and 18 E% in toddlers and 8 and 20 E% in children aged 3–9 years (49).

The present analysis shows a number of differences in nutrient intake between boys and girls that are expected to be related to the higher energy intake in boys compared to girls. Worth noting is that on average preschool boys consumed disproportionately more mono-/disaccharides than their female peers. Boys in the older KiESEL age group consumed more sweets and soft drinks compared to girls (mean: + 19 g/day and + 42 g/day, respectively) (51), likely making them more affected by the adverse effects of free sugar intake.

With nutrition in the early years of life being a key determinant of lifelong health, it is fundamental from a public health perspective to rigorously invest in measures targeting this decisive early phase of life. The present study offers valuable guidance for public health service providers and policymakers as to which nutrients and groups at risk to prioritize and assists in ensuring efficient, need-based resource allocation.

Key strengths of this study are the representative sampling approach and the use of a weighting factor to correct for deviations from the German population, but also the level of detail of data provided by weighed food records (52). Besides, the joint use of the two food composition databases BLS and LEBTAB improves the matching of food items. However, despite the use of a weighting factor, children of parents with low SES were somewhat underrepresented, limiting generalizability. Also, weighed food records entail a high respondent burden, potentially inducing changes in dietary behavior (52), and may be confounded by social desirability bias (53). Besides, a comprehensive assessment of nutrient deficiency risk also requires the analysis of relevant biomarkers. However, feasibility is limited due to high costs, limited parental compliance (54), and a lack of reliable biomarkers (55).

5 Conclusion

Toddlers and preschoolers in Germany show nutrient imbalances consisting of non-attainment of several micronutrient DRVs (particularly vitamin D and iodine), accompanied by unfavorable macronutrient distribution (high share of SFA, mono-/disaccharides, and potentially also protein). Research is urgently needed to determine if routine vitamin D supplementation should be extended beyond infancy. Measures to increase the rate of use of iodized salt by both the food industry and households as well as to lower the intake of SFA and mono-/disaccharides during early childhood are to be strengthened.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval. Requests to access these datasets should be directed to TH, thorsten.heuer@mri.bund.de.

Ethics statement

The study involving humans was approved by the Ethics Committee of the Berlin Chamber of Physicians (Eth-28/13). The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LB: Conceptualization, Formal analysis, Methodology, Writing – original draft. SJ: Conceptualization, Methodology, Writing – review and editing. CS: Conceptualization, Methodology, Writing – review and editing. A-KB: Conceptualization, Methodology, Writing – review and editing. AS: Conceptualization, Methodology, Project administration, Writing – review and editing. UA: Writing – review and editing. SS: Conceptualization, Methodology, Writing – review and editing. RE: Conceptualization, Methodology, Writing – review and editing. TH: Conceptualization, Methodology, Project administration, Supervision, Writing – review and editing.

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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/fnut.2023.1302323/full#supplementary-material

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Differential dietary intake and contribution of ultra-processed foods during pregnancy according to nutritional status

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Introduction: Frequent consumption of ultra-processed foods (UPFs) during pregnancy is linked to excess intake of added sugar, fat, and sodium and inadequacy of several micronutrients. Diet quality during pregnancy should be maximized as inadequate levels of key nutrients and excessive intake of energy and added sugar might influence mother–child health. We aimed to estimate the contribution (% of total calories) of ultra-processed products to the total energy intake by pre-gestational body mass index (BMI) categories and Hb status during pregnancy in participants from the MAS-Lactancia Cohort.

Methods: Pre-gestational weight, hemoglobin levels, 24-h dietary intake recall interviews, and sociodemographic data were collected during the second and third trimesters of pregnancy. Reported consumed foods were categorized using the NOVA classification, and the contribution of calories from each NOVA category was estimated using the Mexican Food Database. We estimated medians and interquartile ranges (p25 and p75) for dietary intake and energy contributions. The comparison of intake between the second and third trimesters was done using the Wilcoxon test. In addition, a quantile regression model with an interaction between pre-gestational BMI and Hb levels status in tertiles over the percentage of energy from UPFs was adjusted by age and socioeconomic status.

Results: The contribution to total energy intake from UPFs was 27.4% in the second trimester and 27% in the third trimester (with no statistical difference). The percentage of energy intake from UPFs was higher in women who started pregnancy with obesity and presented the lowest levels of Hb (1st tertile), 23.1, 35.8, and 44.7% for the 25th, 50th, and 75th percentiles, respectively, compared to those with normal BMI and the highest tertile of Hb levels: 18, 29.0, and 38.6% for the 25th, 50th, and 75th percentiles, respectively.

Conclusion: In conclusion, UPF intake in pregnant women is similar to the general population and was higher for those with pre-gestational obesity and the lowest tertile of Hb levels. UPF contributes also to sugar, saturated fat, and sodium, which may adversely affect the health of mothers and their offspring.

KEYWORDS

ultra-processed foods, hemoglobin levels, NOVA classification, nutritional status, pre-gestational BMI

1 Introduction

Nutritional status in women of reproductive age is crucial for mother and child health, having a major influence on the short- and long-term health of both (1–3). The combined prevalence of overweight and obesity in Mexican women was 75% in 2021, and it is estimated that 41% of Mexican women of reproductive age live with obesity (4). Another recent public health concern in Mexico is anemia during pregnancy, with 35% of pregnant women having serum hemoglobin concentrations below 11 g/dL (5, 6).

Ultra-processed foods (UPFs) are typically characterized as being high in energy density, added sugars, trans and saturated fats, and sodium while being low in fiber and key micronutrients (7, 8). Diets with nutrient-poor, high-energy-density foods, such as UPFs, are taking over fresh and minimally processed foods that are the basis of traditional healthy diets (9). It has been reported that Mexico is the leading country in UPF consumption in Latin America (214 kg/*per capita* annually retail sales in 2013) (10), with close to 30% of the total energy intake contributed by UPF in Mexican adults (11). Thus, on average, the quality of the Mexican diet is low and may be contributing to excessive weight gain and anemia during pregnancy (12).

There is consistent evidence of a higher risk of adverse health outcomes in children and adults associated with the consumption of UPF worldwide (13). Recent literature reported studies of the association between UPF consumption in pregnant women and gestational diabetes mellitus (14), excessive gestational weight gain (15, 16), hypertensive disorders of pregnancy (17), and shortened gestation (18).

Therefore, the aim of this study was to characterize the intake of UPFs in pregnancy as a percentage of total calories consumed and estimate the distribution of calories consumed by UPFs according to the pre-gestational BMI and the levels of Hb during pregnancy. Finally, we estimated that UPF consumption was different according to the pre-gestational BMI status and the levels of Hb during pregnancy.

2 Materials and methods

2.1 Study design and population

For this study, we used data from the MAS-Lactancia birth cohort. Participants in the birth cohort were pregnant women affiliated with the Mexican Social Security Institute (IMSS, acronym in Spanish) located in Morelos, Mexico, which provides health services and social security to private/formal employees and their families. The women were 18–39 years old and recruited during the 16th to 22nd gestational weeks of singleton pregnancies and followed up from week 34 to the pregnancy resolution. More detailed information about the MAS-Lactancia cohort is available elsewhere (19). This project was approved by The National Institute of Public Health (IRB project number 1281 and approval number 1646). All participants who signed the informed consent before data collection during the period from March 2016 to December 2020 were included.

2.2 Sample

We analyzed two sub-samples according to the availability of the main variables (diet, nutritional status, height, weight, and hemoglobin levels). We included 660 participants to analyze diet, maternal weight, and anemia. The analytical sample consists of a subsample of 660 participants with diet available and another subsample of 346 with diet and hemoglobin levels available. We used information from the second and third trimesters and pre-gestational BMI data.

2.3 Dietary information

The diet information was collected using a 24-h recall Multiple-Pass Method (20). The interview was done randomly on different weekdays and weekends in the sample. We estimated the macro and micronutrient intakes using the same methodology as the 24-h recall analysis in the National Health and Nutrition Survey, 2016 (ENSANUT) (21). To obtain the 24-h recall diet information, we used the nutrient retention factor (NRF) to improve the accuracy of the dietary intake estimation. It was estimated in 4 phases: Phase 1.- Review and correction of all the 24-h recall steps (20); Phase 2: Estimation of food intake in grams; Phase 3: Processing. Estimation of energy and nutrients according to the Mexican Food Database version 18.1.1 (BAM (acronym in Spanish: Base de datos de los Alimentos Mexicanos) in which 1978 foods, recipes, and drinks have been listed (22). The NRF was estimated following the United States Department of Agriculture (USDA), Bergstrom and Bognar reference (23–25). In case the reported food information was not available, we used the NRF average value, the NRF group-specific, and the compilation of the European Food Information Resource (EuroFIR) (26); Phase 4: Energy and nutrient data cleaning. We included nutrients, energy, carbohydrates, total fat, saturated fat, sugars, sodium, potassium, calcium, folic acid, vitamin B12, vitamin B6, vitamin C, and iron content. We aggregated the energy and food/ingredient of the nutrient content at the individual level. The review of dietary intake reported plausible values; the equations were developed by the Institute of Medicine (IOM) according to body mass index (BMI (kg/m^2), normal weight, overweight or obese) and age group (21).

Outliers were identified based on the relationship between each nutrient intake and the average requirements. For both macronutrients and micronutrients, according to the proportional distribution of each nutrient, standard deviation values <−3 and >+3 were considered outliers or extreme values according to pregnancy and age groups. Pregnant women who reported an intake of fewer than 500 kilocalories and more than 5,000 kilocalories were excluded from the analysis (21). We also include the intake of supplements (specifically iron and folic acid) in the estimations, as they are regularly prescribed.

The percentage of energy from ultra-processed foods to total dietary energy was estimated after obtaining the detailed diet information and having the food list and ingredients disaggregated from the 24-h recall; we classified foods and beverages according to the industrial processing to preserve, extract, or modify their characteristics using the NOVA approach (8). The diet exposure variables were determined following the NOVA approach, which is classified into four groups: (1) non-processed or minimally processed foods, (2) culinary ingredients, (3) processed foods, and (4) UPFs. After having classified the food and beverages, we estimated the contribution from each food and beverage by NOVA group (1, 2, 3, and 4) to the total energy intake, and then we ranked each food and beverage by NOVA group to obtain the food and beverage that most contributed to the energy intake.

2.4 Nutritional status

For this analysis, we considered two variables to classify nutritional status, pre-gestational BMI status, and Hb levels in the second and third trimesters. Pre-gestational weight was obtained from the IMSS medical files self-reported at their first medical consultation. Pre-gestational BMI was calculated and categorized into three categories: normal pre-gestational BMI ($\geq$18.5–24.9 kg/m^2), overweight ($\geq$25–29.9 kg/m^2), and obesity ($\geq$30 kg/m^2). We obtained information on Hb levels from each participant's clinical files, which were analyzed at the IMSS laboratory hospital (UniCel DxC 600/800 SYNCHRON) and recorded in the electronic medical system. The township of residence determined the altitude adjustment for the hemoglobin level, and all hemoglobin levels were adjusted by altitude. Then, we classified anemia during pregnancy according to the WHO guidelines on hemoglobin levels <11 gm/dl (27).

2.5 Co-variables

The information about maternal age, years of schooling [education level: elementary school (6 years), high school (12 years), and undergraduate (more than 16 years)], socioeconomic status (Household Wealth Index), marital status (single/married), and employment were obtained from medical records and questionnaires within the MAS-Lactancia cohort data.

2.6 Statistical analysis

Continuous variables (age, schooling, and Hb) were estimated as means ± standard deviations, while categorical variables (socioeconomic status, occupation, marital, and nutritional status) were estimated as frequencies and proportions. For dietary variables, we estimated medians and interquartile ranges (p25 and p75) as their distribution was skewed. We compared the intake between the second and third trimesters using the Wilcoxon test.

As dietary data were skewed, the associations were evaluated using a quantile regression. For these models, the outcome is the relationship between a set of predictor variables and the target variable quantile (50th percentile is the most common one) (28). When the median is used instead of the mean to describe the link between the variables, it has advantages over conventional least squares regression, including that the models are more robust or less sensitive to outliers (28, 29). Additionally, it requires no assumptions about the model's distribution or homoscedasticity (29). In terms of the exposure variables, the Hb levels were divided into three categories based on tertiles. We opted for tertiles instead of simply classifying women as anemic or non-anemic because it is widely recognized that pregnant women with moderate-to-severe anemia face a greater risk of adverse outcomes compared to those with mild anemia (30). Moreover, elevated maternal Hb levels have been linked to adverse maternal and infant outcomes such as gestational diabetes mellitus, preterm birth, low birth weight, and fetal death (31–33).

To avoid the assumption of linear relationship or fixed functional ways, the independent variables were categorized as tertials with the outcome variables, therefore providing the model's flexibility alongside ease of interpretation. Covariates included in the quantile model were socioeconomic level. Finally, we generated a quantile regression model with an interaction between pre-gestational BMI (normal, overweight, and obesity) and tertiles of hemoglobin levels status over the percentage of energy from UPF (25th, 50th, and 75th percentiles). Normal pre-gestational BMI and Hb levels in the third tertial (the highest) were taken as the reference. We considered a significance level of $p < 0.05$ for the tests and regressions and $p < 0.1$ for the interaction term. All data were analyzed using the Statistical Package Stata software version 14.0.

3 Results

The sociodemographic characteristics at enrollment are presented in Table 1. We analyzed 660 participants included in the study in the second and third trimesters of pregnancy with a median gestational age of 20 (IQR 18–24) and 34 weeks (IQR 34–35), respectively. The mean age was 26.4 years old, and the mean schooling was 12.9 years. 50.7% of the participants work in the formal sector. The pre-gestational nutritional status was 58, 31, and 11% for normal (BMI <25 Kg/m^2), overweight (BMI $\geq$25 Kg/m^2 & BMI < 30 Kg/m^2), and obesity (BMI >30 Kg/m^2) categories, respectively. It is noteworthy that in the third trimester, these proportions change dramatically to 17.1, 48.7, and 34.2% for normal, overweight, and obesity categories, respectively. On average, participants had a gestational weight gain of 10.3 Kg. Regarding hemoglobin levels, the mean adjusted for altitude levels were 12.3 g/dL and 11.9 g/dL for the second and third trimesters, respectively.

3.1 Diet contributions

We evaluated the daily intake of macronutrients and micronutrients during the second and third trimesters of pregnancy. Medians (interquartile range) of macro and micronutrient daily intake and contribution to the diet are shown in Table 2. The median energy intake in 24 h at enrollment (2nd trimester) was 2,135.3 kcal, with the distribution from carbohydrates, proteins, and total fats of 56.4, 13.1, and 31.3%, respectively.

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TABLE 1 General characteristics of pregnant women participants (*n* = 660).

	Mean (SD) or frequency (%)
<Age (years)[a]	26.4 (5.02)
Sociodemographic	
Schooling (years)[a]	12.9(3.00)
Socioeconomic Status	
Low	212 (32.1)
Medium	221 (33.5)
High	227 (34.4)
Occupation	
Housewife	234 (35.6)
Informal-student	90 (13.7)
Formal	334 (50.7)
Marital Status	
Single	92 (13.9)
Married - unmarried union	566 (86.1)
Nutritional status	
Pregestational BMI categories	
Normal	347 (58)
Overweight	187 (31)
Obesity	68 (11)
BMI 2nd trimester	
Normal	278 (43.1)
Overweight	261 (40.5)
Obesity	106 (16.4)
BMI 3rd trimester	
Normal	39 (17.1)
Overweight	111 (48.7)
Obesity	78 (34.2)
Gestational weight gain (Kg)	10.3 (4.06)
Hemoglobin Levels (g/dL) 2nd trimester[b]	12.3 (1.2)
Hemoglobin Levels (g/dL) 3rd trimester[b]	11.9 (0.9)

[a]Means and standard deviations for continuous variables and frequencies.
[b]Hemoglobin levels are only available in 396 participants.

TABLE 2 Description of diet during pregnancy.

Macro/ micronutrients	Daily intake 2nd trimester	Daily intake 3rd trimester	*p*-value*
	p50 (p25, p75)	p50 (p25, p75)	
Energy (kcal)	2135.3 (1685.5, 2759.9)	2385.2 (1836.1, 2992.1)	< 0.001
Macro Nutrients			
Carbohydrates (g)	293.5 (231.5, 383.6)	335.1 (253.2, 440.7)	< 0.001
Carbs % of energy	56.4 (49.8, 63)	56.3 (49.9, 64.5)	0.449
Fiber(g)	23.1 (16.8, 33.4)	26.7 (18.9, 35.4)	0.002
Total Sugar(g)	125.1 (90, 164.9)	145 (101.8, 193.1)	< 0.001
Total sugar (%)	23.43 (21.35, 23.89)	24.31 (22.17, 25.8)	0.38
Proteins(g)	71.3 (53.7, 96.5)	78.5 (58.9, 107.3)	0.005
Protein % of energy	13.1 (11.1, 15.8)	13.3 (10.9, 15.8)	0.783
Total Fats (g)	74 (51.8, 101.9)	81 (58.7, 117.7)	0.009
Fat % of energy	31.3 (26.2, 37.2)	31.2 (26.2, 37.3)	< 0.001
Saturated Fats (g)	29.1 (19.7, 41.1)	30.9 (21.1, 44.4)	0.055
Saturated Fats (%)	12.26 (10.51, 13.4)	11.65 (10.34, 13.35)	0.01
Micronutrients			
Total Iron(mg)	57.5 (16.4, 82.2)	49.8 (19.7, 83.7)	0.508
Iron Hem(mg)	0.61 (0.26, 1.2)	0.75 (0.4, 1.4)	0.018
Iron no-Hem(mg)	12.7 (8.6, 19.7)	15.4 (10.4, 21.7)	< 0.001
Folate DFE (mcg)	555.7 (376.7, 828.5)	661 (462.8, 1065.8)	< 0.001
B6 Vitamin (mg)	2.2 (1.4, 4.4)	3.2 (1.7, 5.5)	< 0.001
B12 Vitamin (mcg)	4.7 (2.4, 8.1)	6 (3.1, 10.2)	0.003
Vitamin C (mg)	191.8 (96.6, 350.2)	207 (129.6, 336.7)	0.053
Calcium (mg)	1230.5 (927.1, 658.3)	1287.9 (937.2, 1897.2)	0.086
Potassium (mg)	2,950 (2178.9, 3907.5)	3310.9 (2342.1, 4547.5)	< 0.001
Sodium (mg)	2885.4 (2007.8, 3885.1)	3158.3 (2083.9, 4,638)	< 0.001

*Statistical differences were determined using the Wilcoxon test.

The medians of fiber (23.1 g), total sugars (125.1 g), sodium (2885.4 mg), saturated fat (29.1 g), and micronutrients total intake consumed during the 2nd trimester were total iron (57.5 mg), hem-iron (0.61 mg), non-hem-iron (12.7 mg), folate DFE (555.7 μg), B6 vitamin (2.2 mg), B12 vitamin (4.7 mg), vitamin C (191.8 mg), potassium (2,950 mg), and calcium (1230.5 mg). On the other hand, the median estimation of 24 h energy intake at follow-up (3rd trimester) was 2385.2 kcal with almost the same distribution of macronutrients as the percentage of energy intake. The intake of potassium, B12, B6, folate, and non-hem-iron was statistically higher in the third trimester. However, we did not identify significant differences within the daily intake of total iron, iron hem, B12 vitamin, Vitamin C, and calcium between the second and third trimesters. It is important to highlight that even saturated fat decreased from the second to the third trimester; in both trimesters, only 25% of the sample consumed less than 10%, which is the maximum recommended. In the case of sodium, the intake increases from the second to the third trimester, and also only 25% reported consuming 2000 mg/d or less (the amount recommended by WHO).

The median total contribution for energy, total sugar, saturated fat, and sodium intake during the second and third trimesters of the foods classified according to NOVA are shown in Table 3. UPFs (NOVA 4), on average, contribute to 27, 29, 26.5, and 31% of total calories, total sugar, saturated fat, and sodium, respectively (Table 3). The most consumed foods from the NOVA 1 group were traditional tortillas representing 52.5%, followed by milk 12.7%, chicken 9%, beef 7.2%, banana 2.7%, and oatmeal 1.8%. NOVA 2 were vegetable oils (43.3%), sugar (29.7%), brown sugar cane (piloncillo) (4.2%), animal lard (3.9%), butter (2.3%), and vegetable lard (1.4%). NOVA 3 were cheeses (51.7%), corn flour (14.7%), cow's milk acid cream (8.2%), condensed evaporated milk (6.7%), tortilla, toast [corn flour (MASECA)] (5.5%), and dry-salted meat (cecina) (4.7%). The NOVA 4 (UPFs) most consumed foods were sweet bread, white bread, cookies, cakes and donuts (49.7%), breakfast cereals (6.1%), industrialized juices and soda (6.1%), pizza (5.1%), corn chips (fritters) (5.1%), and candies covered with chocolate (3.5%).

Table 4 presents the results of the quantile regressions for the prediction of the 25th, 50th, and 75th percentiles of contribution to energy from the intake of UPF or NOVA 4. The Hb levels were stratified into three categories defined by tertials: T1 mean 11.0 g/dL (range 6.2–11.7), T2 mean 12.2 g/dL (range 11.8–12.7), and T3 mean 13.4 g/dL (12.8–18.9). There is a tendency for the distribution of energy intake from UPF to be higher as pre-gestational BMI categories increase and Hb tertiles decrease. Highlighting in those women that started the pregnancy with obesity (BMI > 30 kg/m^2) and in the lowest tertile of Hb (≤ 11 g/L), there was a statistically higher intake of UPF for percentiles 50th and 75th. These women had an intake of 35.8% (IQR 27.4–44.3%) and 44.7% (IQR 31.5–57.9%) of energy consumed by UPF, respectively.

4 Discussion

This study particularly studied the intake of UPF, including the distribution (median and interquartile range) and the contribution to total calories. We showed that pregnant women have a similar intake of UPF (27% of total calories) as the rest of the Mexican population (30% of total calories) (11), and also agrees with a previous report in a Mexican birth cohort (27.9% of total calories) (34), which can reflect that food quality did not improve according to the gestational status.

Diet quality declines when UPF consumption is increased during pregnancy (35). Our findings indicate that UPFs (NOVA 4) contribute 27, 29, 26.5, and 31% of total calories, total sugar, saturated fat, and sodium, respectively. Previous studies involving American, Norwegian, Brazilian, and Mexican pregnant women have estimated the proportion of UPF in total energy intake, revealing a wide range: over 50% in American women (16, 36), nearly twice the amount found in our study; 46% in Norwegian women; 27.9% in Mexican women; and 20.9% in Brazilian women (34, 37, 38). Furthermore, our analysis highlights the contribution of sodium, saturated fat, and sugar from UPF to the overall nutrient intake during pregnancy.

Furthermore, UPF usually contains some sugar substitutes and other additives that alter intestinal function, interfere/or decrease the bioavailability and absorption, especially of iron, as well as compounds such as acrylamide, which is usually used for the UPF industrialization have been associated with a decrease in hemoglobin biomarkers (39).

Specifically, the highest energy contribution consumed by UPFs (35.8-p50th to 44.7%-p75th) were those with the combination of pre-pregnancy obesity (BMI > 30 kg/m2) and the lowest Hb levels during pregnancy. A previous study in a US cohort showed that the lowest dietary quality among pregnancy was seen in women with pre-pregnancy obesity (40).

Although we did not consider weight gain in the estimations, we observed that average weight gain was 10 kg, with a difference in gestational weight gain only between normal pre-gestational BMI and pre-gestational overweight women (1.2 Kg more in the first group). This could reflect a decline in the normal BMI category from 58% pre-pregnancy to 17% at the end of pregnancy. Concurrently, obesity doubles, rising from 16.4 to 34.2%. In comparison, a study from Brazil estimated that each extra 1% of total calories from UPF led to an increase of 4.17 g/week in the third trimester (15). In addition, a study conducted on US women reported that gestational weight increased by 1.33 kilograms per percentage point, a higher contribution of the UPF to total energy. The same study reported that UPF consumption increases neonatal body fat (16).

Furthermore, a recent meta-analysis identified that maternal consumption of UPF-rich diets was associated with an increased risk of gestational diabetes mellitus and preeclampsia (41). More importantly, pre-gestational UPF consumption could increase the risk of gestational diabetes mellitus (42). Additionally, specific products belonging to UPF categories, such as industrial sweets, bakery products, and pastries, increase the odds of having a small-for-gestational-age newborn (43). Soft drink consumption (>7 times/week) also appears to be a risk factor for gestational hypertension (44). All this evidence underscores the importance of limiting UPF consumption before and during pregnancy to improve maternal and neonatal health.

The strength of this study is that it is nested as a secondary analysis from a cohort, which allows us to have repeated (in both trimesters) measures of Hb and diet. We acknowledge several limitations to this study. First, the included participants were from a secondary-level hospital, i.e., the study population is affiliated with IMSS clinics and is therefore not representative of the general population. Second, we needed a sufficient sample size to ensure sufficient power in the hemoglobin and diet models. Third, the hemoglobin levels were obtained from clinical records, and it was not possible to access serum ferritin measurements to evaluate the etiology of anemia. However, 80% of cases of anemia in pregnancy are due to iron deficiency (45). The pre-gestational BMI was self-reported by the participants and may have produced an error in the estimates, which could lead to an underestimation of the association with maternal weight. When measuring diet through the 24-h recall (20), the information bias is significant since sometimes the participants do not remember or do not want to report food consumption, obtaining an under-reporting of the exposure variable. Covariates such as physical activity and sleep quality that affect energy balance were not measured and considered in the models. Diet was not assessed more frequently within the same trimester.

5 Conclusion

In this cohort, pregnant women have an excessive intake of UPF, particularly those with the double burden of malnutrition, pre-pregnancy obesity, and low levels of Hb. On average, UPF

TABLE 3 Consumed food that contributed the most to energy intake by the NOVA group.

Group	Trimester	% Contribution to total energy intake p50 (p25, p75)	% Contribution to total sugar intake p50 (p25, p75)	% Contribution to total saturated fat intake p50 (p25, p75)	% Contribution to Sodium intake p50 (p25, p75)	Tops foods represented by the NOVA group						
NOVA 1	2nd trim	51 (40.9, 62.9)	41.9 (28.3, 59.4)	34.8 (20.4, 54.9)	15.7 (9.6, 25.7)	Food	Tortilla (Traditional, Nixtamalized Corn)	Milk	Chicken	Beef	Banana	Oatmeal
	3rd trim	53.7 (42.6, 63.3)	42.40 (26.92, 58.72)	37.77 (23.45, 52.41)	15.61 (9.75, 25.35)	Contribution	52.5	12.7	9	7.2	2.7	1.8
NOVA 2	2nd trim	10.4 (4.8, 16.8)	0.1 (0, 0.9)	4.1 (1.1, 9)	27.5 (13.3, 45)	Food	Vegetable oils	Sugar	Brown Cane Sugar (Piloncillo)	Animal's Lard	Butter	Vegetable Lard
	3rd trim	11 (5.4, 17.3)	0.1 (0, 1.1)	4.2 (1.6, 9.1)	28.6 (15.7, 41.9)	Contribution	43.3	29.7	4.2	3.9	2.3	1.4
NOVA 3	2nd trim	3.6 (0.12, 11.1)	18.5 (3.9, 31.4)	19.4 (4.2, 39.6)	13.1 (3.6, 29)	Food	Cheeses	Corn Flour	Cow's milk acid cream	Condensed evaporated milk	Tortilla/Toasts [Corn Flour (MASECA)]	Dry-Salted meat (cecina)
	3rd trim	3. 3(0.3, 9.5)	16.4 (4.3, 29.5)	20 (4.9, 38)	14 (4.1, 27.5)	Contribution	51.7	14.7	8.2	6.7	5.5	4.7
NOVA 4	2nd trim	27.4 (17.5, 38)	29 (13.4, 46.5)	26.3 (9.5, 44.2)	30.6 (13.8, 44.6)	Food	Sweet Bread, White Bread, Cookies, Cakes, and Donuts	Breakfast Cereals	Industrialized Juices and Soda	Pizza	Corn Chips (fritters)	Candies Covered with Chocolate
	3rd trim	27 (17.3, 37)	28.8 (14, 48.9)	27.1 (11.6, 43.1)	31.7 (18.2, 46.1)	Contribution	49.7	6.1	6.1	5.1	5.1	3.5

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TABLE 4 Quantile regression models for the percentiles 25th, 50th, and 75th of the percentage of energy intake from UPFs according to the pregestational BMI and Hb levels ($N = 346$).

	Percentile 25th				Percentile 50th				Percentile 75th			
	Predicted percentage	Standard error	95% intervals		Predicted percentage	Standard error	95% intervals		Predicted percentage	Standard error	95% intervals	
Pregestational BMI												
Normal BMI (*n* = 198)	16.6	1.5	13.8	19.5	27.9	1.6	24.8	31.1	37.8	1.8	34.2	41.4
Overweight (*n* = 104)	19.9	2.1	15.7	24.1	28.6	1.9	24.9	32.2	40.2	2.8	34.6	45.8
Obesity (*n* = 44)	20.1	3.4	13.5	26.7	29.0	2.7	23.7	34.3	37.6	4.5	28.8	46.4
Hb levels												
1st tertile (*n* = 115)	17.7	2.6	12.7	22.7	29.4	1.5	26.4	32.4	39.1	3.0	33.3	44.9
2nd tertile (*n* = 101)	17.0	1.8	13.5	20.4	27.5	2.6	22.4	32.5	38.2	2.6	33.2	43.3
3rd tertile (*n* = 130)	19.2	1.6	16.0	22.3	27.8	1.6	24.6	31.1	38.1	2.1	34.0	42.3
Pregestational BMI*tertiles Hb levels												
Normal BMI *1st tertile Hb (*n* = 69)	15.6	3.0	9.8	21.4	27.8	2.0	23.8	31.8	36.8	3.7	29.7	44.0
Normal BMI *2nd tertile Hb (*n* = 56)	15.6	2.1	11.5	19.6	26.7	3.9	19.1	34.4	37.8	3.2	31.5	44.0
Normal BMI *3rd tertile Hb (*n* = 73)	18.4	2.4	13.6	23.1	29.0	2.2	24.7	33.3	38.6	2.7	33.3	44.0
Overweight*1st tertile Hb (*n* = 31)	19.5	4.8	10.1	28.8	29.8	2.5	24.9	34.8	41.1	5.9	29.5	52.6
Overweight*2nd tertile Hb (*n* = 33)	19.1	4.1	11.0	27.2	29.2	3.9	21.6	36.7	39.1	4.5	30.3	47.9
Overweight*3rd tertile Hb (*n* = 40)	20.8	2.2	16.5	25.2	27.0	3.3	20.6	33.3	40.3	3.9	32.7	47.9
Obesity*1st tertile Hb (*n* = 15)	23.1	8.1	7.3	38.9	**35.8**	**4.3**	**27.4**	**44.3**	**44.7**	**6.7**	**31.5**	**57.9**
Obesity*2nd tertile Hb (*n* = 12)	18.2	3.5	11.3	25.2	26.9	6.7	13.8	39.9	38.4	11.7	15.5	61.4
Obesity*3rd tertile Hb (*n* = 17)	18.9	4.4	10.2	27.5	24.6	3.0	18.8	30.4	30.6	4.7	21.4	39.9

*Models adjusted by maternal age, SES, and total energy intake. Blood values represents statistically significant differences ($p<0.05$).

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contributes to 27, 29, 26.5, and 31% of total calories, total sugar, saturated fat, and sodium, respectively. Urgent actions in the counseling since antenatal care regarding diet quality as high UPF consumption is associated with an increased risk of mortality from all causes, cardiovascular diseases, metabolic syndrome, overweight, obesity, irritable bowel syndrome, different types of cancer in adults (46), and increased weight gain in pregnancy (16), effects that can affect mother and their offspring.

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 humans were approved by The Research Ethics Committee of the National Institute of Public Health (#1281). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AG-A: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. AC-M: Conceptualization, Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. AC: Conceptualization, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. DC: Conceptualization, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing. JM-P: Data curation, Validation, Writing – original draft, Writing – review & editing. LÁ-J: Resources, Writing – original draft, Writing – review & editing. IR-S: Data curation, Project administration, Validation, Writing – original draft, Writing – review & editing. JR: Investigation, Writing – original draft, Writing – review & editing. LG: Writing – original draft, Writing – review & editing. IB: Writing – original draft, Writing – review & editing. HL-F: Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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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