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# Anthropometric assessment

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# Anthropometric assessment

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# Association between phase angle and the nutritional status in pediatric populations: a systematic review

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**Background and aims:** Malnutrition is prevalent in pediatric populations with any disease, and it is also related to changes in body composition. In addition, recent studies have documented relationships between these changes and phase angle (PhA), an important parameter of functional nutritional assessment. PhA could be a new marker of nutritional status. Many studies have generated information about the association between PhA and malnutrition in various pathologies, although the vast majority of this information is from adult populations. In this systematic review, we answered the following question: What is the association between PhA and the nutritional status in pediatric populations?

**Methods:** We performed a systematic search of the Medline/PubMed and Latin American and Caribbean Health Sciences Literature databases (LILACS) databases for studies published up to October 2022. The inclusion criteria were pediatric subjects, which reported the relationship between PhA and the nutritional status with any objective nutritional indicator, and PhA was measured by electric impedance and reported at 50 kHz. We synthesized data from the studies that reported cutoff analysis of PhA with receiver operating characteristic (ROC) curves, mean PhA values presented by nutritional status strata, and correlations between PhA and nutritional status indicators. We assessed the risk of bias by using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and the Quality Assessment for Diagnostic Accuracy Studies.

**Results:** Of the 126 studies we identified, 15 met the inclusion criteria. The included studies reported the association between PhA and objective indicators of nutritional status, including weight-for-age z-score (WAZ) <-1 standard deviation (SD) for malnutrition, height-for-age z-score (HAZ) for malnutrition-stunting, body mass index (BMI) for the starvation state, body mass index z-score (BMIz) and BMI for malnutrition, mid-upper arm circumference (MUAC) < 11 cm for severe acute malnutrition (SAM), and fat-free mass index z-score (FFMIz) <-2 z-score for moderate malnutrition, among others. The report of these associations between PhA and nutritional status was based on cutoff points generated with

ROC curve analysis or comparison of mean PhA values, which were reported stratified by the presence or absence of malnutrition, and correlations between PhA and anthropometric indicators for the evaluation of the nutritional status in the pediatric population. It was difficult to compare the studies due to the heterogeneity of the bioelectrical impedance analysis models used, how PhA was reported (standardized, percentiles, or degrees), and the anthropometric indicators used to diagnose malnutrition.

**Conclusion:** The early identification of malnutrition is relevant to establish the correct nutritional treatment; PhA appears to be a sensitive indicator of nutritional status and is easy to obtain. Although the results of this review are inadequate to establish PhA cutoff points associated with malnutrition in pediatric populations, in most of the studies, there was an association between PhA and objective indicators of nutritional status.

**Systematic review registration:** https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022362413, identifier: PROSPERO 2022 CRD42022362413.

KEYWORDS

**phase angle, children, adolescent and youth, nutritional status, pediatric population**

## Introduction

Malnutrition is prevalent in pediatric populations with any disease. It affects normal growth and response to treatment, as well as other clinical outcomes. Considering the irreversible damage of malnutrition in the pediatric stage, it is essential to assess the nutritional status and ensure an adequate nutritional supply to manage a disease. The nutritional status in pediatric patients has generally focused on evaluation based on anthropometric parameters such as body weight (BW) and height: Individual values are compared with standard growth curves of the population (1). Other anthropometric indicators used to assess the nutritional status are weight-for-age which evaluates wasting (acute malnutrition), height-for-age which evaluates stunting (chronic malnutrition), and body mass index (BMI) compared with appropriate growth charts (percentiles or z-scores). Mid-upper arm circumference (MUAC) and triceps skin fold (TSF) have also been used, but they require a trained professional to obtain the measurements. However, to date, there is not a uniform definition of malnutrition in children. The interdisciplinary American Society for Parenteral and Enteral Nutrition (ASPEN) Working Group defined pediatric malnutrition (undernutrition) as an imbalance between nutrient requirements and intake, resulting in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes (2). Even with this work, there is no consensus as to which anthropometric parameters are ideal. Nevertheless, there are other strategies related to the nutritional status that are based on body composition such as bioelectrical impedance analysis (BIA). This indirect, non-invasive, and easy-to-apply technique is used to measure body compartments such as body cell mass (BCM), fat-free mass (FFM), fat mass (FM), and total body water (TBW). BIA measurements are based on the transition of electrical current through the body to estimate the TBW, which, in turn, is based on the hydration constants of the tissues. FFM is obtained and FM is derived by using a simple equation based on two components (FFM [kg] = total weight [kg]—FM [kg]) (3).

Recent studies have documented changes in the relationship between body composition and phase angle (PhA), an important parameter of functional nutritional assessment. PhA is also measured by BIA, but it is calculated based on the relationship between the indicators of the crude electrical parameters including impedance (Z), resistance (R), and reactance (Xc): PhA = {[arc tangent (Xc/R)] × 180°/π} (4). R measures the opposition of the cell to the passage of electric current; it is determined by the state of hydration of the cell and tissue. The higher the hydration, the lower the R. Xc measures the electrical charge of the system or the capacity of the cell to store energy; it is determined by the cell membrane and the cell size. The greater the integrity of the membrane and greater the cellularity, the higher the Xc (5). PhA can be negatively influenced by various clinical diseases such as

Abbreviations: A, Adolescents; AC, arm circumference; AMAz, arm muscle area z-score; AMC, arm muscle circumference; AUC, area under the curve; BCM, body cell mass; BIA, bioelectrical impedance analysis; BMI, body mass index; BMIz, body mass index z-score; BW, body weight; C, children; CHD, congenital heart disease; CKD, chronic kidney disease; ECW, extracellular water; FFM, fat-free mass; FFMIz, fat-free mass index z-score; FM, fat mass; HAZ, height-for-age z-score; HC, healthy children; I, infants; IBD, inflammatory bowel disease; IBW, ideal body weight; ICW, intracellular water; LILACS, Latin American and Caribbean Health Sciences Literature; MUAC, mid-upper arm circumference; NCHS, National Center for Health Statistics; PhA, phase angle; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines; PROSPERO, International Prospective Register of Systematic Reviews; SAM, severe acute malnutrition; SD, standard deviation; SPhA, standardized phase angle; TBW, total body water; TSF, triceps skinfold thickness; WAZ, weight-for-age z-score; WFH, weight-for-height percentile; WHO, World Health Organization; WHZ, weight-for-height z-score; Xc, reactance; Z, impedance; %AMC, percentage of arm muscle circumference; %IBW, percentage of ideal body weight.

malnutrition. Because PhA is a marker of the quantity and quality of soft tissue mass, as well as the hydration status, many authors consider it a useful marker of nutritional status. In disease-related malnutrition, the characteristic early shift from intracellular water (ICW) to extracellular water (ECW) and an increased ratio of extracellular to BCM are reflected in PhA (6). Alteration of the electrical properties of the tissue that are detectable with BIA has been associated with the presence of malnutrition related to disease (7).

Based on these findings, PhA could identify malnutrition early due to its sensitivity to detect changes in body composition with respect to anthropometric measurements (8). Many studies have generated PhA cutoff points to identify malnutrition in various pathologies, although the vast majority of these studies have been in adults (9–11). PhA cutoff points have also been generated but are associated with survival indicators as a reference standard (12–14). Other researchers have shown how PhA is associated with various anthropometric indicators in pediatric populations, but they have not provided cutoff points (15, 16). The association between PhA and nutritional status is highly variable due to the lack of uniform definitions for malnutrition and because various anthropometric indicators are used for it (2). Hence, in this systematic review, we summarized the evidence regarding the association between PhA and the nutritional status in pediatric populations.

# Methods

We performed a systematic review to answer the following research question: What is the association between PhA and the nutritional status in pediatric populations? We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (17). We registered the protocol at the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42022362413. The protocol was approved by the Instituto Nacional de Pediatría Research and Ethics Committees (number 2022/065) and officially registered at the Office for Human Research Protections of the NIH (http://ohrp.cit.nih.gov/search/search.aspx) with numbers IRB00013674 and IRB00013675.

## Search strategy

Two authors (AFO and EARA) performed the search independently. They searched the online MEDLINE/PubMed and Latin American and Caribbean Health Sciences Literature (LILACS) databases. They used the following Medical Subject Headings (MeSH) and other terms related to the subject as part of the search strategy: ("Phase Angle") AND (Children OR Adolescents OR Pediatrics) AND (Malnutrition OR Undernutrition OR Malnourishment OR "Nutritional Status" OR "Nutrition Status"). They applied no restrictions to the date of publication of papers. They searched for articles published up to October 2022. Table 1 shows the description of the Population, Exposition, Comparators, and Outcomes (PECO) strategy applied in the present systematic review. It is based on pediatric populations (Population); PhA at 50 kHz (Exposition); any objective method to evaluate nutritional status (Comparator); and PhA cutoff points associated with malnutrition (area under the curve [AUC] values, sensitivity, and specificity), comparison of median PhA values among malnutrition strata, and correlations between PhA values and malnutrition indicator values (Outcomes).

TABLE 1 PECO criteria for study selection.

| Criterion | | Description |
|---|---|---|
| **P** | Population | Children <18 years old |
| **E** | Exposition | Phase angle at 50 kHz |
| **C** | Comparator | Objective methods to assess the nutritional status. The comparator was made with objective indicators to assess the state of nutrition, including weight-for-age, height-for-age, weight-for-height, body mass index, mid-upper arm circumference, triceps skinfold thickness, and fat-free mass index. |
| **O** | Outcomes | • Phase angle cutoff points analyzed with receiver operating characteristic curves associated with malnutrition (area under the curve values, sensitivity, and specificity).<br>• Comparison of median phase angle values among malnutrition strata.<br>• Correlation between phase angle values and malnutrition indicators values. |

## Selection of studies

After removing duplicates, the same authors (AFO and EARA) independently screened the titles and abstracts for eligibility evaluation, based on the inclusion criteria. They also carried out data extraction.

## Selection criteria

We included original studies if they met the following criteria: [1] performed on pediatric subjects <18 years of age, [2] reported the relationship between PhA and the nutritional status based on any objective nutritional indicator, [3] measured and reported PhA at 50 kHz, [4] articles written in English or Spanish, and [5] population with any clinical health condition, even a healthy population. The exclusion criteria were: [1] data with adult populations, [2] review articles, and [3] studies reporting PhA reference value tables. We also excluded studies if they contained overlapping subjects with other studies.

## Data extraction and synthesis methods

AFO and EARA independently extracted the following data from each study: [1] first author's name; [2] year of publication; [3] study location; [4] study design; [5] sample size; [6] population sex; [7] population age; [8] clinical health condition; [9] nutritional status indicator; [10] reference for malnutrition; [11] principal results related to the association between PhA and the nutritional status or any nutritional indicator; [12] prevalence of malnutrition with any nutritional indicator; [13] BIA model; [14] BIA usage

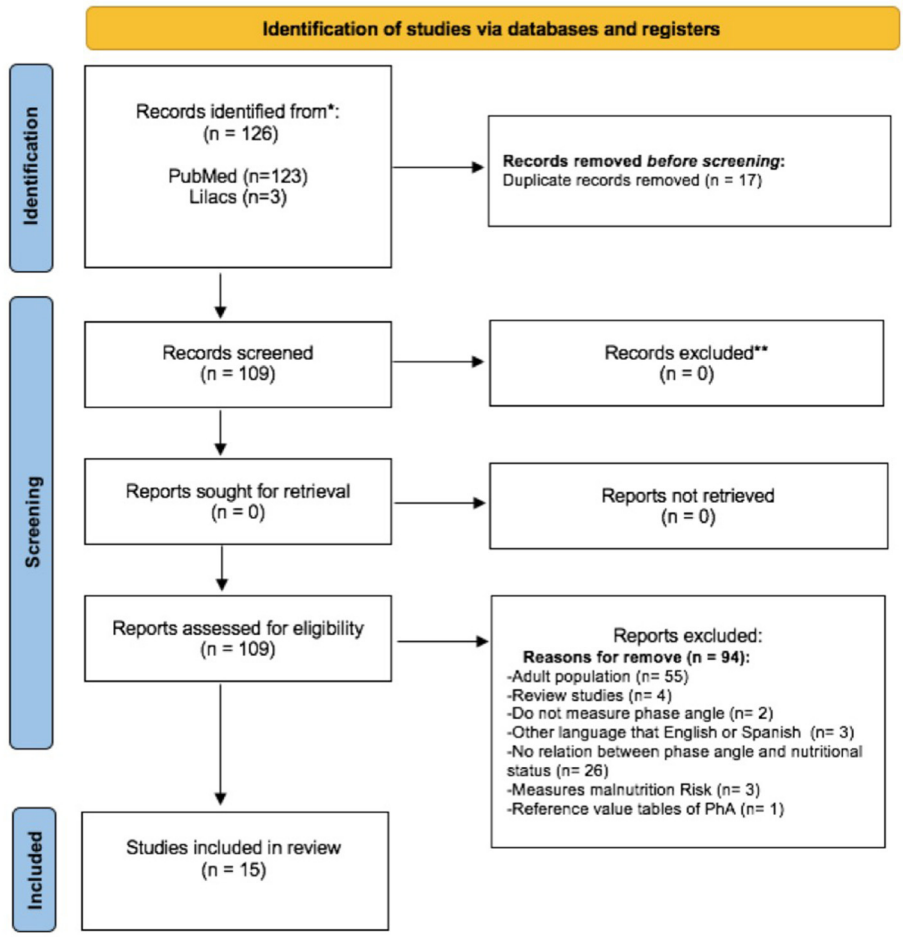


FIGURE 1
Study selection flowchart (17).

specifications; [15] PhA estimation formula used; and [16] measurement position reported. A discrepancy between AFO and EARA was resolved by the opinion of another researcher (IMV or AAN). We synthesized the data from the studies that [1] reported the cutoff analysis of PhA with receiver operating characteristic (ROC) curve analysis (reporting the cutoff point associated with poor nutrition, as well as sensitivity and specificity if included), [2] compared mean PhA values between nutritional status strata, and [3] reported correlations between PhA values and nutritional status indicators. It was difficult to make comparisons among the included studies due to the heterogeneity of the data (age ranges, different diseases, and different objective indicators of nutritional status).

## Risk of bias assessment

We assessed the risk of bias in the cohort and cross-sectional studies by using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed jointly by methodologists from the National Heart, Lung, and Blood Institute (NHLBI) and Research Triangle Institute International (18). The tool assesses potential flaws in the study methodology, including the following sources of bias: patient selection, performance, attrition and detection, confounding, study power, and other factors. A judgment of "good" indicates a low risk of bias, "fair" indicates that the study was susceptible to some bias considered not sufficient to invalidate its results, and "poor" indicates a significant risk of bias. We applied the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (19) to assess the studies that performed concurrent validity analyses. The tool comprises four main domains: patient selection, index test, reference standard, and flow and timing. These domains classify the risk of bias and applicability. The results can be expressed as high, not clear, or low risk of bias. Because there is no reference standard to evaluate the nutritional status in the pediatric population, we considered the anthropometric objective indicators as reference standards.

# Results

## Identification of studies

Our search identified 126 possible studies; of these, we excluded 17 duplicates. Of the remaining 109 studies, we excluded 94 that did not meet the inclusion criteria. Hence, we included 15 articles in this review (Figure 1). Five studies were carried out in Brazil;

three in the United Kingdom; two in Ethiopia; and one each in Greece, Poland, Italy, Malawi, and Japan. They had been published between 2000 and 2021. All selected studies evaluated male and female subjects, except for one: Popiolek et al. (20), which included only female subjects with anorexia nervosa.

## Description of the studies

The clinical health conditions of patients included in the studies were: five studies evaluated children with malnutrition; two evaluated excess weight in 8-year-old children and indigenous children and adolescents; and the remaining studies concerned hematopoietic stem cell transplantation, chronic kidney disease (CKD), anorexia nervosa, congenital heart disease (CHD), autism spectrum disorder, inflammatory bowel disease (IBD), and antineoplastic treatments.

Some of the included studies reported the association between PhA and nutritional status through ROC curve analysis to generate cutoff points. Others compared stratified mean PhA values and the presence or absence of malnutrition. Some of the studies also presented correlation analyses between PhA and anthropometric indicators. Only one study evaluated concordance through the kappa value between PhA and the diagnosis of malnutrition. Some included studies reported more than one of these forms of association between PhA and nutritional status (Table 2). The associations are described below.

## Cutoff points for PhA

Among the 15 articles we included, only four reported potential cutoff points for PhA to detect patients with malnutrition. However, the clinical health conditions differed among the studies. Farias et al. (21) evaluated PhA as a standardized phase angle (SPhA), justifying that the use of this standardized variable could serve to compare among independent studies. After calculating PhA in grades (°), they standardized the data by using reference values for sex and BMI of the German population (46). The equation was: SPhA = {(Observed PhA [°]—PhA median for sex and BMI [°])/(standard deviation [SD] of the PhA for sex and BMI)}. They found the SPhA cutoff point of ≤0 SD to detect malnutrition in patients who had received hematopoietic stem cell transplantation (10.2 ± 4.1 years old), and the nutritional indicator reference was weight-for-age z-score (WAZ). This cutoff point had 92% sensitivity and 70% specificity, with an AUC of 0.637. The mean ± SD SPhA for patients who had received hematopoietic stem cell transplantation was 0.61 ± 0.98. The authors also evaluated the agreement between nutritional indicators and SPhA (≤0 SD) for the malnutrition diagnosis. They reported a kappa value of 0.026 (95% CI: −0.110 to 0.236) for body mass index z-score (BMIz) (<-2 SD), a kappa value of 0.231 (95% CI: −0.240 to 0.493) for WAZ (<-1 SD), and a kappa value of 0.406 (95% CI: 0.197 to 0.611) for ideal body weight (IDW) < 90%. They reported the greatest agreement for TSF (< 90%) (κ = 0.435 [95% CI: 0.192 to 0.653]) and arm muscle circumference (AMC) (< 90%) (κ = 0.441 [95% CI: 0.190 to 0.672]).

Apostolou et al. (24) evaluated PhA as percentiles. They measured 400 children aged 2–18 years with BIA and classified the PhA values as percentiles derived from studies in the national pediatric population. They reported a PhA cutoff point for malnutrition-stunting of <3rd percentile for children with CKD (1–16 years old), but they did not report the sensitivity and specificity. Based on this PhA cutoff, they reported a prevalence of 30% malnutrition-stunting. Popiolek et al. (20) evaluated PhA as a crude variable in grades (°). They estimated a PhA cutoff of > 4.93° to identify the starvation state defined by BMI < 16 kg/m$^2$ in patients with anorexia nervosa (17.38 ± 4.99 years old), with 38.96% sensitivity and 100% specificity. The ROC curve built for BMI had an AUC of 0.69 (95% confidence interval [CI] 0.53–0.82, $p = 0.0164$). The mean ± SD PhA for the entire population was 4.27° ± 1.18°. They also reported the difference in PhA between female subjects who were in a state of starvation and those who were not (BMI < 16 kg/m$^2$, PhA = 4.17° vs. BMI ≥ 16 kg/m$^2$, PhA = 4.52°, $p = 0.0299$). Ashton et al. (27) did not identify a clinically useful PhA cutoff associated with underweight (BMIz < −1) or overweight (BMIz > 1) in pediatric patients with IBD (mean 14.49 years old). The ROC curve analysis yielded an AUC of 0.460 (95% CI 0.339–0.581, $p = 0.487$) for overweight, and an AUC of 0.339 (95% CI 0.265–0.532, $p = 0.177$) for underweight.

## Studies that compared mean PhA values among nutritional status strata

Some authors compared the mean PhA among any conditions related to nutritional status (Figure 2). Bonaccorsi et al. (28) reported the PhA among 8-year-old children with excess BW or without being overweight. They used the following BMI criteria to diagnose excess BW: not overweight, <19.4 kg/m$^2$; overweight, 19.4–25.6 kg/m$^2$; and obesity, >25.6 kg/m$^2$. There was no difference between boys with excess weight and without overweight (not overweight, PhA = 6.4° ± 0.6° vs. overweight/obesity, PhA = 6.4° ± 0.6°). However, in girls, there was a significant difference (not overweight, PhA = 6.3° ± 0.6° vs. overweight/obesity, PhA= 6.6° ± 0.3°, $p < 0.05$). Barufaldi et al. (30) reported the mean PhA values of indigenous children and adolescents (10.8 ± 2.9 years old); it was 5.5° ± 0.6° for children and 6.1° ± 0.8° for adolescents. They compared the mean PhA values between the strata of children and adolescents based on whether they had or did not have overweight based on BMIz. They defined overweight as BMIz > 2 z-score. There were differences in the mean PhA values of children with overweight compared with children without overweight (5.7° ± 0.5° vs. PhA= 5.5° ± 0.6°, $p = 0.004$). In addition, there was a significant difference in the mean PhA values between adolescents with and without overweight (6.3° ± 0.7° vs. 6.1° ± 0.8°, $p = 0.006$).

Girma et al. (32) evaluated the relationship between PhA and nutritional indicators in children (36 ± 24 months) with severe acute malnutrition (SAM), defined as MUAC < 11 cm or weight-for-height percentile (WFH) <70%. The mean ± SD PhA of the group with SAM was different compared with healthy patients (28 ± 15 months) (2.2 ± 0.7° vs. 3.8 ± 0.7°, $p < 0.001$). Additionally, they compared the SAM group considering the presence of edema:

TABLE 2 Summary of evidence.

| References; location | Study design | Clinical health condition, sample size, sex, and age | Nutritional status indicator and reference for malnutrition | Principal results | Malnutrition prevalence |
|---|---|---|---|---|---|
| **Studies with PhA cutoff analysis and nutritional status** | | | | | |
| Farias et al. (21); Brazil | Prospective study | **Hematopoietic stem cell transplantation**<br>$n = 67$<br>58% M, 41% F<br>10.2 ± 4.1 years<br>**Healthy children**<br>$n = 35$<br>5–18 years | Malnutrition BMIz < −2 SD, WAZ <-1 SD Ideal weight < 90% TSF < 90%, AMC < 90% WHO (22) Frisancho (23) | **ROC curve analysis for malnutrition**<br>Cutoff, SPhA ≤ 0 SD<br>Sensitivity of 92% and specificity of 70% AUC = 0.637 compared with WAZ<br>**HSCT:** SPhA = 0.61 ± 0.98<br>**Healthy children:** SPhA = 1 ± 0.6<br>$p = 0.054$<br>**Pearson correlation coefficient with SPhA**<br>BMIz: $r = 0.457$, $p < 0.001$<br>TSF: $r = 0.370$, $p < 0.002$<br>FFM: $r = 0.375$, $p < 0.002$<br>AMC: $r = 0.412$, $p < 0.001$<br>**Agreement diagnosis malnutrition with SPhA (kappa value)**<br>BMIz < −2 SD, k= 0.026 (95% CI: −0.110 to 0.236)<br>WAZ < −1 SD, k = 0.231 (95% CI: −0.240 to 0.493)<br>Ideal weight < 90%, k = 0.406 (95% CI: 0.197 to 0.611)<br>TSF < 90%, k = 0.435 (95% CI: 0.192 to 0.653)<br>AMC < 90% = 0.441 (95% CI: 0.190 to 0.672) | Not reported |
| Apostolou et al. (24); Greece | Cross-sectional study | **Chronic kidney disease**<br>$n = 30$<br>66.6% M, 33.4% F<br>1–16 years | Weight z-score < −2 SD Height z-score < −1.88 SD BMIz < −2 SD AMAz < 1.6 SD WHO (22) KDOQI guidelines (25) | **PhA cutoff point for malnutrition-stunting:** < 3rd percentile<br>**Pearson correlation coefficient with PhA**<br>Weight: $r = 0.483$, $p < 0.05$<br>MUAC: $r = 0.778$, $p < 0.001$ | **Malnutrition-stunting**<br>Weight z-score 27% Height z-score 30% BMIz 20% AMAz 20% PhA < 3rd percentile 30% |
| Popiolek et al. (20); Poland | Longitudinal study | **Anorexia nervosa**<br>$n = 46$<br>100% F<br>16 ± 4.99 years | BMI Underweight: 16–18.5 kg/m$^2$ Severely underweight: 15–15.99 kg/m$^2$ Very severely underweight: < 15 kg/m$^2$ Starvation state: <16 kg/m$^2$ WHO (26) | **ROC curve analysis for starvation**<br>Cutoff: PhA > 4.93°<br>Sensitivity of 38.96% and specificity of 100%<br>AUC = 0.69 (95% CI: 0.53–0.82), $p = 0.0164$ compared with BMI (starvation state < 16 kg/m$^2$)<br>**Entire population:** PhA = 4.27° ± 1.18°<br>**Starvation state:** $p = 0.0299$<br>BMI < 16 kg/m$^2$: PhA = 4.17°<br>BMI ≥16 kg/m$^2$: PhA = 4.52°<br>**Correlation coefficient with PhA**<br>Biceps muscle skinfold: rho = 0.341, $p = 0.0204$<br>AC: rho = 0.42, $p = 0.0037$<br>WHR: rho = 0.366, $p = 0.0221$ | NA |
| Ashton et al. (27); United Kingdom | Prospective study | **Inflammatory bowel disease**<br>$n = 97$<br>41.2% F, 58.8% M<br>14.49 years | BMIz Mild undernutrition: <-1 SD Moderate malnutrition: ≤-2 SD Overweight/obesity: > 1 and > 2 SD WHO Anthro software version 3.3.3 (2011) | **ROC curve analysis for BMIz > 1 SD (overweight)**<br>AUC = 0.460 (95% CI: 0.339–0.581), $p = 0.487$<br>**ROC curve analysis for BMIz < −1 SD (underweight)**<br>AUC = 0.339 (95% CI: 0.265–0.532), $p = 0.177$<br>**Pearson correlation coefficient with PhA**<br>BMIz: $r^2 = 0.02$, $p = 0.78$ | **BMIz**<br>Moderate malnutrition 5.3% Mild undernutrition 8.5% Overweight/obesity 7.5% |
| **Studies comparing mean PhA values and the nutritional status** | | | | | |
| Bonaccorsi et al. (28); Italy | Cross-sectional study | **Eight-year-old children**<br>$n = 449$<br>47% F, 53% M<br>8 years | BMI Not overweight: < 19.4 kg/m$^2$ Overweight: 19.4–25.6 kg/m$^2$ Obesity: > 25.6 kg/m$^2$ Cacciari et al. patterns (29) | **Male:** $p$ = ns<br>Not overweight: PhA = 6.4° ± 0.6°<br>Overweight/obesity: PhA = 6.4° ± 0.6°<br>**Female:** $p < 0.05$<br>Not overweight: PhA = 6.3° ± 0.6°<br>Overweight/obesity: PhA = 6.6° ± 0.3°<br>**Pearson correlation coefficient with PhA**<br>(Male) BMI: $r = 0.084$, $p$ = ns<br>(Female) BMI: $r = 0.336$, $p < 0.05$ | **Male**<br>Overweight 21.3% Obesity 2.1% **Female**<br>Overweight 13.9% Obesity 2.4% |

*(Continued)*

TABLE 2 (Continued)

| References; location | Study design | Clinical health condition, sample size, sex, and age | Nutritional status indicator and reference for malnutrition | Principal results | Malnutrition prevalence |
|---|---|---|---|---|---|
| Barufaldi et al. (30); Brazil | Cross-sectional study | **Indigenous children and adolescents**<br>$n = 3,204$<br>50.6% M, 49.4% F<br>$10.8 \pm 2.9$ years | Overweight BMIz > +2 z-score Stunting HAZ < 2 z-score WHO (31) | **Entire population:** $p < 0.001$<br>Children: PhA=$5.5^\circ \pm 0.6^\circ$<br>Adolescents: PhA= $6.1^\circ \pm 0.8^\circ$<br>**Children:** $p = 0.004$<br>Overweight: PhA = $5.7^\circ \pm 0.5^\circ$<br>Not overweight: PhA = $5.5^\circ \pm 0.6^\circ$<br>**Adolescents:** $p = 0.006$<br>Overweight: PhA = $6.3^\circ \pm 0.7^\circ$<br>Not overweight: PhA = $6.1^\circ \pm 0.8^\circ$ | **Children**<br>**Overweight:** M = 5.5%, F = 5.9%<br>**Stunting:** M = 16.2%, F = 15.0%<br>**Adolescents**<br>**Overweight:** M = 5%, F = 8.6%<br>**Stunting:** M = 21.2%, F = 18.5% |
| Girma et al. (32); Ethiopia | Cross-sectional study | **SAM**<br>$n = 55$<br>60% M, 40% F<br>$36 \pm 24$ months<br>**Healthy reference children**<br>$n = 80$<br>47.5% M, 52.5% F<br>$28 \pm 15$ months | **SAM** MUAC <11 cm or WFH < 70% NCHS growth reference median and/or nutritional edema **Healthy children** WHZ and HAZ within ± 2 SD WHO (not specified) | **Healthy children:** PhA = $3.8^\circ \pm 0.7^\circ$<br>**SAM:** PhA = $2.2^\circ \pm 0.7^\circ$<br>$p < 0.001$<br>**SAM:** $p = 0.12$<br>Non-edematous: PhA = $2.4^\circ \pm 0.8^\circ$<br>Edematous: PhA = $2.1^\circ \pm 0.6^\circ$<br>$p = 0.12$<br>**Pearson correlation coefficient with PhA**<br>MUAC: $r = 0.31$, $p < 0.05$<br>HAZ: $r = -0.25$, $p =$ ns<br>WAZ: $r = -0.03$, $p =$ ns<br>WFH: $r = 0.19$, $p =$ ns | NA |
| Marino et al. (33); United Kingdom | Prospective study | **Primary ciliary dyskinesia**<br>$n = 43$<br>51% M, 49% F<br>$7.0 \pm 5.2$ years | Moderate malnutrition < −2 z-score of HAZ, WHZ, BMIz, and FFMIz WHO (22) | **Entire population:** PhA = $4.5^\circ \pm 0.9^\circ$<br>**Moderate malnutrition:** $p = 0.0002$<br>FFMIz < −2 z-score: PhA = $4.3^\circ \pm 0.4^\circ$<br>FFMIz >-2 z-score: PhA = $4.9^\circ \pm 0.8^\circ$ | **Moderate malnutrition**<br>HAZ 4.6%<br>BMIz 6.9%<br>FFMIz 21% |
| Bourdon et al. (34); Blantyre, Malawi | Prospective observational study | **SAM**<br>$n = 183$<br>54% M, 46% F<br>$23 \pm 12$ months<br>**Community participants**<br>$n = 42$<br>62% M, 38% F<br>$20.1 \pm 12.3$ months | WHZ, WAZ, or HAZ WHO (35) | **Community participants:** PhA = $3.8^\circ \pm 0.8^\circ$<br>**Edematous SAM:** PhA = $2.3^\circ \pm 1.4^\circ$<br>**Severe wasting:** PhA = $2.9^\circ \pm 1.0^\circ$<br>($p < 0.001$) | Severe wasting 45.9%<br>Edematous SAM 54% |
| Girma et al. (36); Ethiopia | Cross-sectional study | **SAM non-edematous**<br>$n = 136$<br>56% M, 44% F<br>Median 29 (IQR:14–60) months<br>**SAM edematous**<br>$n = 214$<br>57% M, 43% F<br>Median 36 (IQR:24–60) months<br>**Healthy children**<br>$n = 120$<br>50% M, 50% F<br>Median 38 (IQR: 22–82) months | **SAM** MUAC < 11 cm or WFH < 70% of the median of the NCHS growth reference and/or nutritional edema **Healthy children** WFH or BMI and HAZ within ± 2 SD of WHO (37) | **Healthy Children:** PhA = $4.3^\circ \pm 1^\circ$<br>**SAM:** PhA = $2.5^\circ \pm 1.1^\circ$<br>**SAM**<br>Non-edematous: PhA = $2.8^\circ \pm 1.2^\circ$<br>edematous: PhA = $2.3^\circ \pm 1^\circ$ | NA |

*(Continued)*

TABLE 2 (Continued)

| References; location | Study design | Clinical health condition, sample size, sex, and age | Nutritional status indicator and reference for malnutrition | Principal results | Malnutrition prevalence |
|---|---|---|---|---|---|
| Macena et al. (38); Brazil | Cross-sectional study | **Children < 5 years of age at risk or in chronic malnutrition**<br>$n = 100$<br>46% M, 54% F<br>$3 \pm 0.78$ years | WAZ, HAZ, BMIz, and MUAC/A WHO (31)<br>HAZ Adequate: (z-score $> -1$) Risk of stunting (z-score $\leq -1$ and $> -2$)<br>Stunted (z-score $\leq 2$) | **Entire population:** PhA $= 4.4^{\circ} \pm 0.6^{\circ}$<br>**HAZ:** $p = 0.19$<br>Adequate HAZ: PhA $= 4.2^{\circ} \pm 0.7^{\circ}$<br>At-risk HAZ: PhA $= 4.5^{\circ} \pm 0.7^{\circ}$<br>Stunted HAZ: PhA $= 4.4^{\circ} \pm 0.6^{\circ}$ | **HAZ** Stunted 37% Risk of stunting 38% |
| Studies that correlated PhA with the nutritional status | | | | | |
| Nagano et al. (39); Japan | Cross-sectional study | **Malnourished patients**<br>$n = 10$<br>100% M<br>$2.6 \pm 2.6$ years<br>**Well-nourished patients**<br>$n = 71$<br>60.5% M, 39.5% F<br>$3.36 \pm 3.12$ years | **Nutritional disturbance %IBW**<br>Mild: 80%−90%<br>Moderate: 70%−80%<br>Severe: <70%<br>Fukuoka reference<br>**Nutritional disturbance %AMC**<br>Mild: 80%−90%<br>Moderate: 60–80%<br>Severe: < 60%<br>Frisancho (40) | **Pearson correlation coefficient with PhA**<br>IBW: $r = 0.818$, $p < 0.001$<br>AMC: $r = 0.90$, $p < 0.001$ | **Nutritional disturbance %IBW**<br>Mild: 70%<br>Moderate: 30%<br>**Nutritional disturbance %AMC**<br>Severe: 10%<br>Moderate: 20%<br>Mild: 70% |
| Castro et al. (41); Brazil | Cross-sectional study | **Autism spectrum disorder**<br>$n = 63$<br>81% M, 19% F<br>$10.5 \pm 4.1$ years | BMI percentiles Underweight: $\leq$ 5th Healthy: > 5th to < 85th Overweight: $\geq$ 85th to < 95th Obesity: $\geq$ 95th CDC (42) | **Spearman correlation with PhA**<br>BMI: $r = -0.072$, $p = 0.05$ | Underweight 15.8% Overweight 38.9% Obesity 36.5% |
| Marino et al. (43); United Kingdom | Prospective study | **Congenital heart disease**<br>$n = 117$<br>61% M, 39% F<br>$44.3 \pm 56$ months | Moderate malnutrition HAZ and WAZ: $< -2$ z-score WHO (22) | **Entire population:** PhA $= 4.2^{\circ} \pm 1.3^{\circ}$<br>**Pearson correlation coefficient with PhA**<br>HAZ: $r = 0.2$, $p = 0.03$<br>WAZ: $r = 0.3$, $p = 0.03$ | **Moderate malnutrition**<br>Infants: HAZ = 28.5%<br>Children: HAZ = 20.6% |
| Guimarães et al. (44); Brazil | Cross-sectional study | **Children receiving antineoplastic treatments.**<br>$n = 13$<br>61.5% M, 38.5% F<br>$103.2 \pm 39.7$ months | WAZ (0–10 years), WHZ (0–5 years), HAZ (0–19 years), BMIz (0–19 years) WHO reference. AM, AMC, and TSF Frisancho (45) | **Pearson correlation coefficient with PhA**<br>Current weight: $r = 0.920$, $p < 0.0001$<br>AMC: $r = 0.569$, $p = 0.042$<br>AM: $r = 0.618$, $p = 0.024$<br>TSF: $r = 0.471$, $p =$ ns | **BMIz** Risk of overweight 7.7% Overweight 23.2% Obesity 15.4% **All the patients had correct height-for-age* |

AM, arm circumference; AMAz, arm muscle area z-score; AMC, arm muscle circumference; AN, anorexia nervosa; AUC, area under the curve; BIVA, bioelectrical vector analysis; BMIz, body mass index z-score; BW, body weight; CDC, Centers for Disease Control and Prevention; CHD, congenital heart disease; F, female; FFMIz, fat-free mass index z-score; HAZ, height-for-age z-score; HSCT, hematopoietic stem cell transplantation; IBW, ideal body weight; IQR, interquartile range; KDOQI, Kidney Disease Outcome Quality Initiative; M, male; MUAC, mid-upper arm circumference; MUAC/A, mid-upper arm circumference for age; NA, not applicable; NCHS, National Center for Health; ns, no significance; PhA, phase angle; SAM, severe acute malnutrition; SPhA, standardized phase angle; TSF, triceps skinfold thickness; WAZ, weight-for-age z-score; WFH, weight-for-height percentile; WHO, World Health Organization; WHR, waist-to-hip ratio; WHZ, weight-for-height z-score.

PhA was not different between the non-edematous and edematous groups ($2.4^{\circ} \pm 0.8^{\circ}$ vs. $2.1^{\circ} \pm 0.6^{\circ}$, $p = 0.12$).

Marino et al. (33) reported a mean ± SD PhA of $4.5^{\circ} \pm 0.9^{\circ}$ in children (7.0 ± 5.2 years old) with primary ciliary dyskinesia. In the study, they evaluated moderate malnutrition with the indicators height-for-age z-score (HAZ), weight-for-height z-score (WHZ), BMIz, and fat-free mass index z-score (FFMIz). They also compared PhA with FFMIz. Patients with moderate malnutrition (FFMIz <-2 z-score) has significantly lower PhA than patients who did not present moderate malnutrition (FFMIz > −2 z-score) ($4.3^{\circ} \pm 0.4^{\circ}$ vs. $4.9^{\circ} \pm 0.8^{\circ}$, $p = 0.0002$). Bourdon et al. (34) also reported the PhA of community participants and children with SAM (20.1 ± 12.3 months), whom they divided into the severe wasting group and the edematous group. They evaluated SAM with the indicators WAZ or HAZ based on the World Health Organization (WHO) definitions. Children with edematous SAM had lower PhA compared with community participants ($2.3^{\circ} \pm 1.4^{\circ}$ vs. $3.8^{\circ} \pm 0.8^{\circ}$, $p < 0.001$). In addition, children with severe wasting had lower PhA compared with community participants ($2.9^{\circ} \pm 1.0^{\circ}$ vs. $3.8^{\circ} \pm 0.8^{\circ}$, $p < 0.001$).

Girma et al. (36) evaluated PhA and nutritional indicators in children with non-edematous SAM (median 29 [IQR:14–60] months) and children with edematous SAM (median 36 [IQR: 24–60] months), who were defined as MUAC < 11 cm or WFH < 70% of the median of the National Center for Health (NCHS) growth reference and/or nutritional edema. They also reported PhA

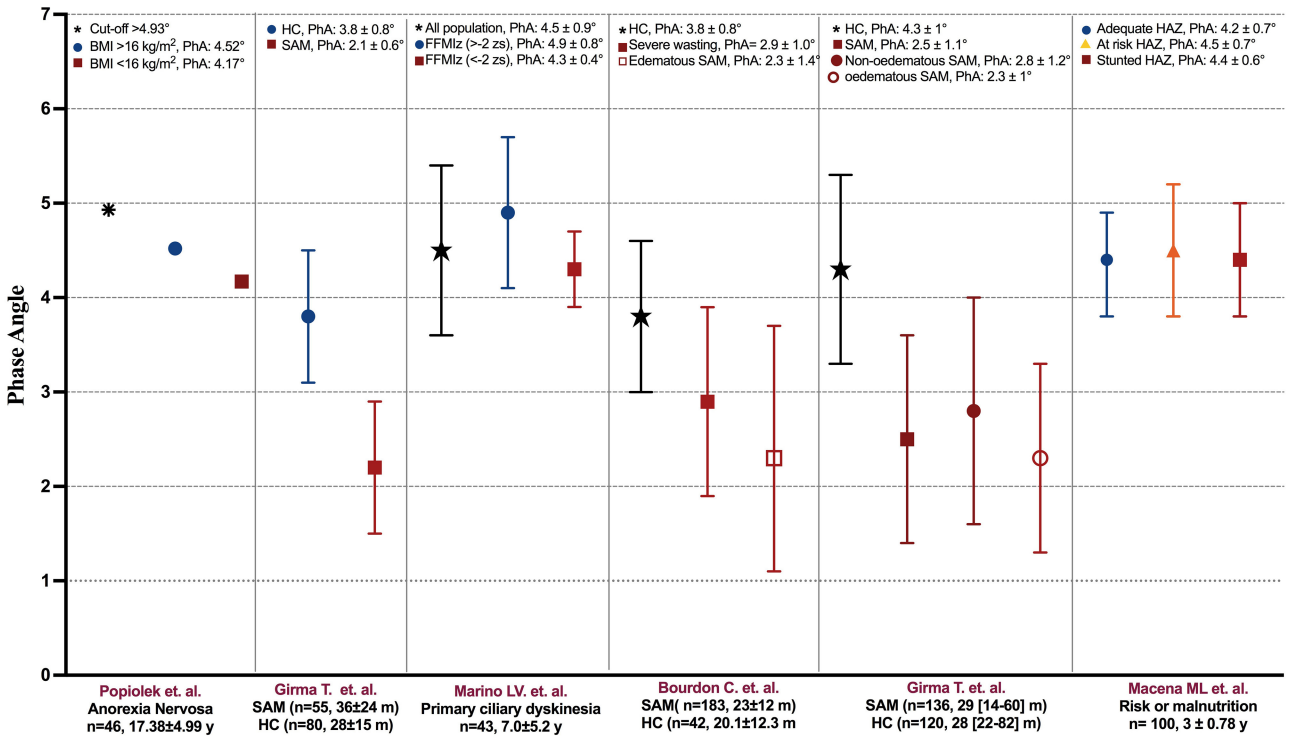


FIGURE 2
Phase angle reported in the studies stratified by the presence of undernourishment. PhA, phase angle; BMI, body mass index; FFMIz, fat-free mass index z-score; HAZ, height-for-age z-score; HC, healthy children; m, months; SAM, severe acute malnutrition; y, years.

in healthy children (HC) (median 38 [IQR: 22–82] months). The mean ± SD PhA was 4.3° ± 1.0° in HC and 2.8° ± 1.1° in children with SAM. When stratifying the SAM group, the mean ± SD PhA was 2.8° ± 1.2° for the non-edematous group and 2.3° ± 1.0° for the edematous group. Macena et al. (38) evaluated children at risk or in chronic malnutrition (3 ± 0.78 years old) based on HAZ and stratified as: adequate (HAZ >-1), risk of stunting (HAZ < −1 and >-2), or stunted = (HAZ < 2). The overall mean ± SD PhA was 4.4° ± 0.6°, and there was no significant difference between the adequate HAZ group (PhA = 4.2° ± 0.7°) and the at-risk HAZ (PhA = 4.5° ± 0.7°) and stunted HAZ (PhA° = 4.4 ± 0.6°) groups ($p = 0.19$).

## Studies that reported correlations between PhA and the nutritional status

Most of the studies correlated the nutritional indicators with PhA. In this sense, we considered the classification of cutoff points of correlations as very strong (r > 0.8), moderately strong ($r$ = 0.6–0.8), fair ($r$ = 0.3–0.6), and poor (r < 0.3) associations (47). Nagano et al. (39) showed very strong positive correlations between PhA and IBW ($r = 0.818$, $p < 0.001$) and AMC ($r = 0.90$, $p < 0.001$) in malnourished patients. Guimarães et al. (44) reported in children receiving antineoplastic treatments a positive very strong correlation between PhA and current weight ($r = 0.920$, $p < 0.0001$), and a positive moderately strong correlation between PhA and arm circumference (AC) ($r = 0.618$, $p = 0.024$). They also reported a fair correlation between PhA and two anthropometric variables: TSF ($r = 0.471$ p > 0.05) and AMC ($r = 0.569$, $p = 0.042$).

Apostolou et al. (24) reported a positive moderately strong correlation between PhA and MUAC ($r = 0.778$, $p < 0.001$) and a positive fair correlation between PhA and BW ($r = 0.483$, $p < 0.05$) in patients with CKD. Farias et al. (21) found a fair correlation between PhA and BMIz ($r = 0.457$, $p < 0.001$), TSF ($r = 0.370$, $p < 0.002$), FFM ($r = 0.375$, $p < 0.002$), and AMC ($r = 0.412$, $p < 0.001$) in patients who had received hematopoietic stem cell transplantation. Popiolek et al. (20) found a fair correlation between PhA and biceps muscle skinfold (rho = 0.341, $p = 0.0204$), AC (rho = 0.42, $p = 0.0037$), and the waist-to-hip ratio (rho = 0.366, $p = 0.0221$) in adolescents with anorexia nervosa.

Bonaccorsi et al. (28) stratified 8-year-old children by sex and analyzed the correlation between PhA and BMI. Only girls showed a positive fair correlation ($r = 0.336$, $p < 0.05$). Marino et al. (43) studied PhA in children with CHD (44.3 ± 56 months) and reported an average PhA of 4.2° ± 1.3°. They reported a fair correlation between PhA and WAZ ($r = 0.3$, $p = 0.03$) and a poor correlation between PhA and HAZ ($r = 0.2$, $p = 0.03$). Girma et al. (32) only found a positive fair correlation between PhA and MUAC ($r = 0.31$, $p < 0.05$) in children with SAM, without correlations with HAZ, WAZ, and WHZ. Castro et al. (41) and Ashton et al. (27) found no significant associations between PhA and BMI in children with autism spectrum disorder (10.5 ± 4.1 years old) and in pediatric patients with IBD (14.49 years old), respectively.

## Prevalence of malnutrition based on any nutritional indicator

The reported prevalence of malnutrition varies among pediatric populations. There is no unified way to carry out this classification due to variations in anthropometric indicators as well as the type of pathology. Thus, as a secondary objective, we have reported the prevalence of malnutrition and the anthropometric indicators that have been used to evaluate it (Figure 3).

Apostolou et al. (24) reported the prevalence of malnutrition-stunting based on various indicators: It was 27% based on weight z-score, 30% based on height z-score, 20% based on BMIz, and 20% based on arm muscle area z-score (AMAz). They also reported a 30% prevalence of malnutrition-stunting in children based on the PhA cutoff point (<3rd percentile). On the other hand, Marino et al. (33) reported a prevalence of moderate malnutrition with HAZ in 43 children with primary ciliary dyskinesia, with a prevalence of 28.5% in infants and 20.6% in children. In another study from the same group (43), the authors considered 117 patients with CHD and reported the prevalence of moderate malnutrition with different indicators: 4.6% based on HAZ, 6.9% based on BMIz, and 21% based on FFMIz.

In children with SAM, Bourdon et al. (34) found that 45.9% had severe wasting and 54% had edematous SAM. Macena et al. (38) reported that in a population with risk of malnutrition, 37% had stunting and 38% had a risk of stunting. Nagano et al. (39) included malnourished patients and reported that according to the percentage of ideal body weight (%IBW), 70% of the children had mild malnutrition and 30% had moderate malnutrition; according to the percentage of arm muscle circumference (%AMC), 10% had severe malnutrition, 20% had moderate malnutrition, and 70% had mild malnutrition. Two studies included extreme malnutrition. Barufaldi et al. (30) reported the prevalence of stunting and overweight in indigenous children and adolescents stratified by sex. They reported that 16.2% of boys and 15.0% of girls had stunting, and 21.2% of male adolescents and 18.5% of female adolescents had stunting. In addition, the prevalence of overweight in the population was 5.5% for male children, 5.9% for female children, 5% for male adolescents, and 8.6% for female adolescents. Castro et al. (41) included people with autism spectrum disorder and reported a prevalence of 15.8% for underweight, 38.9% for overweight, and 36.5% for obesity. Finally, Ashton et al. (27) found a prevalence of 5.3% for moderate malnutrition, 8.5% for mild malnutrition, and 7.5% for overweight/obesity in children with IBD.

Two studies only reported the prevalence of excess BW. Bonaccorsi et al. (28) included 449 8-year-old children and registered 21.3% of male children with overweight, 2.1% of male children with obesity, 13.9% of female children with overweight, and 2.4% of female children with obesity. Guimarães et al. (44) observed a prevalence of 7.7% for the risk of being overweight,

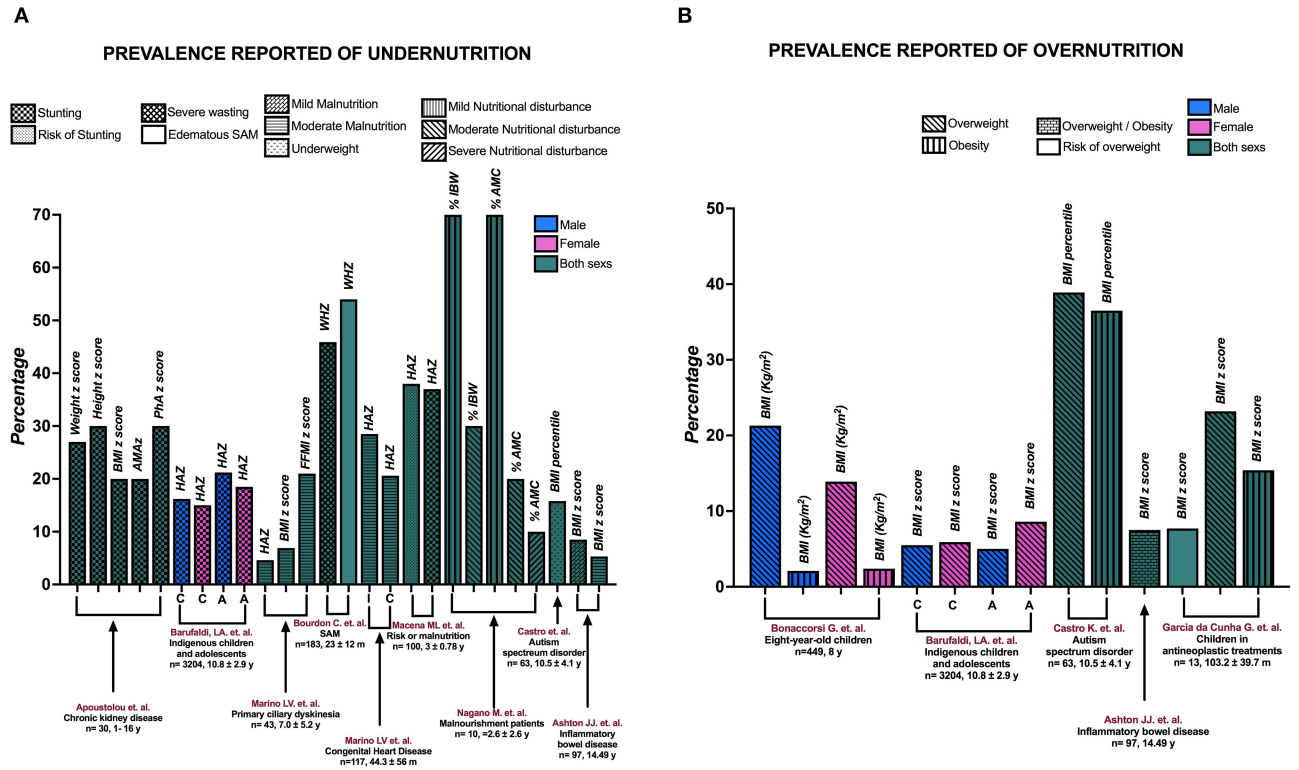


FIGURE 3
The prevalence of **(A)** undernutrition and **(B)** overnutrition reported in the studies. A, adolescents; AMAz, arm muscle area z-score; BMI, body mass index; C, children; FFMI, fat-free mass index; HAZ, height-for-age z-score; I, infants; SAM, severe acute malnutrition; WHZ, weight-for-height z-score; y, years; %AMC, percentage of arm muscle circumference; %IBW, percentage of ideal body weight.

23.2% for overweight, and 15.4% for obesity in children receiving antineoplastic treatments.

## Bioimpedance model and usage specifications of the studies

According to the type of BIA, the researchers used different models and reported the usage specifications in the methodology (Supplementary Table 1). The approaches were diverse according to the type of device used and the type of pathology in which they made the electrical impedance measurements. Among the variations used, BIA included monofrequency (50 kHz) (34) and others used several frequencies (5, 50, 100, and 200 kHz) (36). Within more specific descriptions for the type of pathology, such as the study carried out in patients with CKD (24), patients were measured 1 h after dialysis so that the body fluid compartments were as close to healthy levels as possible. Patients who had received hematopoietic stem cell transplantation were evaluated in the absence of intravenous hydration and fever (21).

An important issue in the estimation of the PhA is the position in which the measurement is made because there could be differences in the BIA results between positions. Among the included studies, nine reported results from the supine position, and three reported results from the lying position, the horizontal position, and the lying in the supine position; however, in three of them, the position of measurement was not reported (24, 33, 44). Of the 15 studies we included, six studies reported the formula they used to calculate PhA (21, 28, 30, 36, 38, 39). Four of the studies did not report the formula (20, 27, 33, 43), but they used the same bioimpedance model reported by Małecka-Massalska et al. (48), who presented the formula in a Supplementary Table. Three other studies did not report the formula, but it was the same model reported by Girma et al. (36), who did report the formula in their study. Finally, for the two studies that did not report the formula, we took the information provided by the manufacturer (Supplementary Table 1).

## Risk of bias

The quality rating was acceptable, with a moderate risk of bias, in 11 of the studies assessed with the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Of these 11 studies, four studies were rated as fair, with some susceptibility to risk of bias, and ssevven studies had an overall good quality rating (Supplementary Table 2). The four studies assessed with the Quality Assessment of Diagnostic Accuracy Studies showed a low risk of bias in almost all domains (Supplementary Table 3).

# Discussion

In this present systematic review, we have synthesized the evidence derived from 15 studies aimed at evaluating the association between PhA and the nutritional status in pediatric populations. Four studies reported different PhA cutoff points. However, it is difficult to compare these cutoff points because the authors reported PhA differently: SPhA (21), percentiles (24), and degrees (20). Ideally, PhA could be standardized so that comparisons could be made among different populations. An alternative would be to report SPhA. However, this measure has a limitation because it is based on reference values of the evaluated population. Although Farias et al. (21) standardized PhA with reference values from the German population (46), not all populations have reference values, and it would be difficult to standardize the measurement.

Another variable that plays an important role is the anthropometric indicator, which is used as a reference standard. Among the studies that reported a cutoff point from ROC curve analysis, the anthropometric indicators were diverse. For example, some authors considered WAZ associated with malnutrition, while another study used BMI to detect the state of starvation defined as BMI $< 16$ kg/m$^2$ or BMIz associated with overweight. When using different anthropometric indicators as a reference standard, the state of nutrition is variable due to the lack of uniform definitions by heterogeneous nutrition screening practices (2). Although a uniform definition of malnutrition in children is not available, the indicator or construct that best defines malnutrition should be standardized in this population, in such a way that it is used as a reference standard, similar to what is found in adult populations with the Global Leadership Initiative on Malnutrition (GLIM) construct (49).

The predictive values of PhA associated with malnutrition evaluated with WAZ had a sensitivity of 92% and a specificity of 70% in patients who had received hematopoietic stem cell transplantation. These values are higher than the predictive values of nutritional screening tools such as STRONGkids (50). In a study carried out to validate this nutritional screening tool, the authors used alterations in one of these anthropometric indicators as a reference for malnutrition: WAZ, weight-for-height, and HAZ, resulting in a sensitivity of 86% and a specificity of 72% (51). For both PhA and the nutritional screening tools, there was greater sensitivity than specificity, which is important when it comes to creating a diagnostic tool, because more positive cases of malnutrition can be detected when used in the population, leading to early interventions.

In acute malnutrition, there is a displacement of intracellular fluids to the extracellular space, leading to a significant decrease in BCM and, consequently, a reduction in PhA (52). We observed this trend in studies comparing patients with SAM to HC, where the observed mean PhA in the SAM group was lower (2.1°-2.8°) compared with HC (3.8°-4.3°) (32, 34, 36). However, these values are different from that reported by Macena et al. (38), who observed no differences in PhA between the population with chronic malnutrition (HAZ $< 2$) or risk of chronic malnutrition (HAZ $<$-1 and $> -2$) and those with adequate HAZ. This phenomenon can be explained by the fact that in chronic malnutrition, there could be an adaptive response to energy restriction that, when there are periods of energy availability, could favor fat storage to the detriment of its use (53). This fat accumulation would increase Xc and, therefore, increase PhA. These changes would explain why a smaller PhA is not observed in children with stunting.

We included studies that showed very strong correlations between PhA and current weight, AMC, and % IBW. These correlations could be explained by the fact that PhA is a parameter

that reflects BCM (54): a decrease in BCM is associated with a decrease in Xc and a decrease in TBW, and PhA decreases alongside a reduction in Xc and an increase in R. BCM is the functional mass, that is, the total mass of all the cellular elements representing the metabolically active components of the body. It is calculated from raw impedance electrical data and height (55), and it is not affected by the hydration status (56). Finally, AMC reflects the total body protein store (57); it is an indicator of skeletal muscle mass, which comprises most of BCM. On the other hand, the fact that PhA in malnourished children (%IBW < 90%) is less than that of well-nourished children indicates that the relationship between BCM and BW is lower in malnourished children than in HC (39). The available evidence suggests that nutritional management with high-calorie, high-protein oral nutritional supplementation with β-hydroxy-β-methylbutyrate increases BW, AMC, and PhA, with a decrease in R and an increase in Xc (56).

Some of the included studies reported associations between PhA and BMI. For example, Farias et al. (21) reported an association with $r = 0.457$ ($p < 0.001$), and Bonaccorsi et al. (28) reported an association with $r = 0.336$ ($p < 0.05$) but only in female patients. However, the evidence shows that in both adult and pediatric populations, BMI is associated with PhA independently of age and sex. The similar magnitude of the association is similar in pediatric subjects ($r = 0.31$, $p < 0.001$) but weak in adults ($r = 0.03$, $p < 0.001$) (46). Interestingly, only two articles reported correlations with anthropometric indicators in pediatric populations, and they showed different trends. Girma et al. (32) found no correlations between PhA and HAZ and WAZ in patients with SAM. However, Marino et al. (43) observed a positive correlation between PhA and HAZ ($r = 0.2$, $p = 0.03$) and WAZ ($r = 0.3$, $p = 0.03$) in patients with CHD. This discrepancy could be due to several factors, such as the population studied and small sample size. Thus, more evidence is needed to determine whether PhA and anthropometric indicators such as HAZ and WAZ really correlate with each other.

We include studies that reported PhA at 50 kHz because these data show good reproducibility. In the literature, this frequency has been used to determine and predict health in healthy populations, and this same frequency has been used to confirm alterations in populations with different diseases and also by examining intracellular and extracellular fluids (4, 58). At frequencies below 5 kHz and above 200 kHz, poor reproducibility has been noted, especially for the reactance at low frequencies. Moreover, most single-frequency BIA analyzers operate at 50 kHz (4) and 50 kHz has been used to estimate body composition (59).

It is important to highlight the development of different techniques used in nutritional evaluation, which can contribute to the comprehensive evaluation of patients. Nevertheless, there are some important considerations when comparing the results between populations and with subsequent measurements in the same patient. It is necessary to consider the position in which the impedance measurement is performed. Wiech et al. (60) demonstrated differences between measurements in the lying, sitting, and standing positions, and they analyzed their data by considering sex. In men, there was a significant difference in PhA when it was measured in the sitting position ($7.23 \pm 1.40$) compared with the standing position ($6.27 \pm 0.68$) ($p = 0.020$). On the other hand, in women, there were differences between the lying and standing positions ($6.35 \pm 1.55$ vs. $5.40 \pm 0.72$, $p = 0.022$) and between the sitting and standing positions ($6.56 \pm 1.54$ vs. $5.40 \pm 0.72$, $p = 0.004$). These position-related differences in impedance measurements are due to the fact that it impacts the resistance and reactivity measurements and is finally reflected in the intracellular and extracellular hydrated tissue and its cell mass. We recommend that researchers report the position of the measurements and make subsequent measurements in the same patients in the same position to avoid bias.

In adult populations with different diseases, PhA is a recognized nutritional status marker (16, 61–63). However, malnutrition is a complex multifactorial phenomenon, and several factors could be associated with inflammation, catabolism, and the presence of edema. These factors could also have an impact on impedance markers, such as PhA (52). In the field of pediatric nutrition, there is still a lack of evidence to fully support the current hypothesis that PhA is a prognostic factor for clinical outcomes and a nutritional status marker. The evidence presented supports an association between PhA and malnutrition in pediatric populations. However, specific PhA cutoff points cannot yet be presented, and additional research is needed.

The present review presents some limitations. The main limitation is the inability to compare the studies due to the variety of BIA models used to obtain PhA and the different ways the researchers reported PhA (SPhA, percentiles, and degrees). In addition, the researchers used several nutritional indicators as a reference for malnutrition, and the included studies focused on several different conditions. Hence, it is difficult to generalize the information reported in this review. However, a strength of this review is that we included studies that evaluated PhA cutoff points and the association between PhA and malnutrition, that showed an association between PhA and anthropometric indicators, and that compared the mean PhA values in the presence and absence of malnutrition. Furthermore, we considered different age groups and different disease entities. Although this approach introduced heterogeneity, we summarized a larger picture of PhA and its association with the nutritional status of pediatric patients.

Carrying out a critical evaluation of our systematic review, our results are considered valid because the chosen articles are pertinent and important to answer the research question. We tried to assess the quality of the studies, although it was difficult to compare the PhA cutoff points, as mentioned above. Ideally, studies should standardize PhA to allow for comparisons across different populations. Nevertheless, our review summarizes a broader picture of PhA and its association with the nutritional status of pediatric patients. Our review demonstrates the benefit of measuring PhA: It is an easy-to-obtain parameter and applicable to address the diagnosis of malnutrition.

## Conclusion

The early identification of malnutrition is relevant to establish the correct nutritional treatment and increase the positive clinical outcomes of inpatient children. This endeavor encourages the development of sensitive markers that can detect malnutrition early in the course of the disease. PhA is generally easy to measure, and it can be seen as a complementary parameter to diagnose

malnutrition because it cannot evaluate the entire construct of the nutritional condition. Although the results of this systematic review are inadequate to establish PhA cutoff points associated with malnutrition in pediatric populations, additional research in various pathologies as well as a consensus on malnutrition construct in pediatric populations could be seen as an area of opportunity for future studies.

## 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.

## Author contributions

IM-V and AÁ-N designed the research. AF-O, AÁ-N, EAR-A, AT-M, ADG-G, BAP-N, JF-S, MG-C, and IM-V performed the research and drafted the manuscript. AF-O, AÁ-N, EAR-A, AT-M, JF-S, and IM-V analyzed the data. 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.2023.1142545/full#supplementary-material

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# Centile reference curves of the ultrasound-based characteristics of the rectus femoris muscle composition in children at 4–11 years old

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Quantitative diagnostic ultrasound has been proposed as a way to characterize muscle structure, but there is a lack of normative data for children. This study aims to establish age-specific normal ranges for echo-intensity (EI), cross-sectional area (CSA), muscular thickness (MT), and subcutaneous adipose thickness (SAT) values of the rectus femoris muscle in typically developing children. The study recruited 497 children (288 boys and 209 girls) aged 4–10.9 years (mean age 7.39 years), and muscle parameters were measured using 2D B-mode ultrasound. Percentile values and reference curves were calculated using the Lambda, Mu, and Sigma method (LMS). The results showed small variation between measurements for boys compared to girls, with the most significant difference in EI, CSA, and MT values. EI decreased with age, with the most pronounced curve in boys. SAT increased in both sexes, with a slightly higher increase in girls after the age of 9.0 years. This study provides the first age-specific reference norms for the rectus femoris muscle architecture in children, and further research is needed to validate these curves and determine their clinical utility.

KEYWORDS

ultrasound, histogram, subcutaneous fat, percentile, reference values

## 1. Introduction

Ultrasound (US) has become the preferred first-line imaging modality for children due to its noninvasive nature, low-cost, and easy accessibility (1). The concept of muscle quality has emerged as a useful construct to explore skeletal muscle function beyond age-related declines in lean body mass (1). Muscle quality and body composition are crucial factors in clinical outcomes (2). While muscle size plays a role in strength and physical functioning, physiological adaptations can occur separately in response to strength training and chronic disuse (3). However, US imaging is operator dependent, requires significant operator training, and has a limited field of view that necessitates detailed anatomical knowledge of the imaged area (4).

Different US parameters such as cross-sectional area (CSA), muscular thickness (MT), and echo-intensity (EI) can be used to quantify muscle quality. Fukumoto et al. (5) reported that MT of the knee extensor and muscle quality assessed from EI measured

using this method independently contribute to isometric knee extension strength in middle-aged and elderly women (51–87 years of age). These parameters provide insight into glucose metabolism, oxidative damage, protein metabolism, intramuscular adipose tissue, capillary density, structural composition, contractility, and fatigability. Muscle quality has been significantly associated with metabolic health (5, 6), risk of cardiovascular events (7), and overall mortality (8). Multiple factors can influence muscle quality, including composition, metabolism, fat infiltration, fibrosis, and neural activation. Poor muscle strength, rather than low muscle mass, has been identified as a major determining factor for functional decline. Obesity and physical inactivity are independent risk factors for poor muscle strength (9). A higher percentage of muscle mass and better muscle quality in quadriceps, i.e., lower EI values, are strongly associated with adverse clinical outcomes (10). Therefore, understanding the factors that influence muscle quality and assessing it using US parameters can have important implications for clinical outcomes in children.

Previously, studies have evaluated the quality of skeletal muscle using computer-aided gray scale analysis, showing that EI is associated with muscle strength independently of age or muscle size in middle-aged and older adults (11). Lower EI values (12) and increased intramuscular fat (13) have been linked to impaired strength and physical function in various conditions, from injury to aging to metabolic disease (14). Lower EI values have also been associated with reduced activation of quadriceps muscles in older adults (15). Muscle mass not only affects muscle strength and mobility, but also overall survival and prognosis related to underlying diseases (15).

Given the rapidly growing population at risk in Spain (16) and the strong association between muscle US parameters and conditions such as sarcopenia or pediatric dynapenia (17), assessing muscle quality is critical for disease prevention (18). In this line, García-Alonso et al. (19) observed a relationship between physical fitness components and muscle US parameters in prepubertal children's rectus femoris muscle. With regard to subcutaneous adipose tissue (SAT) Point. Chmid-Zalaudek et al. (20) studied SAT measured via US in children and adolescents demonstrated that those with excess adiposity, as determined by DXA (%body fat), had significantly higher levels of cardio-metabolic risk factors. In this context, quantitative musculoskeletal diagnostic US has been proposed as a viable method for characterizing muscle structure (21). Reference data is necessary, as a first step, to identify individuals with low muscle quality and/or high SAT across the age spectrum. While use of the US device has become routine practice in adults, the question remains of whether both the technique and the diagnostic cutoff values for adults can be applied to youth. Moreover, published muscle quality data from healthy youth remain scarce (22). Beyond the size of a peripheral muscle, the EI of the muscle is also of great interest, since increased EI, which results from intramuscular fat and interstitial fibrous tissue, is associated with impaired physical functioning (23). Nevertheless, population-specific data are valuable in reducing the risk of misclassifying the muscle quality phenotype among children, as sociodemographic, genetic, and lifestyle factors influence body composition.

Accordingly, the purpose of the present study was to establish age-specific reference norms of EI, CSA, MT, and SAT values in children aged between four and eleven years of age without underlying metabolic disease. These reference values may assist in identifying target populations for primary prevention and guiding population health programs, policies and priorities.

# 2. Materials and methods

## 2.1. Study design and simple

Using a cross-sectional study design from the "Observatorio de Actividad Física en escolares, https://observatorioactividadfisica.es", we examined muscle US parameters in Spanish children. The sample included 497 children aged 4.0–10.9 (288 boys and 209 girls, mean age 7.39 years). Participants were enrolled from four interested schools (a private school, Santa María la Real-Maristas; and three state schools, San Juan de la Cadena, El Lago de Mendillorri and Garcia Galdeano), two sports centers (a private sports center, S.C.D.R Anaitasuna; and a football club, Gazte Berriak C.F), and a health center (C.S Iturrama) from the Metropolitan Region of Pamplona (Navarra), Spain. This sample of the population was chosen due to the lack of muscle US parameters studies (independently of anthropometric values). Parents/guardians of children were informed of the study objectives during meetings and were invited to review the study protocol. Exclusion criteria included injury/surgery in the last month and/or any medical limitation/restrictions on physical ability testing. Informed consent was obtained from the parents/guardians and the children. Evaluations took place from December 2021 to June 2022. The study protocol was completed in accordance with the Helsinki Declaration and was approved by the Ethics Committee of the Universidad Pública de Navarra (ID # CENEDUCA1/2019).

## 2.2. Measurements

The data collection staff had a background in physical fitness and physical activity assessment and were trained by research staff from the coordinating center (e-FIT UPNA Research Group). Age and sex were assessed using a self-report questionnaire. Anthropometric measures (height, weight, and waist circumference) were collected following the CDC-NHANES survey protocol (24), by two members of the research team. Height was measured in the Frankfurt position using a stadiometer (SECA, model 213, GmbH & co. Hamburg, Germany) with 1 mm precision. Body mass was measured in light clothing and bare feet using a TANITA device scale (TANITA DC-430MAS®, Tokyo, Japan) with 100 g precision. The waist circumference measurement was taken midway between the tenth rib and the iliac crest and was recorded to the nearest millimetre. A non-elastic flexible tape measure was

employed with the subject in a standing position (Seca 201, Seca GmbH & co. Hamburg, Germany). Body mass index (BMI in kg/m$^2$) was subsequently derived, and BMI *z*-scores were calculated using age- and sex-specific reference data from the World Health Organization (25). The waist-to-height ratio was calculated as waist circumference/height in cm.

The muscle architecture and echo intensity of rectus femoris was measured by real-time two-dimensional B-mode US (Esaote MyLab$^{TM}$50, Genova, Italy). Participants were asked to lie supine on a bed with extended knee joints and rest completely during the image acquisition. To ensure body fluid shift stabilization, participants were given five minutes of rest in this position. A mark was drawn at 50% of the distance between the anterior superior iliac spine and the mid patella point. The images were obtained by an expert operator (YGA) using a multi-frequency linear transducer (4–15 MHz). To ensure proper probe placement and consistent image capture location, a dotted line was drawn transversely and sagittal along the surface of the skin from the aforementioned location. All measures of muscle morphology were obtained using fixed settings that remained constant throughout the examination of each participant. This approach was employed to minimize any potential bias in the instrumentation, to optimize spatial resolution, and to ensure consistency in the measurement of muscle morphology. Image gain was set at 55 decibels (dB), dynamic range was set at 72, and image depth was set at 45–50 mm. Any optional postprocessing available within the software was switched off and time gain compensation buttons were kept in their neutral positions. Transmission gel (Ultrasound GEL® Ref: 33273, Gima s.p.A Laboratories, Inc., Gessate, MI, Italy) was used for all scans to improve acoustic contact, and minimum pressure was applied to partially visualize the muscle border. Still images were captured in both sagittal and transverse planes, followed by complete images captured with the panoramic function. Rectus femoris architecture parameters were estimated in four ways: (i) EI was determined by tracing the maximum region of interest (ROI, **Figure 1B**) representing the rectus femoris CSA, followed by calculating the mean level of gray within the ROI in 8-bit resolution images (gray levels from 0 to 255, where black = 0 and white = 255) using ImageJ software (ImageJ, National Institutes of Health, USA, version 1.45s). Higher scores indicated increased intramuscular fat and interstitial fibrous tissue (21). The mean and standard deviation (SD) of each histogram were computed. The inner outline of the rectus femoris was manually traced to calculate CSA by a movable cursor on a frozen image, identified by its hyperechoic appearance (**Figure 1B**). The MT was quantified using the line tool at the midpoint of the horizontal distance between the anterior and posterior sides of the rectus femoris. MT was measured as the minimum distance between the inferior border of the superficial aponeurosis and the superior border of the deep aponeurosis. MT value is highlighted in blue (**Figure 1C**) and recorded in mm. The SAT thickness was quantified using line was drawn perpendicular to the epithelium and the superior border of the superficial aponeurosis, and the resulting distance was calculated (26). Data were reported in mm, using internal software on the Esaote MyLab$^{TM}$50. This analysis was similar to previously established methods (21, 27), and anatomical measurement sites are described in detail in **Figures 1A–C**.

## 2.3. Statistical analyses

Sample were categorized according to sex into eight age categories, from 4 to 11 years. Outlier analysis was performed to verify that all values were within a physiologically possible range. Smoothed age-specific and sex- specific percentiles and curves were developed by Cole and Green (28).The least mean squares (LMS) technique estimates 3 parameters: median (M), coefficient of variation (S), and power in the Box–Cox transformation (L). These three parameters vary as a function of independent variables, and worm plots were used to assess goodness of fit. Normality was assessed using Kolmogorov–Smirnov tests. We included in the analysis smoothed LMS curves for the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles of all parameters. All data are presented as the mean 95% CI. Student's *t*-test was used to determine whether significant differences were found between the descriptive characteristics using IBM SPSS version 26.0 statistical software (IBM Corporation, Armonk, NY). The level of statistical significance was set at $p < 0.05$.

# 3. Results

**Table 1** shows the anthropometrics characteristics and US measurements of the participants, consisting of 288 boys and 209 girls aged 4–10.9 years, with a mean age of 7.39 (IC95% 7.22–7.56) years. BMI and waist-to-height ratio were similar in both groups ($p > 0.05$). Age, height, body mass, and waist circumference, was significantly higher in boys than in the girls' group ($p < 0.05$). The EI and SAT (captured in the sagittal and transverse planes) were significantly greater with the girls than with the boys' group ($p < 0.05$). We observed no significant differences in the MT or CSA between sex groups ($p > 0.05$).

The LMS reference curves, which provide information on the distribution of EI, CSA, MT, and SAT for boys and girls based on the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles, are summarized in **Figures 2**, **3**, and **Supplementary Tables S1–S5**. We found that there were small variations between the US measurements (e.g., percentiles 90–97) and least fit (e.g., percentiles 3–10) for boys when compared to girls, particularly for EI, CSA, and MT values. For both sexes, EI decreased as age increased, with the most pronounced curve observed in boys (**Figures 2A,B**). The percentile curves for CSA and MT were similar for boys and girls across all ages, with differences increasing with age (**Figures 2C–F**). In boys, the age-related increase in CSA and MT values tends to stabilise from age 8.0 years onwards (**Figures 2C–E**). Similarly, SAT, as captured in the sagittal and transverse planes (**Figures 3A–D**), increased in both sexes, with a slightly greater increase observed in girls from age 9.0 years onwards.

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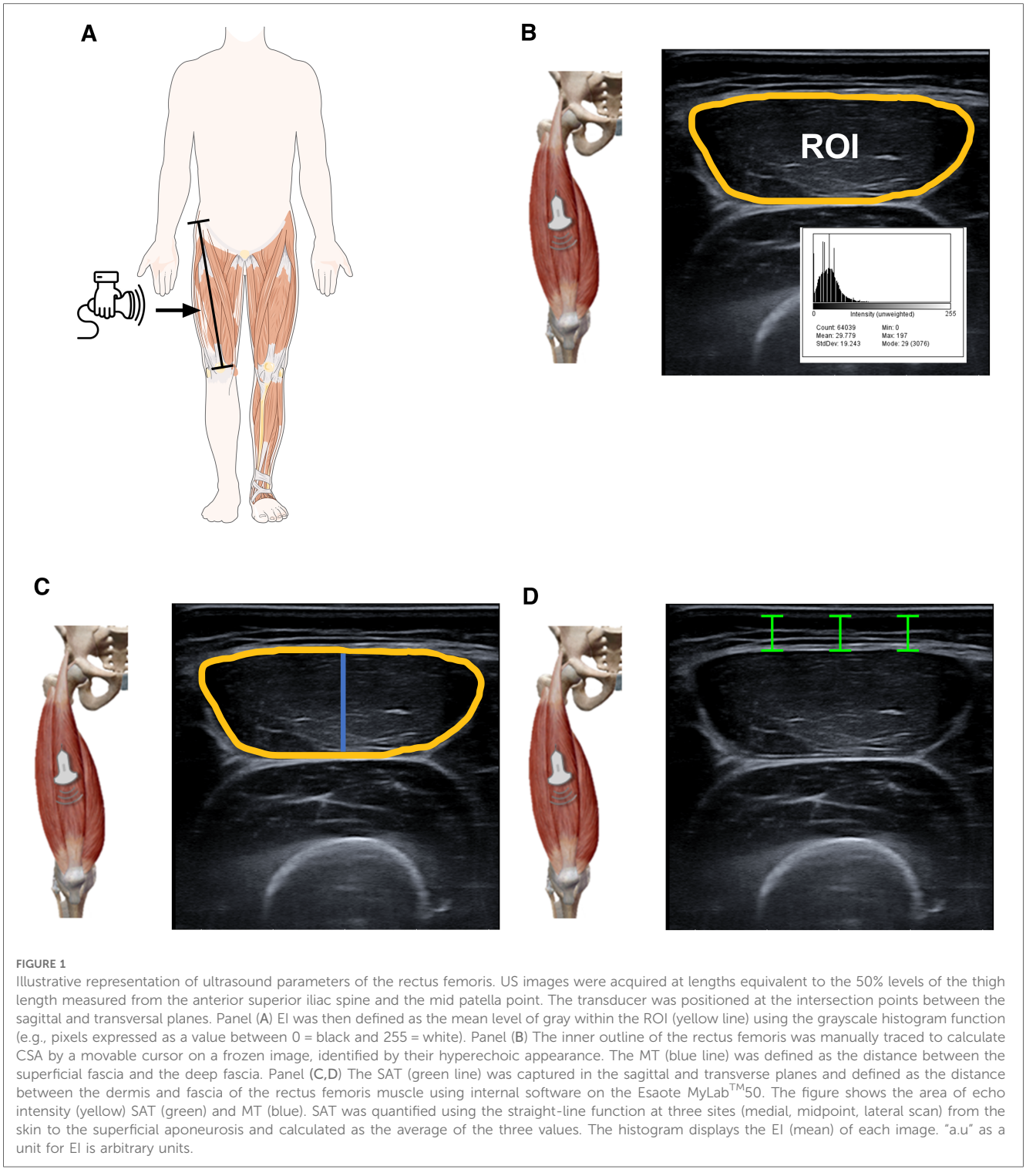


FIGURE 1
Illustrative representation of ultrasound parameters of the rectus femoris. US images were acquired at lengths equivalent to the 50% levels of the thigh length measured from the anterior superior iliac spine and the mid patella point. The transducer was positioned at the intersection points between the sagittal and transversal planes. Panel (**A**) EI was then defined as the mean level of gray within the ROI (yellow line) using the grayscale histogram function (e.g., pixels expressed as a value between 0 = black and 255 = white). Panel (**B**) The inner outline of the rectus femoris was manually traced to calculate CSA by a movable cursor on a frozen image, identified by their hyperechoic appearance. The MT (blue line) was defined as the distance between the superficial fascia and the deep fascia. Panel (**C,D**) The SAT (green line) was captured in the sagittal and transverse planes and defined as the distance between the dermis and fascia of the rectus femoris muscle using internal software on the Esaote MyLab$^{TM}$50. The figure shows the area of echo intensity (yellow) SAT (green) and MT (blue). SAT was quantified using the straight-line function at three sites (medial, midpoint, lateral scan) from the skin to the superficial aponeurosis and calculated as the average of the three values. The histogram displays the EI (mean) of each image. "a.u" as a unit for EI is arbitrary units.

## 4. Discussion

The accuracy of US in assessing skeletal muscle and its potential to predict clinical outcomes has been postulated in previous studies (29, 30). Our study highlights the use of US-based characteristics of the rectus femoris muscle composition in elementary school children, for evaluating peripheral muscle size and EI and may be helpful in monitoring muscle quality. This study should be considered as a first step, and these values can guide pediatricians who wish to apply the technique and can also be a valuable resource in the clinical assessment of muscle function and for comparisons with studies from other countries, as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP2) (31), the SARCUS study (SARCopenia through UltraSound) (32), and on its possible role in diagnosing pediatric dynapenia.

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TABLE 1 Anthropometrics characteristics and US measurements of the participants.

| Variables | Full sample ($n = 497$) | Boys ($n = 288$) | Girls ($n = 209$) |
|---|---|---|---|
| **Anthropometrics parameters** | | | |
| Age (years) | 7.39 (7.22;7.56) | 7.64 (7.41;7.88) | 7.04 (6.81;7.28)[b] |
| Height (cm) | 124.87 (123.70;126.04) | 126.63 (125.03;128.23) | 122.46 (120.78;124.13)[a] |
| Body mass (kg) | 27.24 (26.51;27.96) | 28.19 (27.21;29.16) | 25.94 (24.87;27.00)[a] |
| Body mass index ($kg/m^2$) | 17.08 (16.87;17.28) | 17.19 (16.92;17.46) | 16.93 (16.61;17.25) |
| Body mass index ($z$-score) | −0.00 (−0.08;0.09) | 0.04 (−0.06;0.16) | −0.05 (−0.06;0.16) |
| Waist circumference (cm) | 58.30 (57.67;58.92) | 58.90 (58.08;59.73) | 57.47 (56.52;58.42)[a] |
| Waist-to-height ratio | 0.46 (0.46;0.47) | 0.46 (0.46;0.47) | 0.47 (0.46;0.47) |
| **Muscle ultrasound parameters** | | | |
| Transverse measurements | | | |
| EI (au) | 44.82 (43.61;46.03) | 43.13 (41.45;44.81) | 47.15 (45.48;48.82)[a] |
| CSA ($cm^2$) | 5.36 (5.25;5.46) | 5.38 (5.24;5.53) | 5.32 (5.17;5.48) |
| MT (mm) | 13.00 (12.77;13.23) | 13.14 (12.83;13.48) | 12.81 (12.48;13.15) |
| SAT (mm) | 6.44 (6.17;6.72) | 6.01 (5.68;6.34) | 7.04 (6.59;7.49)[b] |
| Sagittal measurements | | | |
| SAT (mm) | 6.80 (6.56;7.04) | 6.36 (6.04;6.68) | 7.37 (7.02;7.72)[b] |

Values are means and 95% CI. Unpaired $t$-tests were utilized to compare the differences between the sex groups.
EI, echo-intensity; SAT, subcutaneous adipose tissue; MT, muscular thickness; CSA, cross-sectional area.
[a]$P < 0.05$.
[b]$P < 0.01$.

US has the potential to become an imaging-based tool for screening and diagnosing skeletal muscle US parameters, comparable to computed tomography and magnetic resonance imaging, which quantify body composition on the tissue level, and dual-energy x-ray absorptiometry, which assesses the chemical level. Among qualitative measures, muscle EI provides helpful information about the presence of inflammation, fibrosis, and adipose tissue infiltration (33). Previous studies have increasingly integrated the concepts of muscular strength, peak force and body size to assess muscle performance and provide an estimate of muscle quality (34). In older adults, there appears to be a correlation between EI and muscle strength, gait speed, and sit-to-stand test (35). Among children, Garcia-Alonso et al. (19) shown that there are associations between physical fitness components and muscle US parameters in prepuberal children. In addition, muscle architectural characteristics including MT, muscle volume, EI, and CSA are strongly correlated with the maximum muscle strength and power (33, 35).

In our study, we found that boys in the 50th percentile have muscle EI values of 52.13 a.u. in the age range of 4.0–4.9 years, which decreases to 32.15 a.u. in the age range of 10.0–10.9 years. For girls, the 50th percentile, muscle EI values start at 50.32 a.u. in the age range of 4–4.9 years and decrease to 39.56 a.u. in the age range of 10.0–10.9 years. The relationship between age, CSA, and MT was found to be curvilinear, which is consistent with previous studies that have shown age-related changes in muscle mass, CSA, and muscle strength (36–38). During early childhood, there is a consistent pattern of sexual dimorphism and muscle mass quantity which is in line with previous findings from ethnically diverse populations and likely due to hormonal influences (39). We also found gender differences in SAT, which are similar to those observed in adults. In the girls group, we found an increase in SAT percentage as they age, from 5.94 mm in the 4–4.9 age group to 8.69 mm in the 10–10.9 age group (40). These gender differences seem to start from an early age and vary for upper and lower extremity muscle groups. Furthermore, we observed an age-related increase in EI mean values in children, and it is known that, in women, muscle tissue develops increased fatty infiltration, leading to increases in EI (32). Therefore, tracking the development of lean mass during adolescence can be a useful tool in identifying potential interventions for metabolic diseases associated with sarcopenia early in life (13).

Although our analyses were robust, there are several limitations that should be taken into account. Apart from sex differences, other factors, such as nutritional status, environmental factors, or ancestral differences, can influence muscle growth. To address this issue, we included only children living in the city of Pamplona (Spain) to minimalize cultural differences between ancestral groups (e.g., beliefs and traditional food) and living circumstances (e.g., housing, possibility of schools, access to sports clubs). However, it would be interesting to consider these factors in further studies or studies with older children. Additionally, our study design did not involve following up with the same group over time, so we cannot confirm if the observed trends will persist over time. Moreover, the lack of data on dietary patterns limits our ability to interpret the contribution of diet to body composition development. There is no clear criterion for muscle EI value, and the results cannot be readily generalized for different US devices, as EI is influenced by US system hardware and software. Therefore, our normative EI values can only be used with the same ultrasound device and settings, and new values must be established for other cases. However, the measurement of CSA or MT does not depend on equipment settings, so normative data of muscle size presented in this study can be applied in other centers. On the other hand, the reliability of MT, CSA and SAT measurements has been investigated in previous studies (43–45). The coefficient of variation examining the intra and inter-experimenter reliability of the US imaging technique ranged from 0.6 to 2.7%, even by minimally trained or untrained professionals. Based on these results, the experimenters concluded that US is a valid and reliable tool to assess large muscle quality parameters.

Despite these limitations, our study contributes to our understanding of how muscle parameters varies by sex and age in children. This measure can offer valuable insights regarding muscle quality of the normal rectus femoris muscle, which plays a key role in for assessing body composition in all age groups (21). Measuring muscle size and composition from magnetic resonance imaging or computed tomography is expensive and may

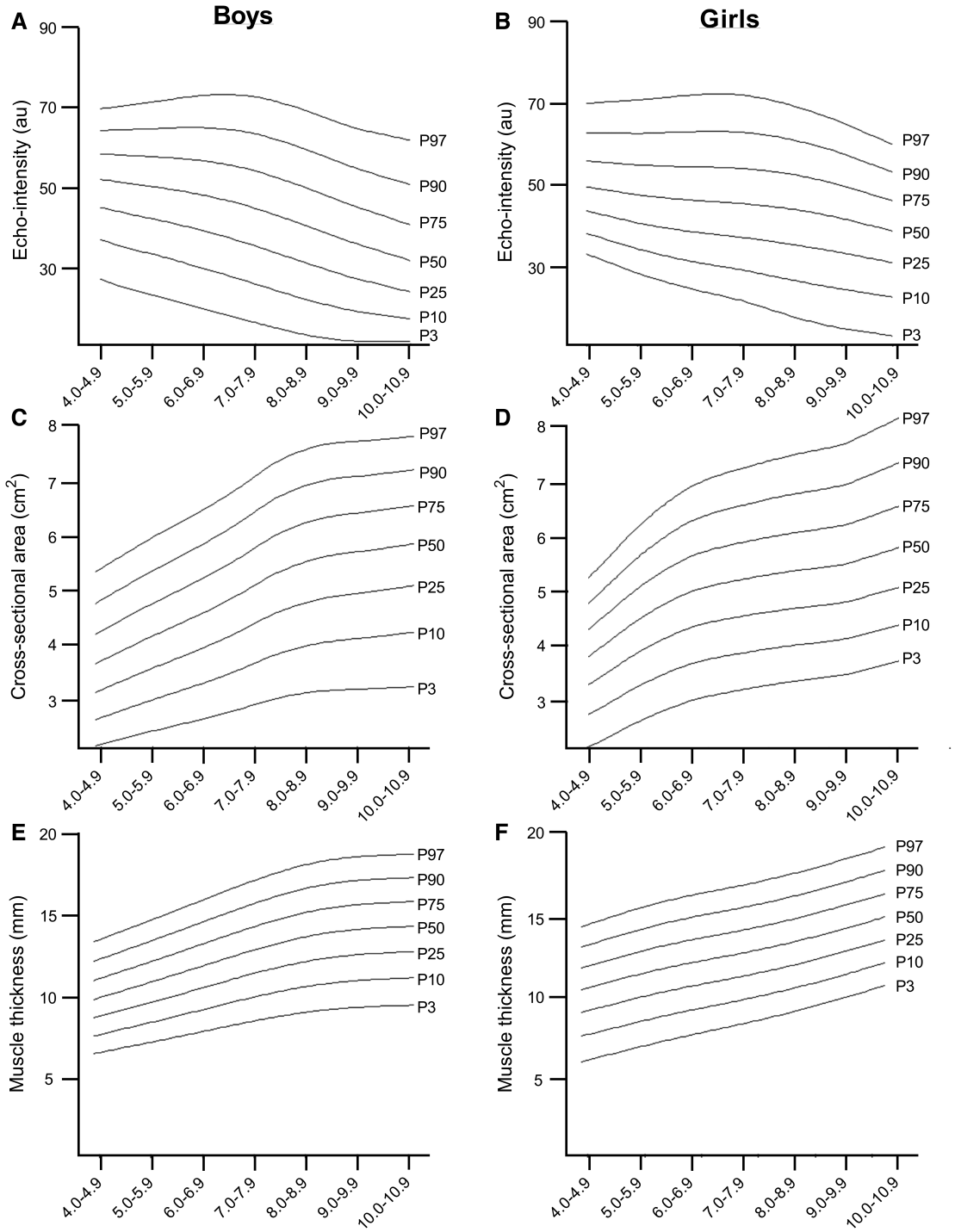


FIGURE 2
Reference curves age-specific and sex-specific of EI, CSA and MT in boys and girls.

not be accessible for youth at the population level. Since US imaging is a more accessible and less expensive technique that provides valuable information about muscle function, muscle composition testing and monitoring will provide valuable insights into the health status of youth at individual and group levels. Although there is no established cut-off for defining healthy quality muscle mass in the pediatric population, the lowest CSA and MT percentiles computed in our study (3rd and 10th percentile), or higher EI percentiles computed in our study (90th and 97th percentile), could be used as an indication of the worsening lean mass phenotype. Investigating the correlation between these muscle US parameters and early adiposity rebound could provide an effective marker of obesity in children and help tailor nutritional and exercise interventions to improve the treatment of metabolic diseases associated with

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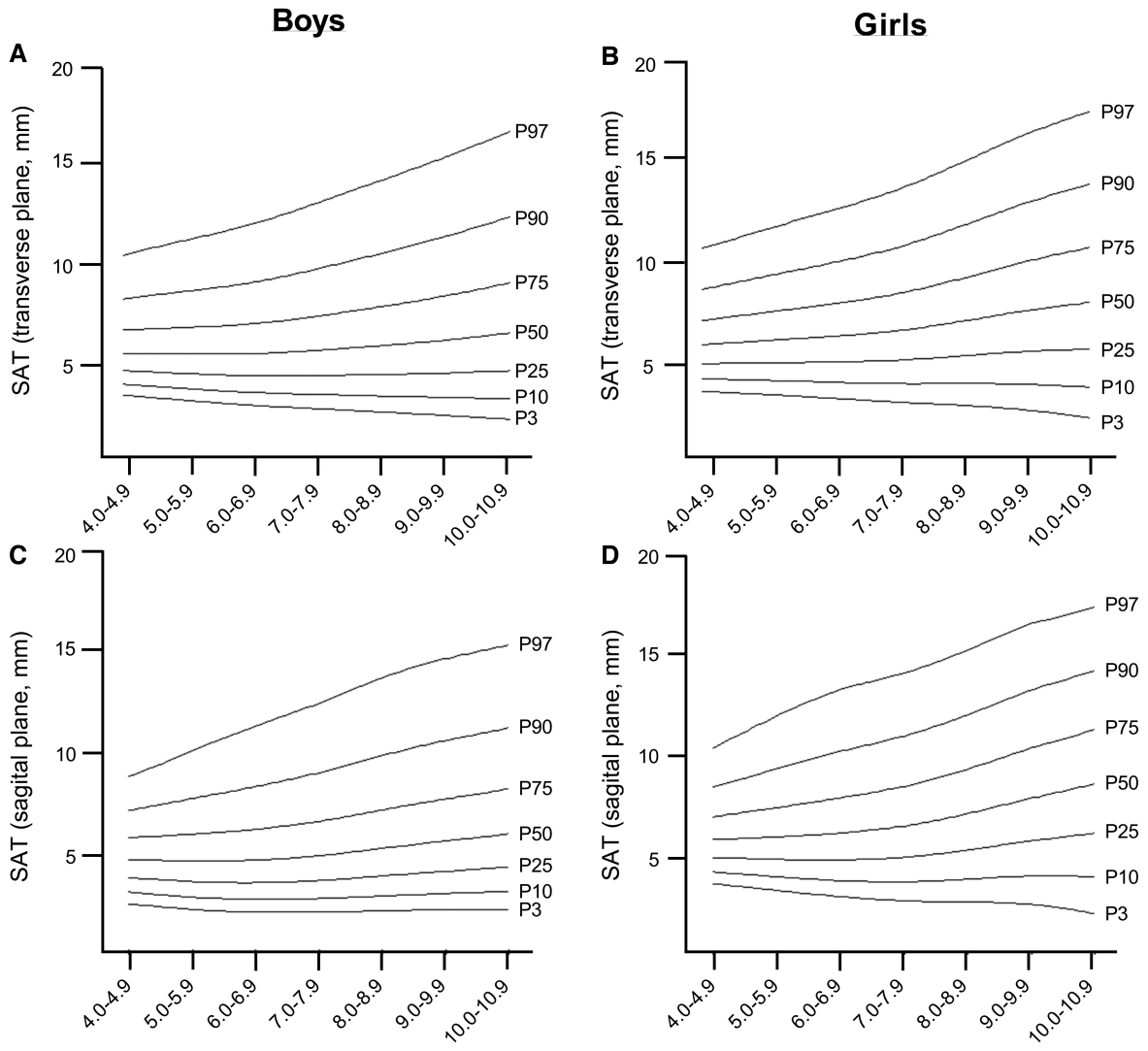


FIGURE 3
Reference curves age-specific and sex-specific of SAT in boys and girls.

sarcopenia in early life (41). Future studies combining these percentiles with functional data (e.g., muscle strength) are required for defining dynapenia and/or low-quality muscle mass among children and adolescents (13).

In situations where resources are limited and longitudinal follow-up is difficult, ultrasonographic measurements of the rectus femoris muscle can serve as a preliminary alternative. Additionally, the LMS analysis is a popular method for obtaining smoothened centile curves for cross-sectional data (42). Thus, our charts can provide valuable information to researchers studying adolescents in this geographic region and can assist healthcare providers in identifying abnormalities in body composition development during youth. In summary, we have presented age- and sex-specific reference data for normal rectus femoris muscle US parameters that are unique to children. These data allow for the identification of the risk of low-quality mass and the provision of targeted treatments, such as nutritional and exercise interventions, as well as the initiation of sports programs in schools through public policies. These measures can prevent associated outcomes, such as pediatric dynapenia, and promote healthy development in children.

## Data availability statement

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

## Ethics statement

All study protocols were approved by the Ethics Committee of the Universidad Pública de Navarra (CENEDUCA1/2019), and all methods were carried out in accordance with relevant guidelines and regulations. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## Author contributions

YG-A, AA-M, MI: study concept and design; GL-G, YG-A, AA-M: data collection; RR-V: statistical analysis; GL-G, YG-A, AA-M, RR-V, AG-H: interpretation of data: GL-G, YG-A, AA-M, RR-V, AG-H: drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1168253/full#supplementary-material

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# Sarcopenia defined with L3-SMI is an independent predictor of survival in male patients with ARLD in mainland China

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**Background:** The burden of alcohol-related liver disease (ARLD) is increasing in China. Patients with ARLD are more likely to have comorbid sarcopenia, which may impair their survival. This study aimed to evaluate the relationship between the prognoses of patients with ARLD and sarcopenia, identified using the skeletal muscle index at the third lumbar vertebra level (L3-SMI).

**Methods:** Hospitalized patients with ARLD were retrospectively enrolled between 2015 and 2018 and followed up for 24months to evaluate their survival profiles. Cox proportional hazards regression models were used to estimate patient survival factors. A receiver operating characteristic curve was created to identify the cut-off point of the L3-SMI for predicting the prognoses of Chinese patients with ARLD.

**Results:** The study enrolled 168 male patients with ARLD who were followed-up for 24 months or until a study endpoint was met. The overall L3-SMI in patients with ARLD was $42.61 \pm 9.15\ cm^2/m^2$, and 42.86% (72/168) of patients with ARLD were comorbid with sarcopenia. The overall survival in patients with ARLD was 77.38% at 24 months. The survival rate of patients with sarcopenia was lower than that of patients without sarcopenia (66.67% vs. 85.42%, $p = 0.004$). Multiple Cox regression analysis showed that sarcopenia, abstinence, and baseline creatinine level were independent prognostic factors of 24-month survival with hazard ratios (95% confidence intervals) of 2.022 (1.025–3.991), 0.275 (0.122–0.617), and 1.018 (1.008–1.027), respectively. The cut-off value of the L3-SMI for predicting 24-month survival was $40.0\ cm^2/m^2$ for male patients with ARLD.

**Conclusion:** Sarcopenia is an independent mortality risk factor in male patients with ARLD in mainland China. Early diagnosis and intervention of sarcopenia are important for optimizing the management of patients with ARLD.

KEYWORDS

**sarcopenia, alcohol-related liver disease, L3-SMI, prognosis, survival**

## 1. Introduction

Alcohol-related liver disease (ARLD) is the leading cause of liver disease, accounting for 50% of all liver disease-related deaths worldwide (1). The incidence of ARLD and related deaths is also on the rise in China (2). Multiple studies have shown that many factors are associated with the prognoses of patients with ARLD, including abstinence, baseline

cirrhosis, and renal dysfunction (3–5). Recently, the relationship between sarcopenia and the prognoses of patients with liver disease has attracted increasing attention (6). Sarcopenia is a common syndrome in patients with chronic liver disease, and is characterized by the progressive and systemic loss of skeletal muscle mass and strength. Studies have shown that sarcopenia is a key risk factor for the survival of patients with cirrhosis (7). The incidence of sarcopenia in patients with ARLD is greater than that in patients with other causes of liver disease. The prevalence of sarcopenia in patients with ARLD is 37–50%, significantly affecting the survival of patients with ARLD (7). However, the relationship between sarcopenia and survival in male patients with ARLD in mainland China remains unclear.

Regarding the diagnosis criteria of sarcopenia, the European Working Group on Sarcopenia in the Elderly (EWGSOP) recommended using handgrip strength, knee flexion/extension strength, usual gait speed, and medical imageology to assess muscle mass and strength (8). According to these guidelines, a diagnosis of sarcopenia can be made in males with a handgrip strength of <30 kg and in females with <20 kg. However, there are some confounding factors; for instance, handgrip strength correlated with leg strength, making the measures vulnerable to error and questionable for routine use. Computed tomography (CT), which is regarded as the gold standard for analyzing body composition, is more accurate (9, 10). In particular, the skeletal muscle index at the third lumbar vertebra (L3-SMI), measured using CT (11, 12), has been validated for evaluating total skeletal muscle and is used for the diagnosis of sarcopenia (13–15). Due to differences in ethnicity, dietary habits, and physical activity, the criteria for L3-SMI in Asian populations is significantly different to that of other populations, such as those from the United States and Europe [45.4 $cm^2/m^2$ in men and 34.4 $cm^2/m^2$ in women from the United States (16), and 43.1 $cm^2/m^2$ in men and 32.7 $cm^2/m^2$ in women from the Netherlands (17)]. Recently Kong et al. (12) reported in China that the cut-off value for the L3-SMI for the diagnosis of sarcopenia was 40.2 $cm^2/m^2$ in male patients and 31.6 $cm^2/m^2$ in female patients. The current study aimed to analyze the relationship between the prognoses of male patients with ARLD and sarcopenia, as defined using the L3-SMI.

# 2. Methods

## 2.1. Patients and study design

Consecutive adult patients with ARLD hospitalized in the Department of Hepatology of Beijing Ditan Hospital between January 2015 and December 2018 were retrospectively enrolled. ARLD was diagnosed in accordance with the EASL Clinical Practice Guidelines for the Management of Alcohol-Related Liver Disease (18). In particular, a diagnosis of ARLD is suspected upon documentation of regular alcohol consumption of >20 g/d in females and > 30 g/d in males, according to the EASL guidelines of ARLD (18). The exclusion criteria were (1) viral hepatitis, autoimmune liver disease, drug-induced liver injury, primary liver cancer, or other liver diseases; (2) previous liver transplantation; and (3) missing follow-up data. Among 550 hospitalized patients initially diagnosed with ARLD and screened using a hospital information system, 324 patients were excluded because of comorbidities with other liver diseases, 226 patients qualified for further screening, and 58 patients excluded for disinterested in research, phone disconnect. Eventually,168 patients were enrolled in this study and finished 24 months follow-up in this study (Figure 1). The data on baseline demographics included sex, age, smoking history, and recidivism; the laboratory tests included complete blood counts, coagulation tests, and liver and renal function tests. The tests for liver cirrhosis decompensation complications included ascites, hepatic encephalopathy, and esophageal–gastric variceal bleeding.

## 2.2. Ct scan and assessment of the L3-SMI

CT scans were performed using a multi-slice spiral CT scanner (Brilliance 256-slice spiral CT scanner, Philips Medical Systems, the Netherlands, or uCT780 256-slice spiral CT scanner, United Imaging Medical Systems, Shanghai, China) with a collimating reconstruction thickness of 1 mm and an interval of 1 mm, according to the standard operating procedures. All participants were placed in the supine position and instructed to hold their breath to reduce breathing and movement artifacts during scanning.

Two independent radiologists analyzed the CT images using SliceOmatic V5.0 software (Rev-8, Tomovision, Montreal, Quebec,

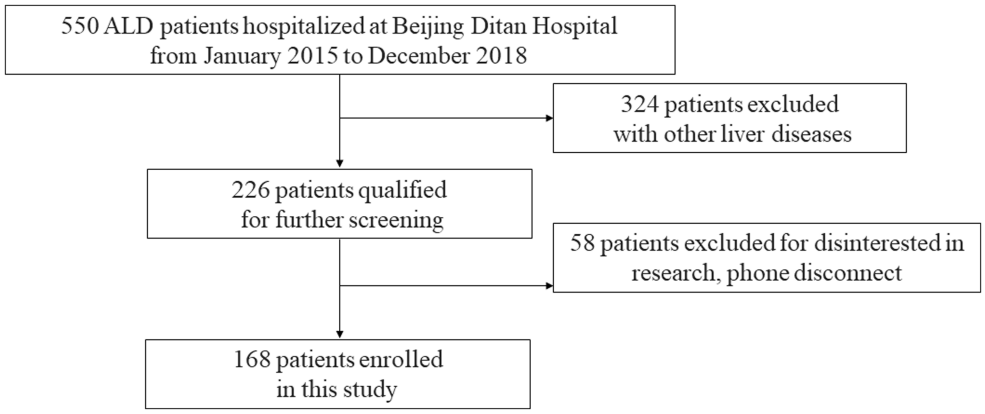


FIGURE 1
Flowchart of the study's design.

Canada). In accordance with a previous study, muscle tissues were identified on CT images based on Hounsfield unit (HU) thresholds ranging from 29 to 150, and subcutaneous and intermuscular adipose tissues were identified using HU thresholds ranging from 30 to 190. In addition, tissues with HU thresholds ranging from 50 to 150 were considered visceral adipose tissues. The skeletal muscles at the L3 level include the psoas major, erector spinalis, quadratus psoas, external abdominal oblique, internal abdominal oblique on the right and left sides, and transverse abdominis. The software automatically calculated the sum of the relevant tissue area, the average density at the L3 level cross-section, the skeletal muscle area, visceral adipose tissue area, subcutaneous adipose tissue area, skeletal muscle density, visceral adipose tissue density, subcutaneous adipose tissue density, and intermuscular adipose tissue density. The L3-SMI, which represents muscle mass, was calculated by dividing the skeletal muscle area at the L3 level by the square of the patient's height ($cm^2/m^2$). The L3-SMI has been suggested for assessing sarcopenia because of the ease of obtaining CT and magnetic resonance imaging data at the level of L3 and the muscles that are imaged, including the psoas muscle, erector spinae, lumbar muscle, transversal abdominis, external oblique muscle, and intra-abdominal oblique muscle (12, 19). Based on a previous study conducted in China (12), the cut-off value for the L3-SMI for the diagnosis of sarcopenia was 40.2 $cm^2/m^2$ in male patients and 31.6 $cm^2/m^2$ in female patients.

## 2.3. Patient follow-up

Patients were followed up every 3–6 months for 24 months using medical records or telephone interviews. The main study endpoint was death or liver transplantation at 24 months of follow-up. Alcohol abstinence and relapse were also assessed at each follow-up visit.

## 2.4. Statistical analysis

Continuous variables are described as the mean (±standard deviation) or median (interquartile range) and were assessed using the independent sample *t*-test or Mann–Whitney U test. Categorical variables are expressed as counts and percentages and were assessed using the chi-squared or Fisher's exact test. The Kaplan–Meier method was used to develop a survival curve, which was compared using the log-rank test. Variables found significant in a univariate analysis were incorporated into a multivariate Cox proportional hazards regression analysis, which was used to identify independent prognostic factors. The cut-off values of the L3-SMI were determined using receiver operating characteristic (ROC) curve analysis with the Youden index. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using SPSS 24.0 and R software (R Foundation for Statistical Computing, Vienna, Austria).

# 3. Results

## 3.1. Baseline characteristics of the patients

The baseline characteristics of the patients are summarized in Table 1. The cohort included 168 male participants aged 20–85 years. All patients were followed-up for 24 months or until a study endpoint was met; 38 (22.62%) patients died within 24 months. The average alcohol consumption of all patients was 134.64 ± 69.82 g/d.

The baseline characteristics of the patients who died or had survived at 24 months are presented in Table 1. Thirty-six patients died of liver-related disorders, such as hepatic encephalopathy, upper gastrointestinal hemorrhage, and septic shock (36/38), one patient died of cerebral hemorrhage (1/38), and one of pulmonary embolism (1/38). Significant differences between the survival and death groups were identified in the relapse rate (48.5% vs. 76.3%, $p = 0.002$), baseline cirrhosis (76.2% vs. 92.1%, $p = 0.038$), ascites (54.6% vs. 76.3%, $p = 0.017$), platelet count (112.20 vs. 71.00, $p = 0.022$), alanine transaminase (33.15 vs. 24.65, $p = 0.006$), total bilirubin (TBil) (33.80 vs. 60.55, $p = 0.016$), creatinine (62.50 vs. 69.50, $p = 0.006$), prothrombin time -INR (PT-INR) (1.26 vs. 1.46, $p = 0.001$), serum Na (139.55 vs. 138.18, $p = 0.006$), MELD (8.24 vs. 14.57, $p < 0.001$), and Maddrey's differential function (15.02 vs. 29.24, $p = 0.001$). There were no significant differences between the survival and death groups regarding age (55.25 ± 10.66 vs. 54.26 ± 11.59, $p = 0.625$), varices bleeding (10.8% vs. 7.9%, $p = 0.765$), and encephalopathy (11.5% vs. 5.4%, $p = 0.06$). In particular, more patients (20) comorbid with sarcopenia died at 24 months of follow-up compared with patients who survived (66.67% vs. 85.42%, $p = 0.004$).

## 3.2. Cumulative survival in patients with and without sarcopenia

A total of 72 patients had comorbid sarcopenia. The cumulative survival rates of patients at 3, 6, 12, and 24 months in this study were 94.05, 91.7, 86.31, and 77.38%, respectively (Figure 2A). Figure 2 illustrates the analysis of patient survival based on the various subgroups. The 24-month survival of patients with comorbid ARLD and sarcopenia was worse than that of patients without sarcopenia ($p = 0.0035$, Figure 2B). The 3-, 6-, 12-, and 24-month cumulative probabilities of survival in patients with ARLD comorbid sarcopenia were 90.28, 86.11, 79.17, and 66.67%, respectively. In comparison, they were 96.88, 95.83, 91.67, and 85.42%, respectively, in patients without sarcopenia.

The survival rate of patients with sarcopenia was worse than that of patients without sarcopenia at 24 months (66.67% vs. 85.42%, $p = 0.004$). In particular, the survival of patients who relapsed from abstinence was worse than that of patients who maintained abstinence (Figure 2c; $p = 0.035$). Furthermore, a comparison of the prognoses of patients with baseline MELD scores of <21 and ≥ 21 and Maddrey scores of <32 and ≥ 32 showed that the survival of patients with a baseline MELD score of ≥21 and Maddrey score of ≥32 was worse (Figures 2D,E; $p = 0.015$, $p < 0.001$, respectively). In addition, the 24-month survival of patients with ARLD and cirrhosis (ALC) was worse than that of patients without ALC.

During the clinical course in the follow-up period, there were 12 cases of hepatic encephalopathy, 8 cases of gastrointestinal hemorrhage, and 47 cases of ascites complications among the 72 patients who had comorbid sarcopenia. In comparison, there were 12 cases of hepatic encephalopathy ($p = 0.507$), 9 cases of gastrointestinal hemorrhage ($p = 0.798$), and 53 cases of ascites complications ($p = 0.207$) in the 96

TABLE 1 Baseline characteristics of the enrolled patients.

| Variable | Survival ($n$ = 130) | Death ($n$ = 38) | $p$ value |
|---|---|---|---|
| Clinical characteristic | | | |
| Age, year | 55.25 ± 10.66 | 54.26 ± 11.59 | 0.625 |
| Abstinence, $n$% | 63 (48.5) | 29 (76.3) | 0.002* |
| Cirrhosis, $n$% | 99 (76.2) | 35 (92.1) | 0.038* |
| Ascites, $n$% | 71(54.6) | 29 (76.3) | 0.017* |
| Varices bleeding, $n$% | 14 (10.8) | 3 (7.9) | 0.765 |
| Encephalopathy, $n$% | 15 (11.5) | 9 (5.4) | 0.060 |
| Laboratory parameters | | | |
| WBC ($10^9$/L) | 4.90 (3.87–7.31) | 4.85 (3.75–7.82) | 0.949 |
| Hb (g/L) | 111.44 ± 29.20 | 110.52 ± 23.16 | 0.840 |
| PLT (g/L) | 112.20 (69.45–152.00) | 71.00 (54.98–130.25) | 0.022* |
| ALT (U/T) | 33.15 (22.03–56.00) | 24.65 (16.48–36.33) | 0.006* |
| AST (U/T) | 60.20 (36.05–99.20) | 55.35 (33.50–87.65) | 0.619 |
| TBil (μmol/L) | 33.80 (16.20–68.25) | 60.55 (22.75–128.20) | 0.016* |
| ALB (g/L) | 32.15 (27.60–37.43) | 31.50 (26.80–34.93) | 0.238 |
| Cr (μmol/L) | 62.50 (55.60–72.65) | 69.50 (59.68–93.10) | 0.006* |
| PT-INR | 1.26 (1.09–1.46) | 1.46 (1.23–1.80) | 0.001* |
| Na (mmol/L) | 139.55 (136.28–142.40) | 138.18 ± 4.19 | 0.006* |
| L3-SMI | 43.73 ± 9.23 | 38.76 ± 7.84 | 0.003* |
| Sarcopenia | 48 (36.9) | 24 (63.16) | 0.004* |
| Alcohol consumption (g/d) | 133.00 ± 69.71 | 140.26 ± 70.84 | 0.835 |
| Scoring system | | | |
| MELD | 8.24 (5.05–13.95) | 14.57 (8.29–19.65) | <0.001* |
| MELD ≥21, $n$% | 7 (5.4) | 6 (3.6) | 0.035* |
| Maddery | 15.02 (6.10–30.11) | 29.24 (11.05–45.05) | 0.001* |
| Maddery ≥32, $n$% | 28 (21.5) | 18 (47.4) | 0.002* |
| Child-Pugh A, $n$% | 33 (25.4) | 4 (10.5) | 0.073 |
| Child-Pugh B/C, $n$% | 97 (74.6) | 34 (89.5) | 0.073 |

Data are reported as counts and percentages, median ± standard deviation, or medians with 25th and 75th percentiles, respectively. WBC, white blood cell; Hb, hemoglobin; PLT, platelet count; ALT, alanine transaminase; AST, aspartate transaminase; TBil, total bilirubin; ALB, albumin; Cr, creatine; PT-INR, prothrombin time-international standardization ratio; L3-SMI, skeletal muscle index at the level of the third lumbar vertebra; MELD score, model for end-stage liver diseases score.

patients without sarcopenia, and there was no significant difference between the two groups. Additionally, the rehospitalization of patients with sarcopenia was more than that of patients without sarcopenia at 24 months (40.70% vs. 51.50%, $p = 0.327$).

## 3.3. Cox regression analysis of independent prognostic factors

A univariate Cox analysis was first performed using the enrolled patient data, identifying that the factors most related to ARLD were abstinence, cirrhosis, ascites, platelet count, TBil, creatinine, the PT-international standardization ratio, $Na^+$, the L3-SMI, sarcopenia, MELD score ≥ 21, and Maddrey score ≥ 32 (Table 2). These variables were entered into a multivariate analysis model, except for the L3-SMI, MELD, and Maddrey scores, since the L3-SMI was included in the diagnosis of sarcopenia, and the MELD and Maddrey scores included other variables. The analysis revealed that sarcopenia, abstinence, and baseline creatinine levels were independent factors for the 24-month prognoses of patients with ARLD, with hazard ratios and 95% confidence intervals (CI) of 2.022 (1.025–3.991), 0.275 (0.122–0.617), and 1.018 (1.008–1.027), respectively (Table 3).

## 3.4. Analysis of the L3-SMI for predicting the prognoses of patients with ARLD

ROC curve analysis was performed to evaluate the performance of the L3-SMI in predicting the prognoses of patients with ARLD. The area under the ROC curve value of the L3-SMI for defining sarcopenia in the entire study group of males was 0.67 (95% CI: 0.569–0.770) (Figure 3), and the cut-off value of the L3-SMI in males was 40.0 $cm^2/m^2$ with 64.6% sensitivity and 63.2% specificity.

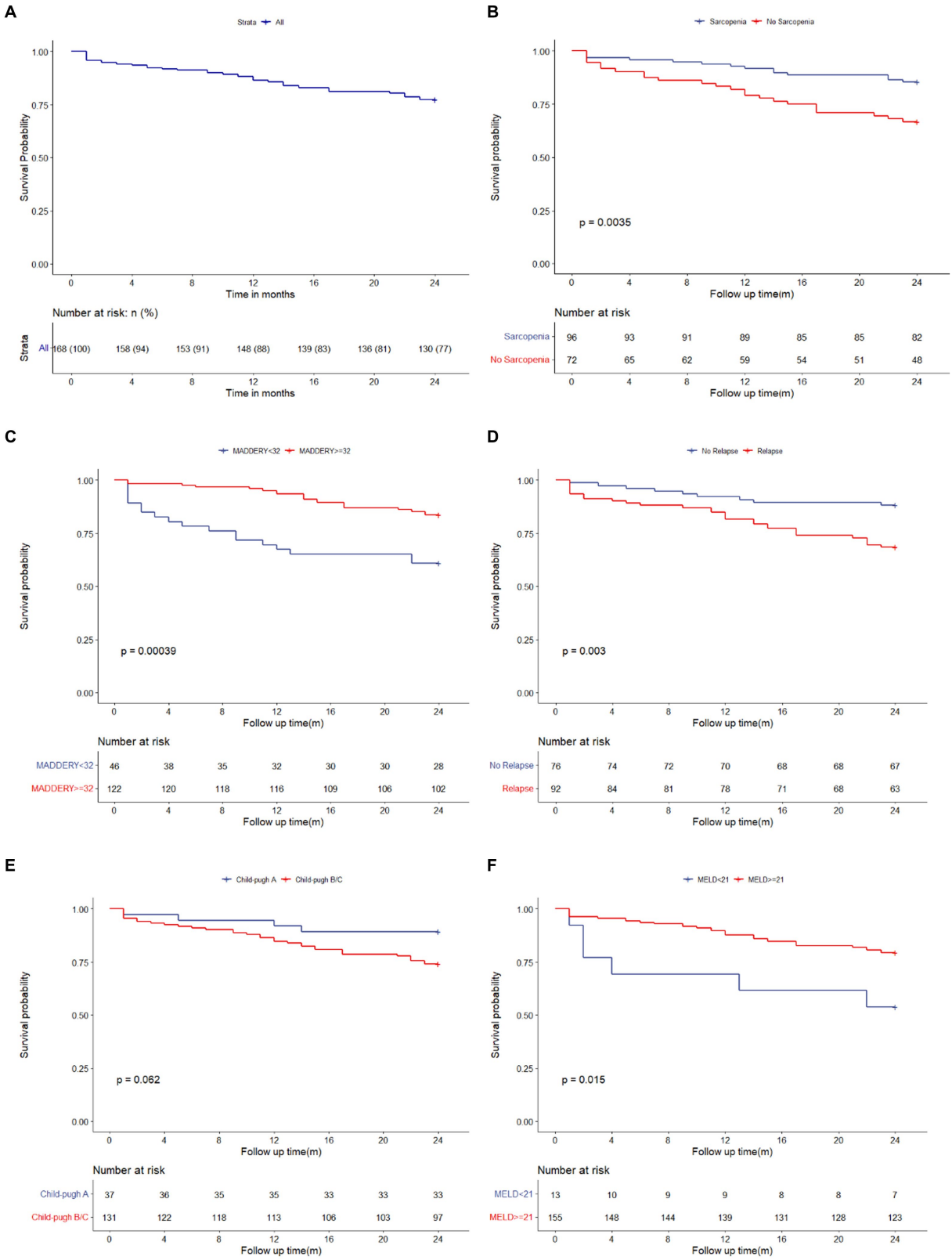


FIGURE 2
Kaplan–Meier estimate of the ARLD patients stratified. Kaplan–Meier curves for total survival of patients with ARLD **(A)**; Kaplan–Meier curves for survival of patients with sarcopenia and without sarcopenia **(B)**; Kaplan–Meier curves for survival of patients who followed abstinence and relapsed from abstinence **(C)**; Kaplan–Meier curves for survival of the patients with MELD score ≥ 21 and with MELD <21 **(D)**; Kaplan–Meier curves for survival of the patients with Maddery score ≥ 32 and with Maddery <32 **(E)**; Kaplan–Meier curves for survival of the patients with Child-Pugh A and with Child-Pugh B/C **(F)**. ARLD, alcohol-related liver disease.

TABLE 2 Univariable analysis of ARLD patients.

| Variable | HR | 95% CI | *p* value |
|---|---|---|---|
| Age | 0.993 | 0.964–1.022 | 0.631 |
| Abstinence | 0.341 | 0.162–0.721 | 0.005* |
| Cirrhosis | 3.216 | 0.989–10.459 | 0.052 |
| Ascites | 2.372 | 1.123–5.013 | 0.024* |
| Varices bleeding | 0.727 | 0.224–2.363 | 0.596 |
| Encephalopathy | 2.131 | 1.008–4.504 | 0.048* |
| WBC ($10^9$/L) | 1.028 | 0.936–1.129 | 0.567 |
| Hb (g/L) | 0.998 | 0.987–1.010 | 0.776 |
| PLT (g/L) | 0.997 | 0.992–1.001 | 0.139 |
| ALT (U/T) | 0.995 | 0.987–1.004 | 0.268 |
| AST (U/T) | 0.999 | 0.996–1.001 | 0.428 |
| TBil (μmol/L) | 1.003 | 1.001–1.006 | 0.022* |
| ALB (g/L) | 0.957 | 0.908–1.009 | 0.104 |
| Cr (μmol/L) | 1.018 | 1.010–1.027 | <0.001* |
| PT-INR | 2.201 | 1.294–3.744 | 0.004* |
| L3-SMI | 0.943 | 0.907–0.980 | 0.003* |
| Sarcopenia | 2.560 | 1.324–4.952 | 0.005* |
| MELD ≥21 | 2.805 | 1.171–6.714 | 0.021* |
| Maddery ≥32 | 2.981 | 1.575–5.643 | 0.001* |
| Child-Pugh B/C | 0.389 | 0.138–1.097 | 0.074 |

*$p$ value <0.05 was considered significant. CI, confidence interval; AH, alcoholic hepatitis; WBC, white blood cell; Hb, hemoglobin; PLT, platelet count; ALT, alanine transaminase; AST, aspartate transaminase; TBil, total bilirubin; ALB, albumin; Cr, creatine; PT-INR, prothrombin time-international standardization ratio; MELD score, model for end-stage liver diseases score.

TABLE 3 Cox regression analysis for identifying independent prognostic factors.

| Variable | HR | 95% CI | *p* value |
|---|---|---|---|
| Abstinence | 0.275 | 0.122–0.617 | 0.002* |
| Ascites | 1.942 | 0.861–4.382 | 0.110 |
| Encephalopathy | 1.316 | 0.568–3.048 | 0.522 |
| TBil (μmol/L) | 1.001 | 0.998–1.004 | 0.557 |
| Cr (μmol/L) | 1.018 | 1.008–1.027 | <0.001* |
| PT-INR | 1.332 | 0.617–2.872 | 0.465 |
| Sarcopenia | 2.022 | 1.025–3.991 | 0.042* |

*$p$ value <0.05 was considered significant. TBil, total bilirubin; Cr, creatine; CI, confidence interval; PT-INR, prothrombin time-international standardization ratio.

## 4. Discussion

Numerous studies have claimed that sarcopenia is highly and independently associated with liver diseases (7, 21). Liver diseases, especially cirrhosis and end-stage liver disease, are characterized by decreased appetite, insufficient energy intake, impaired nutrient digestion and/or malabsorption, and decreased physical activity (10). In addition, patients with cirrhosis and end-stage liver disease commonly have abnormal glycogen metabolism; therefore, more skeletal muscle proteins must be decomposed to provide amino acids for gluconeogenesis, resulting in increased skeletal muscle loss (22, 23). Hormone deficiencies (lower levels of insulin-like growth factor 1, vitamin D, and testosterone), inflammatory cytokine activation [upregulated expression of tumor necrosis factor-α (TNF- α) and interleukin-6 (IL-6)], and other metabolic disorders in cirrhosis also may lead to decreased skeletal muscle protein synthesis and increased autophagy (24).

There have been seldom reports examining patients with ARLD comorbid with sarcopenia and their prognosis in China. Among Chinese patients with cirrhosis, 29.1% of male patients were comorbid with sarcopenia; however, only 61 patients with alcohol-related cirrhosis were analyzed (6). Mindie reported that 35% of patients with cirrhosis were comorbid with sarcopenia, but the incidence of patients with ARLD comorbid was greater than that of cirrhosis from other causes: up to 50% (7). Our cohort enrolled 168 male patients with ARLD and found that 42.86% (72/168) were comorbid with sarcopenia, consistent with previous reports. Alcohol and its metabolites can induce sarcopenia in patients with ARLD *via* a variety of biological mechanisms (20, 25). Ethanol inhibits the mammalian target-of-rapamycin protein complex 1 (mTOR) and mTOR signaling targets, reducing protein synthesis and increasing autophagy. In patients with ARLD and cirrhosis, protein synthesis was deficient, resulting in "anabolic resistance (26, 27)." In addition, ethanol intake reduces hepatocyte ureagenesis and increases muscle ammonia transporter RhBG expression and muscle ammonia levels.

The direct effects of ethanol are synergistic with increased ammonia absorption in generating dysregulated skeletal muscle proteostasis and signaling perturbations, resulting in sarcopenia (28). Ethanol also induces the expression of inflammatory cytokines, including TNFα and IL-6, which accelerate skeletal muscle protein degradation through the ubiquitin-protease pathway (29). Ethanol promotes mitochondrial dysfunction in skeletal muscle, reduces protein synthesis, and increases autophagy by targeting mitochondrial reactive oxygen species (30). These factors may have caused the observed higher rate of sarcopenia in patients with ARLD.

In our cohort, comorbid sarcopenia was associated with a two-fold risk of 24-month mortality in male patients with ARLD in mainland China. This finding is consistent with a previous study that showed a two-fold greater risk of global mortality in patients with cirrhosis (31–33). This study also identified abstinence as an independent prognostic factor for patients with ARLD. Identifying patients at a high risk of recidivism during the follow-up period is crucial for early relapse intervention in patients with ARLD, and multidisciplinary intervention to maintain abstinence is needed as a crucial part of ARLD management (34, 35). In addition, we also found that kidney dysfunction was an independent prognostic factor in patients with ARLD. ARLD, especially alcoholic hepatitis and alcohol-related cirrhosis, is closely related to hemodynamic disorders, including portal hypertension and systemic inflammatory response syndrome, which place patients at high risk for kidney dysfunction. The prognostic significance of kidney dysfunction is well recognized; serum creatinine or urea is included in several ARLD prognostic scores, including the MELD score, ABIC, GAHS, and the Lille model.

The present study used the L3-SMI to diagnose sarcopenia. Skeletal muscle mass, as measured by CT, represents whole-body muscle mass and can be linked positively with the patient's grip strength, walking speed, and other physical performance metrics; thus, it represents the patient's overall sarcopenia while also representing the body's muscle mass (36). However, the L3-SMI cut-off value for diagnosing sarcopenia was not determined in Chinese patients until the multicenter report by Kong et al.; the cut-off value for males was 40.2 $cm^2/m^2$. In our study,

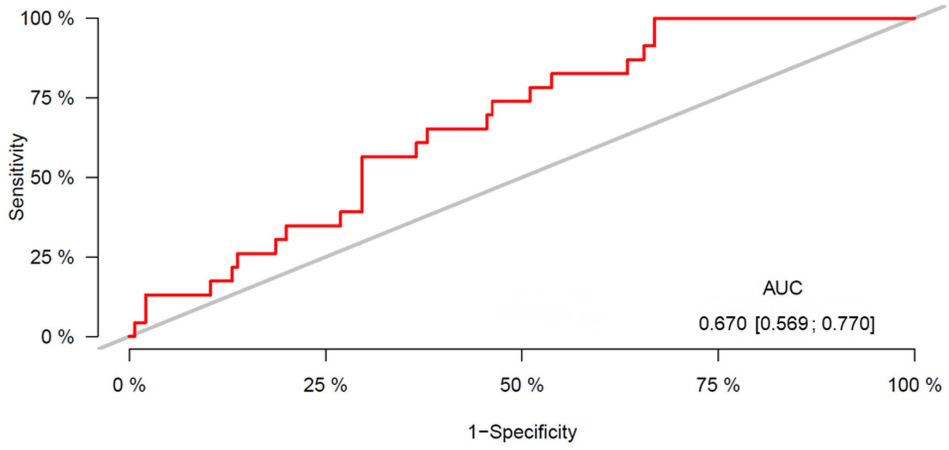


FIGURE 3
ROC curve for the L3-SMI. Area under the curve (AUC) = 0.67; confidence interval 0.569–0.770; cut-off 40.00; sensitivity 64.6% and specificity 63.2%. ROC, receiver operating characteristic; SMI, skeletal muscle index.

we used this cut-off value to define sarcopenia. In addition, we verified the L3-SMI cut-off value for prognostic prediction in patients with ARLD. The cut-off value for L3-SMI for males in mainland China was 40.0 $cm^2/m^2$, consistent with Kong et al.'s report. However, the threshold values of different detection methods used in studies on patients with ARLD-comorbid sarcopenia urgently need to be centralized. The relevance of L3-SMI in the diagnoses of sarcopenia in patients with ARLD had previously not been investigated.

The current study found that the overall 24-month survival rate of Chinese patients with ARLD was 77.38%, with an overall sarcopenia prevalence of 42.86%, consistent with other studies (7, 37). This study is the first to use sarcopenia diagnosed using the L3-SMI to predict the prognoses of Chinese patients with ARLD. The prognosis of patients with ARLD and comorbid sarcopenia is an extremely serious and widespread phenomenon that requires adequate attention in the clinical setting. Consequently, in addition to managing abstinence and complications, attention should focus on managing and evaluating sarcopenia in patients with ARLD, particularly those with severe alcoholic hepatitis. Our study showed that sarcopenia is an independent prognostic factor in patients with ARLD.

This study has several limitations. First, because this study was performed in a single center and retrospectively, an external validation cohort and additional measure of muscle strength/function were not available. Second, the participants were all male; thus, these data cannot be generalized to females, and further research involving female patients is needed. As a retrospective study, 58/226 patients were excluded for phone disconnect or personal reasons during screening period, which might cause a selection bias. However, all patients enrolled finished 2 years follow-up. Nevertheless, in China, this study is the first to be conducted on patients with ARLD-comorbid sarcopenia, and the analysis revealed significant results. A further multicenter prospective study with a larger sample size is currently in progress to validate our study results.

## Data availability statement

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

## Ethics statement

Ethical approval was not required for the studies involving humans because the study used retrospective anonymised data. The studies were conducted in accordance with the local legislation and institutional requirements.

## Author contributions

SY accepts full responsibility for the conduct of the study, has access to the data, and has control of the decision to publish. YZ proposed the concept, contributed to the study design, wrote the manuscript, and performed statistical analysis. CC and LW contributed to the study design and performed statistical analysis. FD and MQ contributed to data collection. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# High resting energy expenditure, less fat-free mass, and less muscle strength in HIV-infected children: a matched, cross-sectional study

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**Background and aims:** Many improvements have been made in the treatment of human immunodeficiency virus (HIV) in pediatric patients; however, challenges remain in terms of achieving normal growth, body composition, and metabolism during treatment, etc. Current nutritional recommendations are based on studies performed in adults, with limited data on the HIV-infected pediatric population. Therefore, this study aimed to compare the resting energy expenditure (REE) of asymptomatic HIV-infected pediatric patients with healthy counterparts and to compare body composition, dietary intake, and physical activity between the two groups.

**Methods:** This was a cross-sectional study of asymptomatic HIV-infected children who were receiving antiretroviral therapy; the infected group was compared with the uninfected group, matched by age (± 6 months), sex, and body mass index (± 0.5 z-score). Participants were recruited between 2021 and 2022, as outpatients. In both groups, REE was determined by indirect calorimetry and body composition by bioelectrical impedance analysis and hand strength, measured using a hydraulic hand dynamometer.

**Results:** Seventy-eight participants were enrolled, where $n = 39$ HIV-infected children and $n = 39$ controls, with a mean age of 11.6 ± 3.4 years old. REE was significantly higher in the HIV group (1254.4 ± 334.7 kcal/day vs. 1124.7 ± 321 kcal/day, $p = 0.013$) than in the control group. Fat-free mass (FFM) was lower in the HIV group (28.2 ± 10.5 kg vs. 32 ± 11.2 kg, $p = 0.001$); this trend continued when the index skeletal muscle was evaluated (7.2 ± 1.2 vs. 7.6 ± 1.5, $p = 0.04$). The strength of the dominant hand was also lower in the HIV group (12 (8–18) kg vs. 20 (10.5–26) kg, $p < 0.0001$).

**Conclusions:** Children with asymptomatic HIV infection have higher REE than their uninfected peers. They also present decreased FFM, skeletal muscle mass index, and muscle strength. These parameters should be considered during

nutritional assessment in this population to have a favorable impact on nutritional status and growth.

KEYWORDS

HIV-infected, children, adolescents, resting energy expenditure, fat free mass, handgrip strength

# 1. Introduction

Resting energy expenditure (REE) refers to the energy expended by an individual in a fasting state, under resting conditions, and in a thermostable environment (1, 2). REE is measured by employing calorimetric methods or evaluated by energy estimating equations. Indirect calorimetry is the most accurate method for measuring REE (3).

Increased REE, protein catabolism, lipodystrophy, and dyslipidemia have been described in human immunodeficiency virus (HIV)-infected adults (4). A meta-analysis that included studies in the adult population living with HIV reported that the mean of REE per fat-free mass (FFM) was significantly higher in 732 HIV-positive subjects than in 340 control subjects, with a mean of 11.93 kJ/kg (95% CI: 8.44,15.43 kJ/kg) (5). In addition, the energy requirements of asymptomatic untreated HIV-infected adults are 7–15% higher than those of uninfected controls such that maintaining body weight in this population requires increasing energy intake by ∼10% (6). In HIV-infected children, the energy balance and REE determination are crucial, as there is a high prevalence of failure to thrive in this population (7). A mean REE of 57 ± 7 kcal/day/kg has been reported in HIV-infected children aged 2–11 years (8). Nevertheless, there is currently limited evidence on the energy requirements of HIV-infected pediatric patients, and current nutritional recommendations are based on studies performed in adults (9). In pediatrics, it is particularly important to cover energy needs to continue with growth (6).

Therefore, this study aimed to compare the REE of asymptomatic HIV-infected pediatric patients with that of healthy controls. We hypothesized that the group with HIV has 10% more REE than the control group. Our secondary objective was to compare the body composition, handgrip strength, dietary intake, and physical activity of HIV-infected pediatric patients with those of the control group.

# 2. Methods

## 2.1. Study design

We performed a cross-sectional study of HIV-infected children and uninfected children as a control group matched by gender, age (± 6 months), and body mass index for age (BMI-for-age) (± 0.5 z-score). Participants were recruited between 2021 and 2022 as outpatients in the Infectious Disease Department of the Instituto Nacional de Pediatría, a third-level pediatric hospital in Mexico City, México. The control group was recruited from schools nearby that were healthy.

Patients aged 6–18 years were included; in the HIV-infected group, only patients who were receiving highly active antiretroviral therapy were included. Participants in both groups were excluded if they were taking anabolic agents, stimulants, or any drugs known to alter metabolism. They were also excluded if they had diabetes; an active opportunistic infection; malignancy; or hepatic disease, including chronic hepatitis, pulmonary disease, and severe immune compromise defined by CD4+ count <200 cells/mm$^3$. This was an exclusion criterion because severe immune compromise is generally accompanied by infectious processes that increase REE (10).

## 2.2. Clinical evaluations and anthropometric parameters

Parents or primary caregivers were asked about their personal and family history, as well as the presence of symptoms at the time of evaluation. The date of diagnosis was obtained from patients' medical records. Participants were weighed on a calibrated digital scale (SECA 813; Seca GmbH&Co., Hamburg, Germany), and height was measured with an ultrasonic stadiometer (InLab S50; InBody Co., Seoul, Korea). Waist, hip, thigh, calf circumferences, and mid-upper arm circumference (MUAC) were measured with a tape measure (SECA 201; Seca GmbH&Co., Hamburg, Germany). All measurements were taken with the patients standing up. Waist circumference was measured with the arms crossed in front of the chest; the measurement was taken between the lower edge of the 10th rib and the iliac crest. Hip circumference was measured by placing a tape measure at the biggest protuberance of the buttock; thigh circumference was measured with the legs separated, and the tape was wrapped around the mid-point between the hip bone and the knee bone. Calf circumference was measured with the arms by the side of the body; the measurement was taken at the biggest protuberance of the calf; Finally, MUAC was measured with the arms by the side of the body; the measurement tape was positioned halfway between the acromion and the radius measurements (11, 12).

## 2.3. Resting energy expenditure

REE was measured by using the ReeVue$^{TM}$ device, (indirect calorimeter, Korr Technologies Inc, Salt Lake City, Utah, USA). Measurements were performed in a room with a stable room temperature (21°C) and a quiet environment. $O_2$ flows were measured directly with a mask and an 18 mm diameter flowmeter.

Flowmeter calibration was performed before each test. All measurements were performed in the morning (between 08:00 and 09:30), with 8 to 12 h of fasting. Participants were instructed to refrain from exercise for at least 12 h (vigorous and resistance exercise for 24 h prior to testing). Upon arrival at the clinic, the participants sat for ∼20–30 min while the study was explained to them; they signed consent and assent letters, and their medical history was taken. Participants were tested in the supine position for a period of at least 20 min with minimal movement, ensuring that each individual was physically comfortable and in the proper position for measurements.

## 2.4. Nutritional status and body composition assessment

Nutritional status was assessed by the z-score of BMI-for-age and height-for-age, according to the classification and values established by the CDC and WHO. To obtain the z-score of BMI-for-age, the PediTools program was used (13), in which data such as gender, date of birth, date of evaluation, weight, and height were entered. The reference points were classified according to the WHO, where $< -3$ SD = severe malnutrition, $-3$ to $-2$ SD = moderate malnutrition, $\geq -2$ to 1 SD = standard, $>1$ to $<2$ SD = overweight, and $>2$ SD = obesity (14). The height-for-age indicator was evaluated using the AnthroPlus software (15), in which the height/age was obtained using the same data. The cut-off points were classified according to the WHO: 1.99 to $-1.99$ SD standard height, $<$-2 SD short height, and $>2$ SD tall height (14). Body composition was assessed by using a multifrequency bioimpedance device, employing bioelectrical impedance analysis (BIA) (InBody S10®, InBody Co., Ltd., Seoul, Korea) with the standard technique; BIA's internal equation was used. Measurements were performed with the patient in a supine position, with the arms separated from the trunk by ∼30 degrees and the legs separated by ∼45 degrees; there was no contact with the metal frame of the bed, and the room temperature was ambient. The patients had to lie in position for 5 min and were not allowed to eat or make any major physical effort in the preceding 8 h; they were also not allowed to drink in the preceding 3 h. Body weight and height were entered into the device. The area where the electrodes were to be placed was cleaned first with alcohol and then with electroconductive wet wipes for the use of impedance equipment; the electrodes were placed on both the hands and the feet, according to the manufacturer's instructions (InBody Co). The electrodes were kept in a sealed bag to protect against heat; the machine was calibrated before use with a circuit of known impedance, as per the manufacturer's guidelines. A standardized healthcare professional performed the measurements using the same device to avoid interobserver and inter-device variability. Phase angle at 50 kHz was reported, and the following formula was used to determine it [Arc tangent (Xc/R)] $\times$ (180/Π). The skeletal muscle mass index (SMI) was calculated by dividing skeletal muscle mass (kg) by the square of the height ($m^2$), and the impedance ratio was calculated as the quotient of Z at 250 kHz between Z at 5 kHz. Additionally, the total body water (TBW) = (height$^2$/ impedance (R), skeletal muscle mass (SMM) = FFM (right arm + left arm + right leg + left leg)/0.75, and body cell mass (BCM) = intracellular water (ICW) + proteins were estimated by internal equations of BIA.

## 2.5. Handgrip strength evaluation

Handgrip strength, an indirect indicator of muscle function, was measured with a Lafayette hydraulic hand dynamometer (Jamar model J00105 Lafayette Instrument Company, USA 90k g capacity and 727 g weight). The measurement of grip strength was performed on the dominant hand in triplicate, and the best measurement was recorded. The posture for measuring the grip strength involved standing with legs straight and weight bearing balanced on both feet; the feet were positioned shoulder-width apart, shoulders were adducted and neutrally rotated, elbows were flexed to 90°, forearms were in a neutral position, and the wrists were between 0° and 30° of dorsiflexion and between 0° and 15° of ulnar deviation (16).

## 2.6. Routinary serum biochemical parameters

The most recent laboratory results of the following biochemical parameters were obtained from the medical record: viral load, CD4+ cell count, CD8+ cell count, lipid profile, hemoglobin, transaminases, albumin, glucose, creatinine, and glomerular filtration rate. These labs were routinely requested by the treating service as part of the follow-up consultation (only for the HIV-infected group).

## 2.7. Physical activity

Body movement produced by skeletal muscles was estimated using the Physical Activity Questionnaire for Children (PAQ-C) for children aged 8–14 years and the Physical Activity Questionnaire for Adolescents (PAQ-A) for children $>$ 14 years. The questionnaires consist of questions structured to discern low (score 1) to high (score 5) physical activity during the last 7 days (17). All score items were then summed and divided by the number of questions to yield the final activity summary score, which was finally classified as follows: $\geq$ 2.151 was classified as active, meeting 60 min of moderate-to vigorous-intensity physical activity (MVPA), and $<$ 2.151 was classified as not active (18).

## 2.8. Dietary evaluation

To assess dietary intake, 24-h multi-step recall was performed with FAO methodology (19). The information was analyzed using the NIH software, ASA24 (20). In addition to counting calories, macronutrients, and micronutrients, recommendations for target amounts of food groups, calories, macronutrients, and micronutrients by gender and age were obtained from each participant using the following sources: The 2015–2020 Dietary

Guidelines for Americans https://www.dietaryguidelines.gov and https://www.dietaryguidelines.gov and the Dietary Reference Intakes https://www.nal.usda.gov/fnic/macronutrients and https://www.nal.usda.gov/fnic/macronutrients. Therefore, the diet analysis was not only compared between the groups but also with the recommended intake by gender and age. The questionary "Index of global food quality" (21) was also evaluated to assess the overall diet quality. This index is a food frequency survey with 12 variables: 5 healthy foods, 4 unhealthy foods, and 3 main meals. Each variable was scored from 1 (less healthy) to 10 (recommended by the Ministry of Health). The total scores were used to classify diets as healthy (90–120), in need of change (60–89), and unhealthy (<60).

## 2.9. Statistical analysis

Sample size calculation was carried out, where it was considered that the REE of pediatric patients with HIV infection is >10% (6) when compared with that of uninfected children. Furthermore, a type 1 error (α) of 0.05 and a type II error (β) of 0.2 were considered. A sample of 40 per group was obtained. 3 To compare quantitative variables between the HIV-infected group and the uninfected group, including REE and body composition parameters (lean mass, fat mass, and phase angle), as well as dietary assessment variables (kilocalories, grams of protein, carbohydrate, fat, and micronutrients), Student's *t*-test for paired samples or the Wilcoxon test was performed, depending on the distribution of the variable. To compare the categorical variables, an $Xi^2$ analysis was performed. An analysis of covariance (ANCOVA) was also performed to examine the differences in REE by groups (HIV-infected vs. control group). This analysis accounted for FFM, FM, height, body weight, and physical activity, each separately as a covariate but also as a set of variables: height, FFM, and FM for model A and FFM, FM, height, and physical activity for model B. FFM and FM were included in the models to analyze the weight of the body composition, height was included because it differed between groups, and physical activity was included because it is an important variable that can influence body composition. A significant *p*-value was established as $\leq 0.05$. The data were analyzed using SPSS (25 version, SPSS Inc, Chicago, IL) and GraphPad Prism (version 9.0, GraphPad Software, La Jolla California, USA).

## 2.10. Ethical statement

The protocol was approved by Instituto Nacional de Pediatría Research and Ethics Committees with number 2020/026, officially registered at the Office for Human Research Protections of the NIH (http://ohrp.cit.nih.gov/search/search.aspx), with numbers IRB00013674 and IRB00013675. All the subjects' information was handled confidentially. Each participant and parents or primary caregivers signed a written informed assent and consent form, respectively, before enrollment.

# 3. Results

## 3.1. Demographics

Forty pediatric patients with HIV were evaluated. As the patients in the HIV-infected group entered the study, a paired search for uninfected children was performed. One patient was removed from the HIV-infected group because he presented a z-score for BMI-for-age of – 4 SD; it was not possible to find a participant with this characteristic, without pathology. Therefore, the results of 39 patients in the HIV-infected group paired with 39 uninfected patients are reported. All HIV-infected children included in the analysis were asymptomatic at the time of evaluation and were receiving highly active antiretroviral therapy; 49% of HIV-infected children were on abacavir, lamivudine, lopinavir, and ritonavir, and 32% were on bictegravir, emcitarabine, tenofovir, and alafenamide. The remaining patients were receiving antiretroviral therapy, which was guided by resistant patterns, where highly active antiretrovirals such as dolutegavi, raltegravir, and efavirenz were included in follow-up as outpatients by the pediatric infectious disease department. All HIV-infected patients had vertically transmitted infection and CD4+ levels above 600 cells/$mm^3$, and 82% ($n = 32$) of the patients had undetectable viral load (Supplementary Table 1). When compared between groups, a high prevalence was observed in boys (64%) in each group, and there was no significant difference in age and diagnosis of nutritional status evaluated by the BMI-for-age between groups. However, there were differences in almost all anthropometric variables, except for waist circumference. Additionally, it was observed that 39.5% ($n = 15$) of the children in the HIV-infected group showed stunting, while only 5.1% ($n = 2$) in the control group showed stunting (Table 1).

Furthermore, we observed a strong correlation between anthropometric indicators and BIA indicators, as well as a high positive correlation between body weight and FFM, SMM, BCM, and TBW (Supplementary Figure 1).

## 3.2. Comparison of resting energy expenditure

In the HIV-infected group, there was an increase in REE compared with the control group (1254.4 ± 334.7 kcal/day vs. 1124.7 ± 321 kcal/day, $p = 0.013$) (Figure 1A). Additionally, we evaluated the REE by body weight, and we also observed an increase in REE by kg (38.1 ± 13.6 kcal/day/kg vs. 30.4 ± 11.2 kcal/day/kg, $p < 0.0001$) (Figure 1B). When adjusted for FMM, this upward trend continued (Figure 1C). We also adjusted for FM, but no differences were observed ($p = 0.083$) (Figure 1D). Furthermore, we calculated the percentage of increase in REE in the HIV-infected group compared with the control group and observed an increase of 8.2% (CI 95% 3.1–20.9%) in the total REE, 22.5% (CI 95% 11.6–35.2%) more per kilogram of body weight.

In the unadjusted analyses, we observed differences in REE between groups. However, after accounting for relevant covariates in the analysis, including body weight, REE was higher in the HIV-

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infected group 1269.7± 47.7 [SE] kcal/day vs. 1117.3 ± 45.4 [SE] kcal/day, $p = 0.020$. The same high REE trend was observed in the HIV-infected group when covariates such as height and FFM were analyzed, but when we analyzed FM as a covariate, we did not observe any statistical differences. Furthermore, we analyzed a model where FFM, FM, and height were included (Table 2). Sensitivity analysis was also performed in the HIV-infected group to compare REE between patients who had an undetectable viral load (<40 copies/ml of blood) ($n = 32$) and those who had >40 copies/ml of blood ($n = 7$); no significant difference was observed [1217 (968–1570) kcal/day vs. 1238 (1109–1498) kcal/day, $p = 0.781$]. Similarly, another analysis was performed, eliminating those with >40 copies/ml of blood, and only 32 patients in the HIV-infected group were compared with patients in the control group ($n = 32$). The HIV-infected group had higher REE (1245 ± 355 kcal/day vs. 1122 ± 331 kcal/day, $p = 0.02$).

## 3.3. Body composition, phase angle, and handgrip strength

When we analyzed the body composition between groups, significant differences were observed in TBW, FFM, and BCM. However, no significant differences were observed in or in the area of visceral fat and total phase angle. Interestingly, the phase angle of the lower extremities was higher in the control group (Table 3). Regarding FFM, less mass was observed in the HIV-infected group (28.2 ± 10.5 vs. 32 ± 11.2, $p = 0.001$). This trend continued when index skeletal muscle was evaluated (7.2 ± 1.2 kg/m$^2$ vs. 7.6 ± 1.5 kg/m$^2$, $p = 0.04$). When the strength of the dominant hand was compared (12 [8–18] vs. 20 [10.5–26] kg, $p < 0.0001$), it was lower in the HIV-infected group. However, the percentage of body fat mass (21.6 ± 7.7 vs. 19.3 ± 8.2 %, $p = 0.131$) did not present any differences between groups (Figure 2).

TABLE 1 Baseline characteristics of the participants.

| Variables | HIV-infected group $n = 39$ | Control group $n = 39$ | $p$ |
|---|---|---|---|
| Age, years | 11.6 ± 3.5 | 11.6 ± 3.4 | 0.934 |
| Gender: Girls/Boys, *n* (%) | 14 (36)/25 (64) | 14 (36)/25 (64) | 1 |
| Body weight, kg | 36.4 ± 14.4 | 40.3 ± 14.9 | 0.001 |
| Height, cm | 138.3 ± 18.2 | 146.1 ± 17.6 | < 0.0001 |
| Nutritional status*, *n* (%) | | | |
| Undernourishment | 2 (5.2) | 2 (5.2) | 1 |
| Normal | 32 (82.1) | 32 (82.1) | |
| Overweight | 5 (12.9) | 5 (12.9) | |
| Height-for-age, *n* (%) | | | 0.001 |
| Normal height | 24 (60.5) | 36 (92.3) | |
| Short height | 15 (39.5) | 2 (5.1) | |
| Tall height | 0 (0) | 1(2.6) | |
| Anthropometric assessment | | | |
| BMI-for-age | −0.5 ± 1.17 | −0.009 ± 1.13 | 0.490 |
| Height-for-age, z-score | −1.30 ± 0.9 | −0.10 ± 1.2 | < 0.0001 |
| Waist circumference, cm | 65.2 ± 10.7 | 66 ± 9.8 | 0.424 |
| Waist/height index | 0.47 ± 0.05 | 0.45 ± 0.05 | 0.008 |
| Hip circumference, cm | 72.7 ± 12 | 76.9 ± 13.4 | < 0.0001 |
| Thigh circumference, cm | 38.2 ± 6.6 | 40.3 ± 8.1 | 0.014 |
| Leg circumference, cm | 27.1 ± 5.3 | 29.6 ± 5.1 | 0.002 |
| MUAC, cm | 21.4 ± 4 | 22 ± 4.2 | 0.035 |

Data are shown as mean ± standard deviation and as frequency and percentage. Student's t-statistical analysis for paired samples and Xi$^2$ of trend. p < 0.05. kg, kilograms; cm, centimeters; m, meter; and MUAC, mid-upper arm circumference. *Evaluated by the BMI-for-age indicator.

## 3.4. Diet analysis and diet quality

In the analysis of the participants' diet, the HIV-infected group showed a significant reduction in energy consumption compared to the control group (1660 ± 557 kcal vs. 2092 ± 591 kcal, $p = 0.001$), with energy being lower in the HIV-infected group. However, in the analysis of energy consumption per kg of body weight, we did not observe any statistically significant differences, although the trend showed lower calorie consumption in the HIV-infected group (48.2 ± 21 kcal/kg vs. 56.9 ± 18.6 kcal/kg, $p = 0.06$). Regarding the percentage of macronutrients referring to the caloric value total, no significant differences were observed in the consumption of carbohydrates (46.4 ± 8.3% vs. 45.1 ± 8.7%, $p = 0.495$), proteins (21.2 ± 6 % vs. 20.8 ± 5.7%, $p = 0.773$), or fats (32.2 ± 7 % vs. 34.6 ± 6.3 5, $p = 0.152$) between the HIV-infected group and the control group. However, in the food consumption analysis, we observed that the HIV-infected group showed lower grain consumption (144.3 [76.4–195.2] g vs. 198.1 [141.5–249] g, $p = 0.029$). As for the recommendation considering age and gender (169.8 [169.8–198.1] g of grains) (Figure 3A), the median of the control group was above the recommendation, but that of the HIV-infected was below the recommendation. When analyzed by the type of grain consumed, the consumption of whole grains was null in the HIV-infected group (0 [ 0–0] g vs. 8.4 [0–31.1] g, $p = 0.003$), and in the consumption of refined grains was higher (135.8 [76.4–195.2] g vs. 175.4 [110.3–217.9] g, $p = 0.106$) (Figure 3B). Vegetable consumption did not differ between groups (1.3 [0.5–2.2] cups vs. 1.1 [0.5–2.2] cups, $p = 0.992$), and the consumption of neither group reached the recommendation (2.5 [2.5–3] cups) (Figure 3C). Fruit consumption did not differ between groups (0.7 [0–1.7] cups vs. 1 (0.4–1.7] cups, $p = 0.472$); the consumption of both groups was below the median recommendation (2 [1.5–2] cups) (Figure 3D). The consumption of food of animal origin was above the median of recommendation for both groups (155.6 [141.5–169.8] g), but there was no difference in the consumption between groups (209.4 [124.5–311.3] g vs. 226.4 [133–314.1] g, $p = 0.839$) (Figure 3E). Finally, dairy consumption was higher in the control group (2.1 [1–2.9] cups vs. 2.8 [1.6–3.9] cups, $p = 0.015$)

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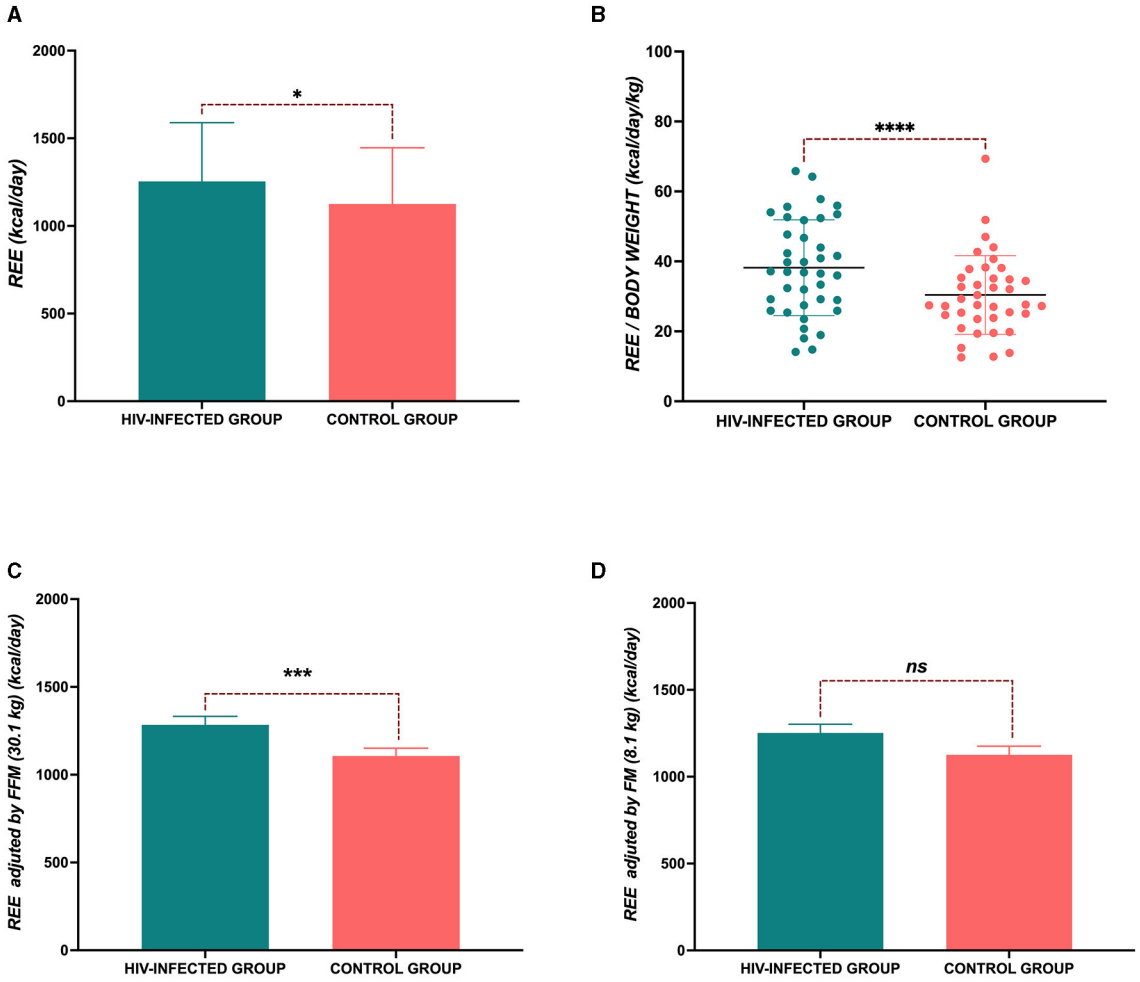


FIGURE 1
Resting energy expenditure (REE). **(A)** Total REE; **(B)** REE per kg of body weight; **(C)** REE adjusted by fat-free mass (FFM); and **(D)** REE adjusted by fat mass (FM). *P*-value: $^{*}p < 0.05$; $^{****}p < 0.0001$.

TABLE 2 ANCOVA analysis comparing REE between groups.

| ANCOVA adjusted by | Adjusted REE (kcal/day) Mean ± SE | | Difference in adjusted mean change (HIV-infected group–Uninfected group) | | |
|---|---|---|---|---|---|
| | HIV-infected group, ($n = 39$) | Uninfected group, ($n = 39$) | Mean ± SE | 95% CI | *P*-value |
| Body weight (38.4 kg) | 1269.7 ± 47.7 | 1117.3 ± 45.4 | 152.4 ± 64 | 24.8, 279.9 | 0.020 |
| Height (142.2 cm) | 1286.1 ± 49.5 | 1098 ± 48.2 | 188 ± 69.6 | 49.3, 326.8 | 0.009 |
| Fat-free mass (30.1 kg) | 1284.5 ± 48.3 | 1106 ± 45.4 | 178.5 ± 64.8 | 49.3, 307.7 | 0.007 |
| Fat mass (8.1 kg) | 1252.5 ± 50 | 1126 ± 50 | 125.9 ± 71 | −17, 268.8 | 0.083 |
| Physical activity (PAQ=2.3) | 1252.5 ± 52 | 1126.5 ± 51 | 126 ± 75 | −23.7, 275 | 0.098 |
| Model A | 1276.5 ± 49.4 | 1102 ± 54.1 | 173.9 ± 71 | 32, 315.8 | 0.017 |
| Model B | 1280.1 ± 50 | 1099 ± 49 | 181.1 ± 72.4 | 36.7, 325.5 | 0.015 |

A: Model adjusted by FFM = 30.1 kg, FM = 8.1 kg, and height = 142.2 cm. B: Model adjusted by FFM = 30.1 kg, FM = 8.1 kg, height = 142.2 cm, and PAQ = 2.3.

than in the HIV-infected group; the median of recommendation for dairy was 3 [3–3] cups (Figure 3F).

As for micronutrient consumption, calcium consumption was lower in the HIV-infected group (887.5 ± 454 mg vs. 1214.2 ± 484.8 mg, $p = 0.004$); the recommendation for calcium was 1300 [1300–1300] mg. Vitamin D consumption was lower in both groups, based on the recommendation (600 600–600] IU), and it did not differ between groups (296.6 ± 244.2 IU vs. 296.2 ±

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152 IU, $p = 0.994$). Fiber consumption was also lower in both groups, based on the recommendation (31 [26–31] g), and the consumption did not differ between groups (12 [9–18] g vs. 16 [13–22] g, $p = 0.079$). However, sodium consumption was higher in the control group (2548 [1928–3363] mg vs. 3238 [2384–4076] mg, $p = 0.014$), and the consumption of both groups was above the recommendation (1800 [1800–2300] mg). When the diet quality index was analyzed, no significant difference was observed in the average score between both groups in terms of the consumption of other micronutrients such as vitamins. (82.1 ± 13.4 vs. 81 ± 15.2, $p = 0.725$). Using the stratification of the index, the percentage of participants in the "healthy" stratum was 25.6% in the HIV-infected group and 28.2% in the control group. In the "need for changes" stratum, it was 66.7 and 64.7% in the HIV-infected and control groups, respectively. Finally, the "unhealthy" stratum was 7.7% in both groups (Figure 4A). The frequency of consumption of foods from the index was highly similar between groups. This highlighted that in both groups, the consumption of fish was higher, with the frequency of "occasionally or never" being 61.5% in both groups. It stood out for the consumption of legumes, as 23.1% of the participants in the HIV-infected group ate legumes once a day, whereas in the control group, the frequency was 15.4% (Figures 4B, C).

TABLE 3 Body composition measured by bioelectrical impedance of groups.

| Variables | HIV-infected group $n = 39$ | Control group $n = 39$ | $p$ |
|---|---|---|---|
| Intracellular water, L | 12.8 ± 4.8 | 14.4 ± 5.1 | 0.003 |
| Extracellular water, L | 7.8 ± 2.8 | 8.7 ± 2.9 | 0.004 |
| Total body water, L | 20.7 ± 7.7 | 23.2 ± 8 | 0.003 |
| Proteins, kg | 5.5 ± 2.1 | 6.2 ± 2.2 | 0.003 |
| Minerals, kg | 1.9 ± 0.7 | 2.3 ± 0.8 | <0.0001 |
| Soft lean mass, kg | 26.6 ± 9.9 | 30 ± 10.4 | 0.002 |
| Skeletal muscle mass, kg | 14.7 ± 6.3 | 16.9 ± 6.8 | 0.003 |
| Body cell mass, kg | 18.3 ± 7 | 20.8 ± 7.5 | 0.002 |
| Visceral fat area, $cm^2$ | 33.3 ± 24.6 | 30.8 ± 20.1 | 0.443 |
| Total phase angle, ° | 5.2 ± 0.7 | 5.4 ± 0.8 | 0.170 |
| Right arm phase angle, ° | 4.9 ± 0.5 | 4.7 ± 0.6 | 0.171 |
| Left arm phase angle, ° | 4.9 ± 0.6 | 4.5 ± 0.6 | 0.006 |
| Trunk phase angle, ° | 6 ± 1.0 | 5.9 ± 1.0 | 0.315 |
| Right leg phase angle, ° | 5.7 ± 1.1 | 6.3 ± 1.0 | 0.004 |
| Left leg phase angle, ° | 5.5 ± 0.9 | 6 ± 1.0 | 0.001 |
| Impedance ratio 250/50 kHz, ° | 0.89 ± 0.01 | 0.89 ± 0.00 | 0.132 |

Data are shown as mean ± standard deviation. Student's t-statistical analysis for paired samples. P < 0.05. L: liters; kg: kilograms; %: percentage; and $cm^2$: square centimeters.

## 3.5. Physical activity

According to the physical activity questionnaires, there were no differences in the scoring (2.2 ± 0.9 vs. 2.4 ± 0.6, $p = 0.226$) between groups. When the strata analysis was performed, 30.8% of children in the control group were not active (<60 min of MVPA level), and 51.3% of children in the HIV-infected group were not active ($p = 0.066$) (Supplementary Figure 2).

# 4. Discussion

Our results showed that REE was significantly higher among children diagnosed with HIV infection than children in the control group, matched by BMI, gender, and age. To our knowledge, this is the first study to compare REE paired with these variables in the pediatric population. Although the WHO recommends a 10% increase in REE in HIV-infected pediatric patients (22), the available studies referenced are from the adult population (10, 23–26). However, Henderson et al. reported no significant differences between 29 pediatric patients with HIV (2–11 years) and 9 uninfected pediatric patients (57 ± 7 kcal/kg/day vs. 50 ± 13 kcal/kg/day) (8), although the sample size of the control group was a limitation in their study.

Similar findings have been reported in the adult population. Grinspoon et al. (27) evaluated 33 HIV-infected premenopausal women and 26 healthy premenopausal women who were part of the control group; the women were matched for body weight. The researchers concluded that REE was higher in the HIV-infected women than in the control women (1624 ± 329 vs. 1437 ±145 kcal/d), $p = 0.0096$); they also concluded that FFM was the main determinant of REE in the HIV-infected women. Supporting these findings, Lane et al. (28) also evaluated REE in asymptomatic and newly diagnosed HIV-infected women (35 ± 7 years), who were compared with a control group matched by age, BMI, and FFM. They observed that REE was higher in the HIV+ group when the REE adjusted for differences in body composition (31.4 ± 1.75 vs. 29.9 ± 2.5 kcal/kg FM and FFM, $p = 0.04$) in the early stages of the disease. Likewise, in a comparative study carried out by Hommes et al. (23), it was observed that asymptomatic HIV-infected patients had 8% ($p < 0.05$) higher REE rates than healthy control subjects; suggesting that HIV infection affects host metabolism in the early asymptomatic stage.

The proposed mechanisms for elevated REE in people with HIV may be related to viral load, CD4+ cell count, the use of antiretroviral drugs, body composition, hormones, and proinflammatory cytokines (4). An increase in REE can lead to wasting syndrome in patients, so comprehensive evaluation of pediatric patients with HIV is extremely important, ideally in situations where REE measurement by indirect calorimetry is accessible. Otherwise, it must be taken into account that the use of REE prediction equations could present an estimation bias because there are no predictive equations for pediatric patients with HIV, and the existing equations are based on a healthy population (29). Furthermore, a great clinical variety exists among subjects, and the lack of inclusion of muscle mass as a variable in the equations must also be taken into account. Thus, future research could take into

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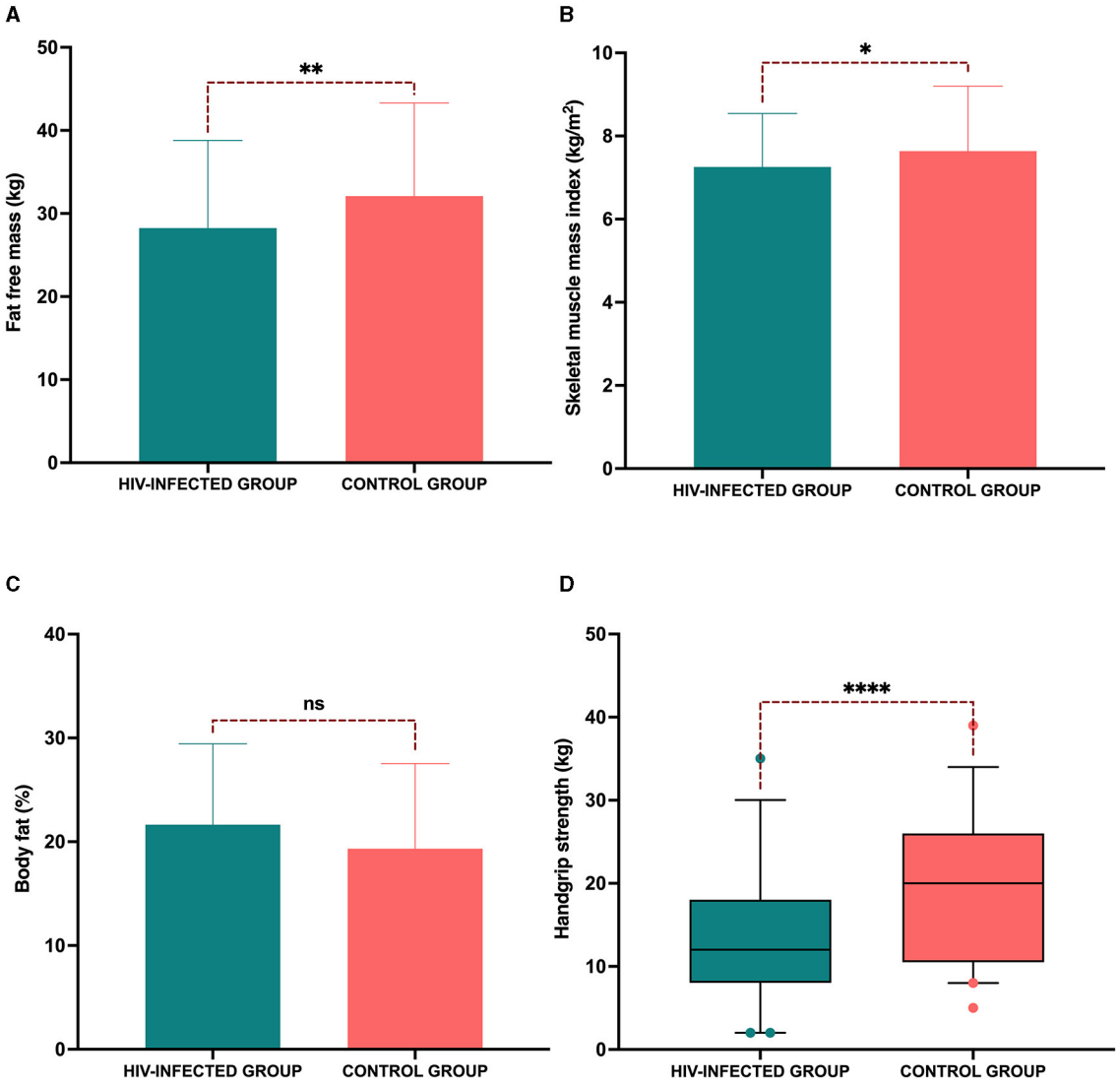


FIGURE 2
Reduced fat-free mass and muscle strength in the HIV-infected group. **(A)** Fat-free mass; **(B)** skeletal muscle mass index; **(C)** percentage of body fat; and **(D)** handgrip strength in the dominant hand. *P*-value: *$p < 0.05$; **$p < 0.001$, ****$p < 0.0001$.

account the design of an REE prediction equation in a pediatric population with HIV to minimize prediction bias.

Interestingly, we found that children with HIV had lower FFM than the control group. Several studies have been conducted on body composition in HIV-infected patients using multifrequency BIA; this technique is non-invasive, safe, and portable and measures body compartments such as FFM, FM, and TBW (intracellular and extracellular water). These studies have reported a reduction in body weight, total body potassium, subcutaneous FM, and SMM, as well as a disproportionate reduction in BCM relative to weight reduction in HIV-infected patients; a reduction in BCM has also been reported to occur in the early stages of the disease (30).

These alterations in body composition can be explained by the presence of proinflammatory cytokines, particularly in high concentrations of TNF-α, which is involved in the degradation of protein because it can inhibit the secretion of the hormone testosterone. Testosterone regulates muscle mass, affects the sensitivity of tissues to hormonal signaling, and directly stimulates the degradation of proteins and FFM (31, 32). Likewise, it has been documented that people infected with HIV experience changes at multiple levels of the hypothalamic-pituitary-adrenal axis, which can cause elevated cortisol levels (33). This alteration, being a potent catabolic pathway, could also increase protein degradation rates and slow down protein synthesis rates, especially in muscle mass; this is why it is implicated in muscle wasting associated with HIV infection (34).

These alterations might affect muscle characteristics and functions such as strength. In this sense, our results showed that in the HIV-infected group, there was a significant decrease of −11% (95% CI: −18, −3%) in handgrip strength, measured by dynamometry; this could be explained by muscle wasting, which reduces muscle mass and strength and increases fatigue (35). In fact, it has been reported that handgrip strength has a greater influence on muscle function than muscle mass (36). In

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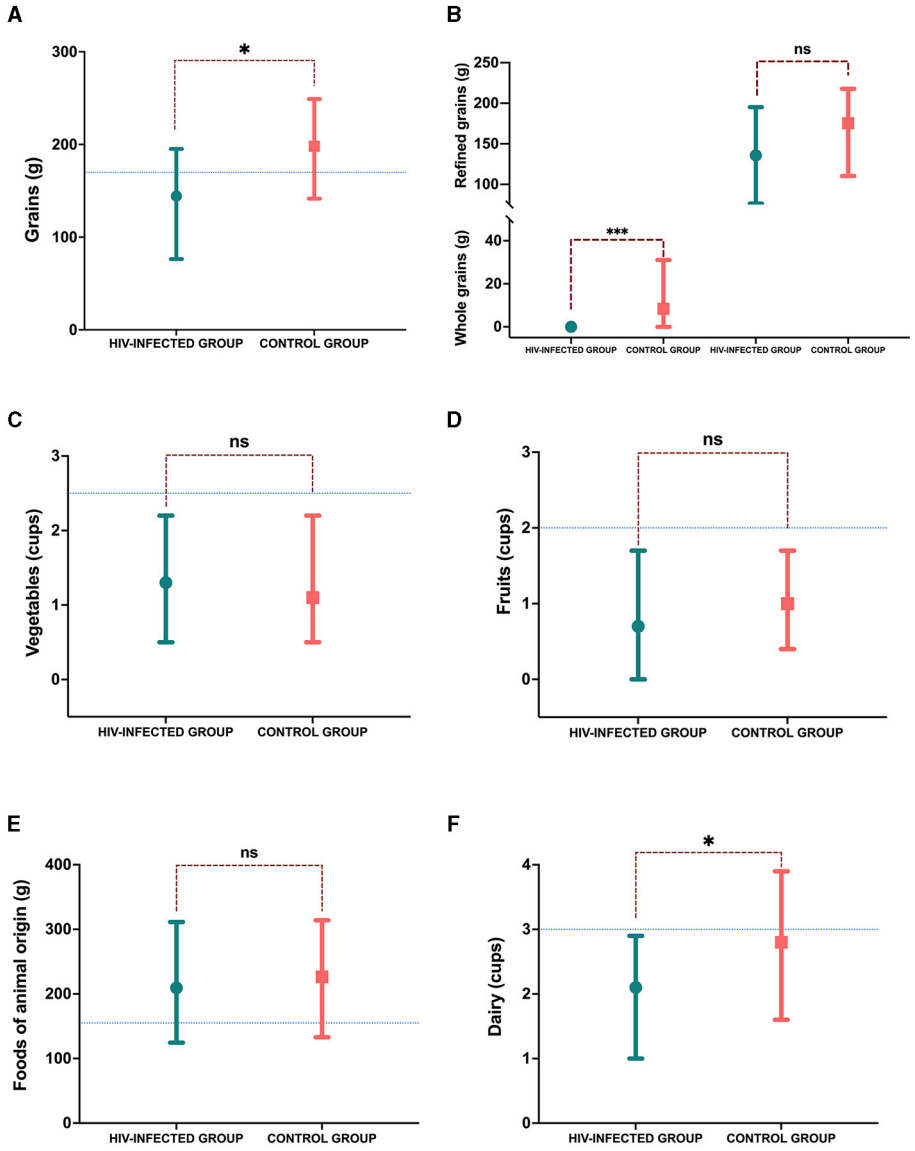


FIGURE 3
Consumption of food groups. **(A)** Grains consumption in grams; **(B)** grain consumption divided by whole and refined in grams; **(C)** vegetable consumption in cups; **(D)** fruit consumption in cups; **(E)** foods of animal origin in grams; and **(F)** dairy consumption in cups. The blue line marks the median recommendation for sex and age; $p$-value: $*p < 0.05$.

addition, we found a strong positive association between FFM and handgrip strength in the HIV-infected group ($r = 0.918$, $p = 0.0001$); a similar trend was observed in the control group but to a lesser magnitude ($r = 0.846$, $p = 0.0001$). However, other studies have not reported any differences in muscle strength between children who acquired HIV perinatally and children who were HIV-uninfected (37).

Another important finding was in the diet analysis, where we observed that calorie intake was significantly lower in the HIV-infected group than in the control group, even with a higher REE, which is a source of alert. In addition to this, we observed that the quality of the diet in both groups is incorrect for their age and gender. It is important to emphasize that a higher REE and lower FMM in patients with HIV are impressive because they can trigger a negative balance of energy. If patients do not consume adequate energy in their diet according to their demands, they could develop macronutrient and micronutrient deficiencies, and they could also accelerate immunodeficiency development and the appearance of opportunistic infections, thereby increasing the risk of mortality (2). In addition, in pediatric patients, high REE can cause inadequate growth and development (6), so it is essential to determine the adequate nutritional needs of these patients. Furthermore, energy imbalance is more serious in children than in adults because a high proportion of energy is required for growth in healthy children and for catch-up growth in children recovering from an opportunistic infection, which can

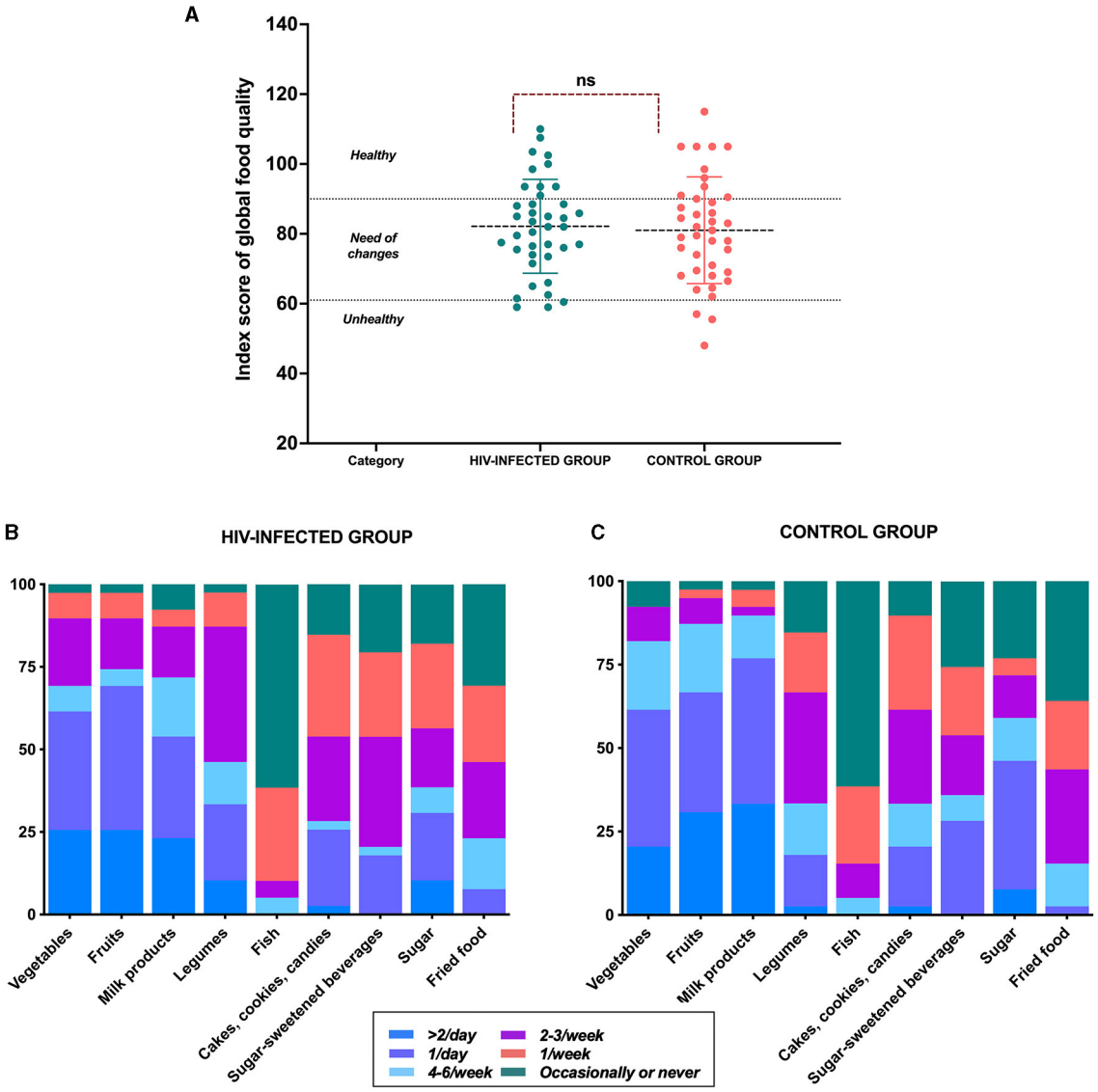


FIGURE 4
Index score of global food quality. **(A)** Index score of global food quality comparison; **(B)** frequency of consumption of food groups in the HIV-infected group, and **(C)** control group.

consequently change their REE. Although factors that contribute to the total daily energy expenditure include physical activity, growth, and diet-induced thermogenesis, these are not accounted for in the REE measurement, and the variation in the results of energy expenditure measurements is likely due to differences in dietary intake, nutritional status, physical activity, severity of illness, and opportunistic infection (38).

Although the phase angle does not contribute to changes in REE, having higher REE and not being able to meet caloric requirements may be associated with a lower phase angle, reflected in reduced cellular health and worsened disease prognosis. Some studies have associated a lower phase angle with states of malnutrition (39); we did not see phase angle differences because the groups were matched by BMI-for-age. Furthermore, while biochemical parameters do not directly influence REE, they can serve as indirect indicators of disease. For instance, cytopenia, such as neutropenia, anemia, or thrombocytopenia, can be predictors of active infections and liver enzymes may suggest liver damage. Although the biochemical parameters are not directly related to REE, the presence of infection or diseases could increase the REE due to disease catabolism (40).

Finally, in terms of physical activity, we did not find significant differences between the two groups. However, we observed that most of the participants in the HIV-infected group were classified as not active. This means that they did not comply with the recommendation for MVPA, which could also be contributing to muscle wasting and lack of functionality (41). Regular physical activity is linked to many positive outcomes in children and

adolescents. Active children have higher levels of cardiovascular fitness than their non-active counterparts. In HIV-infected children, the use of highly active antiretroviral therapy may develop unfavorable metabolic profiles that put them at risk of future cardiovascular disease, and these children may be predisposed to conditioning due to a combination of psychosociological and physiological factors, including a predisposition to a sedentary lifestyle due to the nature of their disease and/or long-term exposure to medications. In this population, exercise can help control some of the risk factors, such as cardiometabolic factors and adiposity (42). However, we know that the use of questionnaires to determine the physical activity level may have some limitations because there may be a lack of answers that require responding from memory, and exercise may be over- or under-reported.

One limitation of this study could be the equipment used to determine the REE, the Korr, which measures only $VO_2$ and is self-calibrated for each participant and uses an RQ of 0.85 in a modified Weir equation to calculate REE (43). However, there are studies where this equipment has been compared to the Deltatrac Metabolic Monitor® (Datex, Finland), manufactured 35 years ago, which is often considered the reference device (44–46). In this study, the validity of the calorimeter used compared with this reference calorimeter was 14 kcal/day. A small coefficient of variation (11.9%) was also observed (47).

Another limitation is that the Tanner stage was not considered in the population analyzed. Tanner stage is an additional determinant of REE, and studies have reported higher $VO_2$ max in pubertal boys than in prepubertal boys. It was also higher in pubertal boys than in pubertal girls. However, the greater changes in REE and maximal aerobic power observed in boys may also be due to variations in the hormonal status and the metabolic activity of muscle tissue. Therefore, increases in physical capacities and REE during the onset of puberty indicate gender differences, which could be explained mainly by alterations in body composition in boys and girls and by changes in hormonal status in boys. Despite this, in several studies, the regression analysis of the significant determinants of REE has been controversial because the Tanner stage is not considered one of the significant variables (48, 49); nevertheless, it is plausible to consider the Tanner stage in the determination of REE. However, height remained a significant factor in the model analysis of REE, reflecting the influence of the Tanner stage. We consider this to be an important limitation of our study.

Contrarily, BIA validation studies in the pediatric population in the context of HIV have been limited in terms of comparing the technique with the dilution of isotopes and dual-energy X-ray absorptiometry. Most of the evidence is focused on predicting FFM and FM (50–52). Therefore, a limitation of BIA for predicting body composition in HIV-infected children is the absence of validation studies for the internal equations.

## 6. Conclusion

In pediatric patients with asymptomatic HIV infection, higher resting energy expenditure, lower FFM and strength, and lower dietary calorie intake were observed, despite the lack of difference in the level of physical activity.

## Data availability statement

The raw data supporting the conclusions of this article will be provided by the authors upon reasonable request.

## Ethics statement

The studies involving humans were approved by the Comité de Investigación del Instituto Nacional de Pediatría with number 2020/026. 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

MCM-S-H, XL-L, JO-O, and IM-V: contributed to the conception and design of the study. AF-O, MCM-S-H, XL-L, BP-N, ALP-G, AG-G, LG-P, and IM-V: contributed to the acquisition of data. AF-O, MG-C, AA-N, and IM-V: contributed to the analysis and interpretation of data. AF-O and IM-V: contributed to the drafting of the article. All authors gave their final approval of the version to be submitted.

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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.2023.1220013/full#supplementary-material

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# Effect of the Mediterranean diet supplemented with nicotinamide riboside and pterostilbene and/or coconut oil on anthropometric variables in amyotrophic lateral sclerosis. A pilot study

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Amyotrophic Lateral Sclerosis (ALS) is a chronic and progressive neurodegenerative disease that causes the death of motor neurons and alters patients' body composition. Supplementation with the antioxidants nicotinamide riboside (NR) and pterostilbene (PTER) can combat associated oxidative stress. Additionally, coconut oil is an alternative energy substrate that can address mitochondrial dysfunction. The aim of the present study is to assess the impact of a Mediterranean Diet supplemented with NR and PTER and/or with coconut oil on the anthropometric variables of patients with ALS. A prospective, mixed, randomized, analytical and experimental pilot study in humans was performed through a clinical trial (registered with ClinicalTrials.gov under number NCT03489200) with pre- and post-intervention assessments. The sample was made up of 40 subjects categorized into four study groups (Control, Antioxidants, Coconut oil, and Antioxidants + Coconut oil). Pre- and post-intervention anthropometric assessments were carried out to determine the following data: weight, percentage of fat and muscle mass, skinfolds, body perimeters, Body Mass Index (BMI), Waste-to-Hip Index (WHI) and Waist-Height Ratio (WHR). Compared to the Control group, GAx significantly increased muscle mass percentage and decreased fat mass percentage, triceps, iliac crest, and abdominal skinfolds. GCoco significantly increased muscle mass percentage and decreased fat mass percentage, subscapular skinfolds, and abdominal skinfolds. GAx+coco significantly increased muscle mass percentage and decreased abdominal skinfolds. Therefore, our results suggest that the Mediterranean Diet supplemented with NR and PTER and the Mediterranean Diet supplemented with coconut oil (ketogenic diet) are the two nutritional interventions that have reported the greatest benefits, at anthropometric level.

KEYWORDS

**amyotrophic lateral sclerosis, nicotinamide riboside, pterostilbene, coconut oil, nutrition, anthropometry**

# 1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a chronic and progressive neurodegenerative disease of the Central Nervous System (CNS), of a neuromuscular type, characterized by the degeneration and selective dysfunction of upper and lower motor neurons (1). It is associated with a degeneration of the neuromuscular junctions that lead to skeletal muscle atrophy (2), difficulty performing voluntary movements, decreased motor autonomy and impaired oral communication, swallowing and breathing (3). It occurs in adults aged between 55 and 65, with peak incidence between 50 and 75 (4), although cases have been identified in patients younger than 25 (5). There is a crude prevalence and incidence of ALS worldwide of 4.42 (95% CI 3.92–4.96) per 100,000 population and 1.59 (95% CI 1.39–1.81) per 100,000 person-years, respectively (6). Males are considered more at risk, with an incidence rate of 1.6 in males compared to 1.2 in females (7).

Scientific evidence has identified Oxidative Stress (OS) as one of the multiple pathogenic mechanisms contributing to the development and progression of the disease (8). In addition, a deficient antioxidant capacity of the organism that increases the disruption in redox homeostasis and motor neuron death has been described (9). OS is accompanied by mitochondrial dysfunction, impaired functioning of the enzyme superoxide dismutase 1 (SOD1), excitotoxicity caused by increased neurotransmitter glutamate, neuroinflammation, decreased nicotinamide adenine dinucleotide ($NAD^+$) levels and difficulty replenishing them (10).

The precursor nicotinamide riboside (NR) has been scientifically proven to replenish $NAD^+$ levels (11). NR (vitamin B3 or niacin) is a nucleoside made up of nicotinamide and a ribose group that can be found in vegetables, eggs, fish, milk and fortified products (12). Animal and human studies have shown that NR supplementation may be an effective and safe way to replenish $NAD^+$ levels (13). There is also interest in pterostilbene (PTER) as an antioxidant treatment. PTER (trans-3,5-dimethoxy-4 hydroxystilbene) is a dimethylated natural stilbene comprising 1 hydroxyl group and 2 methoxy groups (14). It belongs to the family of polyphenols, and is present in fruits, vegetables, legumes, whole grains, seeds, nuts and extra virgin olive oil (15). It can activate metabolic pathways related to protection against OS, neuroinflammation, regulation of excitotoxicity and preservation of cognitive functions. For this reason, it could be a promising therapeutic strategy in diseases associated with OS and neurological damage, such as ALS (16).

Mitochondrial dysfunction involves a reduction in metabolic energy production (17) that compromises the supply of glucose and ATP to motor neurons and increases the risk of neurodegeneration (18), production of reactive oxygen species (ROS), oxidative damage and cell apoptosis (19). Consequently, it has been suggested that the activation of alternative metabolic pathways such as fatty acid beta oxidation could be a useful strategy to address the high energy demand of neuronal tissues (20). Furthermore, the synthesis of ketone bodies is an alternative energy source to the impaired glycolytic pathway (21). In addition, they act on metabolic pathways that regulate neuroinflammatory processes, glutamate regulation and excitotoxicity (22). Ketone bodies have shown anabolic and anti-catabolic effects in skeletal muscle, being especially relevant in ALS, due to the negative impact that this disease produces on muscle mass (23).

Medium chain triglycerides (MCT) are considered effective in the synthesis of ketone bodies since they require less energy and can be absorbed from the intestine to move through the portal vein directly to the liver without the need to circulate through the lymphatic system (24). Coconut oil has a nutritional composition characterized by a high contribution of MCT, representing up to 60–70% of total fat, the majority being caproic, caprylic, capric and lauric acids (25). Because of the above, nutritional supplementation with coconut oil could be a good way to promote the synthesis of ketone bodies as an alternative energy substrate to address the ineffectiveness of the glycolytic pathway identified in ALS (26).

Regrettably, there is no definitive cure for ALS and approved pharmacological therapies include Riluzol, Edaravone (Radicava®) (27), Relyvrio® (Sodium phenylbutyrate-taurursodiol) (28) and Qalsody® (Tofersen) (29). In addition to the negative impact that the multisystemic degeneration has on patient health, only 25% of patients affected by this disease live longer than 5 years after diagnosis and 5–10% longer than 10 (30). However, a healthy nutritional diet has been identified as increasing patients' long-term survival and as being a determining factor in the evolution of the disease (31). Specifically, the Mediterranean Diet provides antioxidant and anti-inflammatory substances that help preserve nutritional status. In addition, this diet is a neuroprotective factor that prevents neuronal degeneration and decreases the risk of developing neurodegenerative diseases (32).

Based on the above, the aim of this study was to evaluate the effect of the Mediterranean Diet supplemented with the antioxidants nicotinamide riboside and pterostilbene and/or coconut oil on anthropometric variables in patients affected by ALS.

# 2. Materials and methods

A prospective, mixed, randomized, analytical and experimental pilot study in humans was performed through a clinical trial with pre- and post-intervention assessment.

## 2.1. Subjects

### 2.1.1. Sample size

Prior to sample selection, the sample size was determined by considering the possible difficulties that might be encountered in establishing a large sample: e.g. displacement of patients residing in different Autonomous Communities of Spain and insufficient degree of motivation to adhere to the study, among others.

The pwr package was used included in the R programming environment. Calculations were carried out considering a one factor analysis of variance (ANOVA) and balanced groups, with a large effect size (Cohen's f equal to 0.6), a statistical power equal to 0.8, and a significance level of 0.05. The variables of interest were fat mass and muscle mass percentages. It was estimated that nine participants per group would provide an appropriate size to determine differences in anthropometric variables between pre- and post-intervention measurements. Thus, it was estimated a minimum sample size of 36 subjects.

### 2.1.2. Inclusion and exclusion criteria

In order to obtain the study sample, the Spanish Foundation for the "Fundación Española para el Fomento de la Investigación de la Esclerosis Lateral Amiotrófica" (FUNDELA) was contacted, with the

aim of identifying potential participants. Sixty potential candidates residing in different Autonomous Communities of Spain were recruited.

The following inclusion criteria were applied: patients older than 18, diagnosed with ALS (spinal, bulbar or familial) with a minimum of six months' evolution of the disease determined by the "Criterios de El Escorial" and able to eat their food orally. Exclusion criteria included: pregnant or lactating women; patients with tracheostomy, who need invasive or non-invasive ventilation; patients with evidence of alcohol and other drug use; undergoing gastrectomy; fully or partially consuming their food through Percutaneous Endoscopic Gastrostomy (PEG); had suffered a heart attack or present cardiac complications; infected with hepatitis B or C and/or Human Immunodeficiency Virus (HIV); present renal damage or creatine levels 2 times higher than normal and patients who present evidence of dementia. A sample of 40 male and female patients was obtained, as shown in the Consort Diagram (Figure 1) (33).

### 2.1.3. Ethical concerns

This study was approved by the University of Valencia Institutional Review Board on Human Studies and all the procedures related to the participants were approved by the University of Valencia Ethics Committee under reference number H1479983999044. This study was registered with ClinicalTrials.gov under number NCT03489200. All the interventions carried out followed the guidelines established by the Declaration of Helsinki (34). Participants were provided with a written informed consent form after being informed of the procedures and the nature of the study.

### 2.1.4. Intervention groups

A simple randomization methodology was followed. The 40 participants were distributed to configure the control group (GControl) and three experimental groups: antioxidant group (GAx), coconut oil group (GCoco) and antioxidant + coconut oil group (GAx + coco). Although patients were randomly allocated in the different groups based on the age parameter, we found no statistical difference among those groups. Moreover, the rest of parameters displayed in Table 1 (particularly, ALS duration, ALSFRS-R and body mass index) show that the patient population in the different groups reflects an acceptable homogeneity.

All the study groups underwent a pre-intervention clinical and dietary-nutritional anamnesis assessment. They also underwent pre- and post-intervention anthropometric assessments. Each group followed a meal plan along with its corresponding nutritional supplementation, with the exception of GControl, which did not receive any of the previous prescriptions and continued with their usual eating habits.

GAx: followed a Mediterranean diet + NR and PTER antioxidants.

GCoco: followed a Ketogenic Mediterranean diet + coconut oil.

GAx + coco: followed a Ketogenic Mediterranean diet + coconut oil + NR and PTER antioxidants.

All participants (n = 40) completed pre- (time = 0) and post-intervention (after 4 months) measurements and assessments.

## 2.2. Procedures

Procedures were carried out in clinical facilities located in the city of Valencia (Spain) and adapted to the study. Family members and/or caregivers were also involved, especially in those situations in which the patient had mobility or communication difficulties.

### 2.2.1. Clinical and dietary-nutritional anamnesis

It was carried out a pre-intervention clinical anamnesis assessment on all study groups to characterize their individual clinical context. This procedure allowed us to collect certain sociodemographic and clinical variables: place of residence, age, ALS clinical phenotype, onset of symptoms, date of diagnosis, personal history, family history, among others.

It was carried out a dietary-nutritional anamnesis using a Food Frequency Questionnaire (FFQ) (35) and a food diary. A characterization of the usual eating habits of each patient was obtained. This gave provided an understanding of how frequently per week or month food was consumed, the number of meals per day, ingredients included in the meals and how dishes were prepared. This information was considered during the preparation of the meal plan and to individualize the diet to the particularities of each patient in terms of frequency of consumed foods, food preferences and/or aversions, among others.

### 2.2.2. Anthropometric assessment

It was carried out pre- and post-intervention anthropometric assessments in all study groups, before and four months after the intervention. In both measurements, the anthropometric method followed was the protocol established by the International Society for the Advancement of Kinanthropometry (ISAK) and accepted by the Spanish Group of Kinanthropometry (GREC) (36). Measurements were taken by an ISAK level III certified anthropometrist.

Body weight was measured with a portable clinical scale, SECA model with a capacity of 150–200 kg and precision of 100 g. In cases of reduced mobility, an electronic chair-type scale was used, model SECA 954 with a maximum capacity of 300 kg and precision of 100 g. In order to measure height, it was used a SECA 220 Hamburg, Germany stadiometer, with a precision of 0.1 cm, after locating the Frankfort plane. A mechanical calliper, Holtain LTD Crymych UK model, with a precision of 0.2 mm and a measurement range of 0 to 48 mm, was used in order to measure skinfolds (triceps, subscapular, iliac and abdominal crest). Body perimeters (waist and hip) were taken using a flexible steel anthropometric tape, model Lufkin W606ME. A bicondylar pachymeter, Holtain model, was used for small bone diameters (humerus, bistyloid, and femur), with a minimum precision of 1 mm, and a measurement range from 0 to 140 mm, for the measurement of body diameters.

The anthropometric indexes of Body Mass Index (BMI), Waist-Hip Index (WHI) and Waist-Height Ratio (WHR) were determined. Body compartments were calculated as the percentage of fat mass using the Faulkner equation (37). Bone weight was calculated with the Rocha formula (38) and the Matiegka formula (39) was used to calculate muscle weight, which was used to obtain muscle mass percentage.

### 2.2.3. Dietary plan

For the design of the dietary plans to be followed by the experimental groups (GAx, GCoco and Gax + coco), it was used the dietary-nutritional software "Nutrición y Salud" version 2.0 (University of Granada, Spain) and a weight guide for home measurements and usual consumption rations (40).

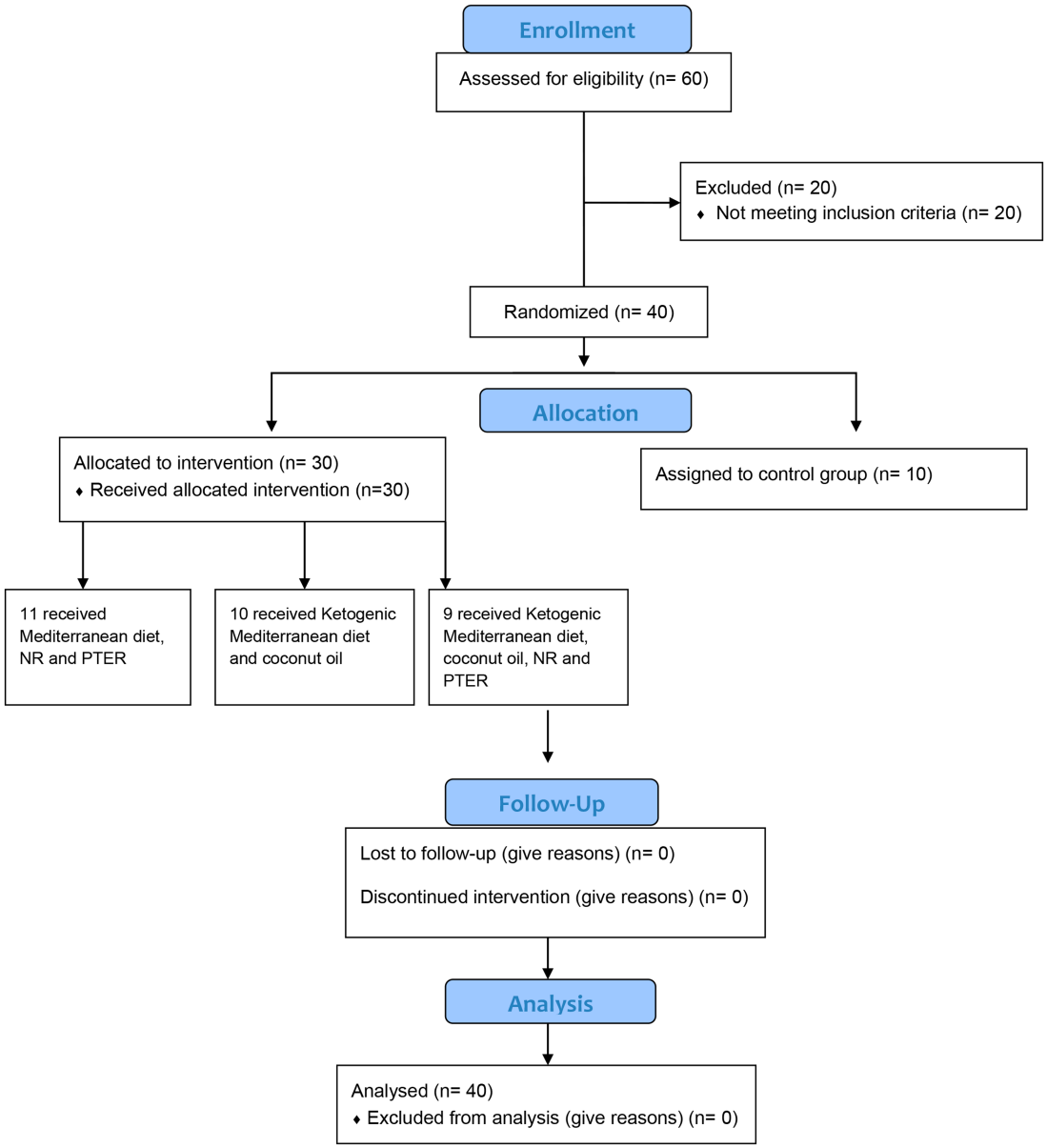


FIGURE 1
CONSORT Flow Diagram for the allocation of the sample.

A seven-day dietary plan was developed, and the average weekly nutritional value was collected. The percentage distribution of macronutrients (carbohydrates, proteins and lipids) was adjusted to the nutritional objectives for the Spanish population established by "Sociedad Española de Nutrición Comunitaria" (SENC) (41). The contribution of micronutrients (vitamins and minerals) was adjusted taking into account the Dietary Reference Intakes (DRI) established by the "Federación Española de Sociedades de Nutrición, Alimentación y Dietética" (42) in 2010. The dietary plans were designed using the basic characteristics of the Mediterranean Diet. On certain occasions, the dietary plan had to be adapted to personal circumstances to facilitate adherence (texture and consistency adaptation in cases of dysphagia, food avoidance in cases of allergies or food intolerances). However, the caloric intake, the percentage distribution of macronutrients and the DRI of micronutrients were respected when this occurred.

#### 2.2.3.1. Dietary plan based on the Mediterranean diet

The Mediterranean Diet provided approximately 2,300 kcal distributed in five meals per day. It included 35 mL of extra virgin olive oil, distributed as follows: 5 mL at breakfast or morning snack, 15 mL at lunch and 15 mL at dinner. Table 2 shows the average nutritional contribution of this meal plan.

#### 2.2.3.2. Mediterranean dietary plan supplemented with coconut oil

Comprised a ketogenic Mediterranean dietary plan that provided 2,300 kcal divided into five meals per day. It included a total of 60 mL of coconut oil distributed as follows: 20 mL at

TABLE 1 Demographic and clinical characteristics of the study sample at the beginning of the study.

| Variable | GControl ($n = 10$) | GAx ($n = 11$) | GCoco ($n = 10$) | GAx + coco ($n = 9$) |
|---|---|---|---|---|
| *Sex, n* | | | | |
| Males | 5 | 8 | 5 | 7 |
| Females | 5 | 3 | 5 | 2 |
| Age (years), Mean ± SD | 48.70 ± 6.50 | 56.73 ± 12.13 | 57.90 ± 9.84 | 55.33 ± 9.97 |
| Age (years), min-max | 37–58 | 38–80 | 44–78 | 45–70 |
| *Origin, n* | | | | |
| Valencian community | 6 | 2 | 6 | 2 |
| Other communities | 4 | 9 | 4 | 7 |
| *Clinical phenotype, n* | | | | |
| Spinal ALS | 6 | 7 | 6 | 4 |
| Bulbar ALS | 3 | 4 | 1 | 5 |
| Familial ALS | 1 | 0 | 3 | 0 |
| Diagnosis time (years), min-max | 0–4 | 0–3 | 0–4 | 1–2 |
| ALS duration (years), min-max | 2–6 | 1–6 | 1–5 | 2–8 |
| ALSFRS-R | 40.30 ± 5.10 | 39.10 ± 4.90 | 40.40 ± 5.20 | 40.70 ± 5.40 |
| Weight (kg), mean ± SD | 63.33 ± 6.06 | 68.56 ± 6.61 | 70.49 ± 12.71 | 69.69 ± 8.08 |
| Height (cm), mean ± SD | 164.3 ± 9.12 | 170.55 ± 7.09 | 167.30 ± 10.11 | 169.00 ± 8.83 |
| BMI (kg/m$^2$), mean ± SD | 23.61 ± 2.23 | 23.60 ± 1.85 | 25.01 ± 2.66 | 24.44 ± 3.52 |
| Fat mass (%), mean ± SD | 21.74 ± 6.37 | 20.60 ± 8.63 | 26.00 ± 6.57 | 19.03 ± 3.89 |
| Muscle mass (%), mean ± SD | 34.75 ± 6.04 | 33.94 ± 6.65 | 31.68 ± 3.87 | 35.77 ± 3.68 |

GControl, Control group; GAx, Antioxidant group; GCoco, Coconut oil group; GAx + coco, Antioxidant group and coconut oil; ALS, Amyotrophic Lateral Sclerosis; ALSFRS-R, revised ALS functional rating scale; SD, Standard Deviation; BMI, Body Mass Index; max, maximum; min, minimum; *n*: sample number. The descriptive analysis values are shown as sample number, mean ± standard deviation, and minimum-maximum interval. The time to diagnosis (years) refers to the time elapsed from the onset of symptoms until diagnosis, with the minimum time being 0 years (diagnosis confirmed the same year as onset of symptoms) and the maximum time being four years (diagnosis four years from onset of symptoms). The duration of ALS (years) refers to the duration of the disease since identification of the onset of symptoms by the patient, until the time of the study, presenting the minimum and maximum time elapsed. The data available in the clinical file of each patient were used to determine the mean time elapsed between the onset of symptoms and the moment the disease was diagnosed, in addition to the information provided during the interview and clinical anamnesis. This allowed to determine whether the diagnosis was made in the same year as the onset of symptoms or whether it was sometime later.

TABLE 2 Mean nutritional contribution of the dietary plan based on a Mediterranean diet.

| Nutrient | Average weekly contribution | DRI |
|---|---|---|
| Energy (kcal) | 2,339 | 1875–3,000 |
| Carbohydrates (%) | 51 | 50–55 |
| Proteins (%) | 16 | 10–20 |
| Lipids (%) | 33 | 30–35 |
| Monounsaturated fatty acids (%) | 16.58 | 20 |
| Polyunsaturated fatty acids (%) | 7.16 | 5 |
| Saturated fatty acids (%) | 5.64 | 7–8 |
| Cholesterol (mg) | 209.19 | 300 |
| Fiber (*g*) | 43.63 | 25–35 |

The percentage distribution of macronutrients (carbohydrates, proteins and lipids) is expressed compared to the total caloric volume (TCV) of the dietary plan. The contribution of macronutrients, fiber, and cholesterol was adjusted to the nutritional objectives for the Spanish population stipulated in the "Sociedad Española de Nutrición Comunitaria" (SENC) consensus. DRI: Dietary Reference Intakes.

breakfast, 20 mL at lunch and 20 mL at dinner, or 30 mL at lunch and 30 mL at dinner. Table 3 shows the mean nutritional contribution.

Regarding the coconut oil, it was recommended heating it in a bain-marie to facilitate ingestion. The option of eating it directly or mixing it with juice was given to improve palatability.

The contribution of saturated fatty acids from coconut oil predominates in this dietary plan, as it provides up to 85.5 grams per 100 mL. On the other side, the contribution of monounsaturated fatty acids and polyunsaturated fatty acids is lower compared to other types of oils, such as olive oil. For this reason, the lipid profile of this meal plan did not comply with the DRI, since these have not been established based on a meal plan that provides coconut oil as the main fat.

### 2.2.3.3. Nutritional supplementation with NR and PTER antioxidants

A combination of 1-(beta-D-ribofuranosyl) nicotinamide chloride and 3,5-dimethoxy-4′-hydroxy-trans-stilbene was used from compound EH301. It was administered in a capsule at a dose of 15 mg NR and 2.5 mg PTER/kg body weight/day. One capsule of compound EH301 was provided for every 10 kg of participant body weight. The total number of EH301 capsules was distributed into two doses: half in the morning (mid-morning) and the other half in the afternoon. There were taken with water and by the GAx and GAx + coco groups.

TABLE 3 Mean nutritional contribution of the dietary plan based on a ketogenic Mediterranean diet.

| Nutrient | Average weekly contribution | DRI |
|---|---|---|
| Energy (kcal) | 2,342 | 1875–3,000 |
| Carbohydrates (%) | 40 | 50–55 |
| Proteins (%) | 20 | 10–20 |
| Lipids (%) | 40 | 30–35 |
| Monounsaturated fatty acids (%) | 7.10 | 20 |
| Polyunsaturated fatty acids (%) | 5.26 | 5 |
| Saturated fatty acids (%) | 23.21 | 7–8 |
| Cholesterol (mg) | 266.03 | 300 |
| Fibre (g) | 38.59 | 25–35 |

The percentage distribution of macronutrients (carbohydrates, proteins and lipids) is expressed compared to the total caloric volume (TCV) of the dietary plan. The contribution of macronutrients, fibre and cholesterol was adjusted to the nutritional objectives for the Spanish population stipulated in the "Sociedad Española de Nutrición Comunitaria" (SENC) consensus. DRI: Dietary Reference Intakes.

#### 2.2.4. ALSFRS-R test

The revised ALS functional rating scale (ALSFRS-R test) was performed in all study groups at baseline evaluation and 4 months after the intervention. It is a sensitive, accurate and reproducible scale, which assesses functional ability taking into account the domains of impairment: bulbar, upper limb, lower limb and respiratory (43).

#### 2.2.5. Monitoring

The data collected in the pre-intervention clinical, dietary-nutritional anamnesis and anthropometric assessments were analyzed to prepare an individualized report on nutritional status. Each patient was provided with the corresponding dietary plan and nutritional supplementation, along with personalized dietary recommendations to improve eating habits.

After starting the intervention, individualized follow-up phone-call were established to discuss any issues and talk about possible difficulties in swallowing, taste changes or tolerance to textures. These monitoring sessions were used to make necessary adaptations in the dietary plan to ensure adherence.

### 2.3. Statistical analysis

The statistical analysis was carried out using R software. It was performed a descriptive analysis of all the dependent variables of the study according to the group and when the assessments were carried out. The results are presented as mean ± standard deviation or as the number of patients compared to the total sample number. To determine the effect of the diets on the anthropometric variables analyzed, an ANOVA test was applied to the pre-post differences. The normality of the variables was analyzed using the Shapiro–Wilk test and Q-Q plots (quantile comparison). Homoscedasticity was checked using Levene's test. When the studied variable did not meet the normality and homoscedasticity criteria, the Kruskal-Wallis non-parametric test was applied. All effects were considered significant when a value of $p \leq 0.05$ was obtained. When the existence of differences between the study groups was determined, a Tukey Post-Hoc Analysis was applied in order to identify the groups with statistically significant differences.

## 3. Results

### 3.1. Demographic and clinical characteristics of the different study groups

Table 1 describes the demographic and clinical characteristics the beginning of the study.

The sample comprised 40 people, 25 males (62.5%) and 15 females (37.5%). The mean age was 54.7 years, with an age range of 37–80. The youngest mean age was observed in GControl (48.70 ± 6.50), while the oldest mean age was seen in GCoco (57.90 ± 9.84). GAx presented the widest age range (38–80 years). 14% of the sample (16 subjects) resided in the Valencian Community, while the remaining 60% (24 subjects) came from other Autonomous Communities of Spain.

The predominant clinical ALS phenotype was spinal, identified in 23 subjects (57.5%). The time elapsed from the onset of symptoms to the time of this study ranged from a minimum of one year to a maximum of eight years. The GAx + coco presented the widest range of disease duration, between two and eight years.

At the beginning of the study the scores obtained in ALSFRS-R were: for GControl 40.30 ± 5.10; for GAx 39.10 ± 4.90; for GCoco was 40.40 ± 5.20; and for GAx + coco 40.70 ± 5.40. These values do not show significant differences, so the functional capacity of the four groups was similar at the beginning of the study. Likewise, the study groups were homogeneous according to weight ($p = 0.166$) and BMI ($p = 0.551$) at the beginning of the study. Regarding body weight, the total sample presented a mean weight (kg) of 67.99 ± 8.85 and a mean height (cm) of 167.83 ± 8.79. Mean BMI (kg/m$^2$) was 24.14 ± 2.56. According to the classification scale (44), this was normal weight. The study groups were homogeneous regarding fat mass ($p = 0.141$) and muscle mass ($p = 0.387$) percentages. The total sample presented a mean fat mass (%) of 21.88 ± 6.94. Regarding the muscle mass percentage, the total sample presented an average equivalent to 33.99 ± 5.31.

### 3.2. Effect of nutritional intervention on anthropometric variables

#### 3.2.1. Analysis of weight, fat mass, and muscle mass variation

Table 4 shows the initial and final values of body weight, fat mass and muscle mass in the four study groups.

The weight analysis (Figure 2A) shows that the study groups presented a similar behavior, obtaining very slight weight variations, with no significant changes. The GAx presented the greatest weight loss, while GAx + coco was the only group that showed a slight weight gain. No statistically significant differences were identified ($p = 0.5459$). Fat mass percentage (Figure 2B) decreased in all study groups, except for GControl, which presented an increase in this anthropometric variable. The greatest loss, (2.41%) was observed in GAx, followed by GCoco (1.84%) and GAx + coco (less than 1%). A statistically significant decrease in the fat mass percentage was identified in GAx

and GCoco compared to GControl ($p = 0.0045$; $p = 0.0216$, respectively). There was a statistically significant increase in muscle mass percentage (Figure 2C) in GAx ($p = 0.0002$), GCoco ($p = 0.0011$) and GAx + coco ($p = 0.0060$), compared to GControl, which was the only group that showed a decrease. GAx had the highest muscle gain (1.41%), followed by GCoco (1.10%), and GAx + coco (0.76%).

### 3.2.2. Anthropometric skinfold variation analysis

All the study groups presented a decrease in triceps skinfold (Figure 3A), except for GControl, in which there was an increase. GAx showed the greatest decrease in this skinfold, being equivalent to 1.62 mm, which was statistically significant ($p = 0.0077$) when compared to GControl. A similar result was obtained in the subscapular skinfold measurements (Figure 3B): GAx, GCoco, and GAx + coco presented a decrease, while there was an increase in the GControl. A 2.46 mm decrease in the skinfold was seen in the GCoco that was statistically significant ($p = 0.0439$). Regarding the iliac crest skinfold (Figure 3C), GAx presented the greatest decrease of 1.89 mm, which was statistically significant ($p = 0.0331$) compared to GControl. The abdominal skinfold (Figure 3D) showed the highest number of significant effects. The greatest decrease was seen in GAx (4 mm), followed by GCoco (3.50 mm) and GAx + coco (2.40 mm). However, GControl presented an increase of 3.20 mm in this variable. The identified decrease was significant in GAx ($p = 0.0004$), GCoco ($p = 0.0015$) and GAx + coco ($p = 0.0115$) compared to GControl.

### 3.2.3. Analysis of variation of body perimeters, anthropometric indexes, and functional capacity

The results related to the analysis of body perimeters and anthropometric indexes are shown in Table 5.

Regarding waist circumference (Table 5), a decrease was observed in GAx, GCoco and GAx + coco, with GAx presenting the greatest decrease. However, no statistically significant effects were identified ($p = 0.1266$). The variations of hip circumference (Table 5) were very slight, and no statistically significant effects were identified ($p = 0.3427$). When comparing the different study groups, the anthropometric indices (BMI, WHI and WHR) (Table 5) did not show an interaction effect. Regarding BMI, a similar behavior was observed in all groups, with very slight variations between the pre- and post-intervention assessments. A decrease in GAx and GAx + coco was seen in the WHI, while no variations were observed in GCoco and GControl. A decrease in the WHR was identified in GAx, GCoco and GAx + coco. On the contrary, GControl was the only group that obtained an increase in this variable.

In relation to the ALSFRS-R score, a statistically significant decrease ($-5.50 \pm 7.60$) was observed in GControl. A slight decrease ($-0.50 \pm 2.40$) was found in GCoco. A decrease equivalent to $-1.20 \pm 2.50$ was observed in GAx + coco. In contrast, GAx was the intervention group with an increase equal to $2.00 \pm 4.00$.

## 4. Discussion

An adequate diet is important for ALS patients, since it ensures the nutritional needs and can minimizes the impact that the disease has on the nutritional status (45). It is suspected that the Mediterranean Diet may be beneficial since it includes foods that are rich in antioxidants, which have shown potential neuroprotective effect (46). Consequently, *t* is also thought that additional nutritional supplementations may exert further benefits The effects of both strategies require further exploration, which is why this present study conducted an analysis of the variation of anthropometric parameters.

We based our study on a sample of patients who had a stable weight, which is beneficial because a decrease in body weight is common in ALS patients and associate with progression, worse prognosis and increased mortality (47). Since the weight did not change, no significant changes were identified in associated variables such as BMI. This parameter remained constant in all groups (Table 5), being indicative of a normal weight. This is a positive finding because a BMI less than 18.5 kg/m$^2$ or greater than

TABLE 4 Analysis of the variation in body weight, fat mass, and muscle mass as a function during the study in the different groups.

| Variable | Group (*n*) | Pre-intervention assessment Mean ± SD | Post-intervention assessment Mean ± SD | Post – Pre-intervention assessments Mean ± SD | *p*-value |
|---|---|---|---|---|---|
| Weight (Kg) | GControl (10) | 21.74 ± 6.37 | 23.30 ± 7.11 | 1.56 ± 1.14 | 0.5459 |
| | GAx (11) | 20.60 ± 8.63 | 18.19 ± 5.83 | −2.41 ± 3.56 | |
| | GCoco (10) | 26.00 ± 6.57 | 24.16 ± 6.00 | −1.84 ± 2.93 | |
| | GAx + coco (9) | 19.03 ± 3.89 | 18.37 ± 3.84 | −0.66 ± 1.00 | |
| Fat mass (%) | GControl (10) | 21.74 ± 6.37 | 23.30 ± 7.11 | 1.56 ± 1.14 | 0.0049 |
| | GAx (11) | 20.60 ± 8.63 | 18.19 ± 5.83 | −2.41 ± 3.56 | |
| | GCoco (10) | 26.00 ± 6.57 | 24.16 ± 6.00 | −1.84 ± 2.93 | |
| | GAx + coco (9) | 19.03 ± 3.89 | 18.37 ± 3.84 | −0.66 ± 1.00 | |
| Muscle mass (%) | GControl (10) | 34.75 ± 6.04 | 33.14 ± 6.26 | −1.61 ± 1.12 | 0.0001 |
| | GAx (11) | 33.94 ± 6.65 | 35.35 ± 4.83 | 1.41 ± 2.00 | |
| | GCoco (10) | 31.68 ± 3.87 | 32.78 ± 3.53 | 1.10 ± 1.38 | |
| | GAx + coco (9) | 35.77 ± 3.68 | 36.53 ± 3.77 | 0.76 ± 1.06 | |

GControl, Control group; GAx, Antioxidant group; GCoco, Coconut oil group; GAx + coco, Antioxidant group and coconut oil; SD, Standard deviation; n, sample number. Descriptive analysis values are shown as Mean ± SD. All effects are considered significant with value of $p \leq 0.05$.

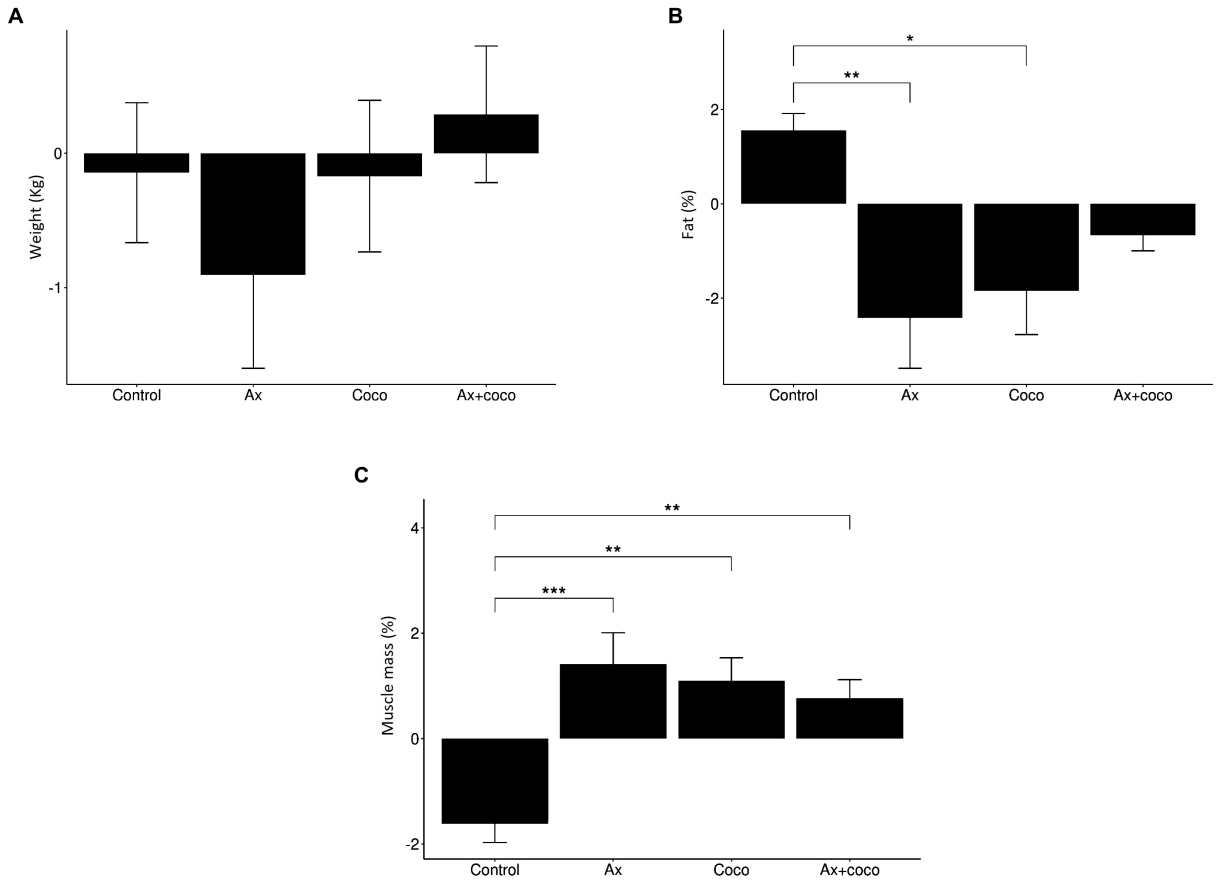


FIGURE 2
Variation in weight **(A)**, fat mass percentage **(B)** and muscle mass percentage **(C)** depending on study group. The statistical difference is indicated as: ***$p \leq 0.001$ **$p \leq 0.01$; *$p \leq 0.05$.

35 kg/m$^2$ is associated with lower survival rates (48). Moreover, maintenance of BMI is indicative of good nutritional status and better prognosis of ALS, as it is associated with increased energy reserve, which is indispensable to compensate the increased caloric needs due to hypermetabolism (49). However, it is unclear that BMI can act as an anthropometric indicator due to its high specificity (97%) and low sensitivity (42%), such that its analysis may not specifically address the impact on body compartments (50). Because of this, fat and muscle mass were analyzed (Table 4; Figure 2).

In the analysis of the anthropometric skinfolds of the triceps, subscapular, iliac crest, and abdominal, a decrease that contributed to the reduction of body fat mass was observed (Figure 3). Furthermore, we found that GAx, GCoco and GAx + coco induced a decrease in the fat mass percentage compared to GControl (Figure 2), which could be considered a protective factor for ALS since a decrease in body fat is related to a decrease in proinflammatory cytokines, i.e., IL-6 or TNF-α, both involved in the pathogenic mechanism of inflammation that underlies the disease (51).

The decrease in fat mass percentage in GAx could be the consequence of following a Mediterranean Diet (52). It has been reported in animals models that polyphenols such as PTER also act on adipose tissue (53) by reducing lipogenesis and increasing fatty acid oxidation in the liver (54). Oral administration of MCT (coconut oil in our case) increases adipose tissue signaling (55) and lipolysis; two which may explain the decrease in fat mass (56). Coconut oil MCTs have a high oxidation rate and are used as an energy source instead of being stored in adipose tissue. Even so, further research is needed as these findings came from studies carried out in mice. Moreover, the discrepancy regarding the role of fat mass in ALS persists since some authors have indicated that adipose tissue could play a beneficial role in this disease and improve in survival rates (57).

ALS is associated with increased muscle catabolism, a factor that hinders the maintenance and synthesis of muscle (49). Despite this, all groups (GAx, GCoco, and GAx + coco) show an increase in their muscle mass percentage (Table 4; Figure 2), a positive result as a higher muscle mass percentage is directly associated with a slower rate of disease progression (58). Loss of $NAD^+$ homeostasis promotes skeletal muscle degeneration (59), but NR supplementation restores its levels by activating the sirtuins, which is associated with an improvement of the oxidative capacity of the muscle, reducing the risk of loss of muscle mass (60). This could be why GAx presented the greatest increase in muscle mass, although we must note here that the effects of NR consumption on skeletal muscle in humans has not yet been completely proven (61). Moreover, adherence to the Mediterranean Diet followed by GAx is a protective factor for muscle mass, especially in middle-aged adults and during the ageing process (62, 63). Some studies have reported that the consumption of coconut

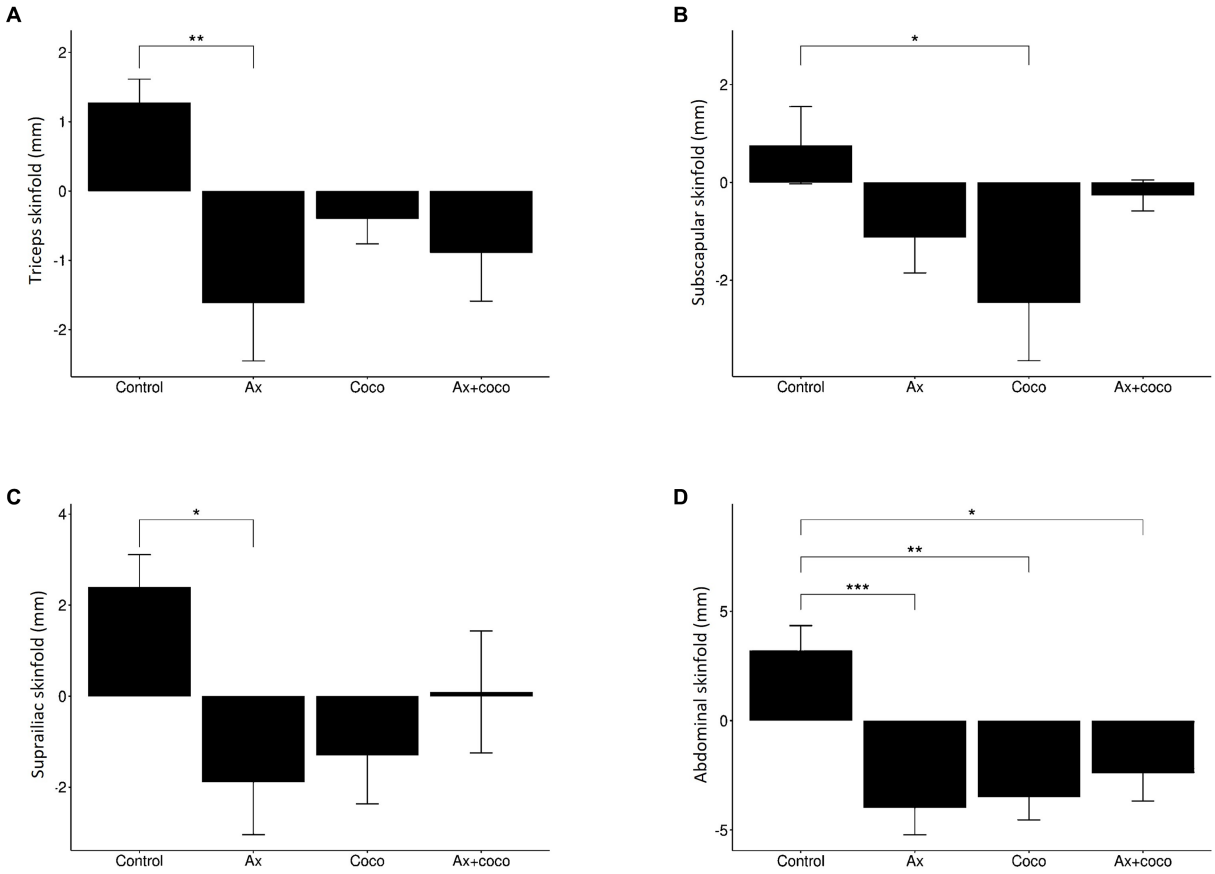


FIGURE 3
Variations of the triceps **(A)**, subscapular **(B)**, iliac crest **(C)** and abdominal **(D)** skinfolds according to study group. The statistical difference is indicated as: ***$p \leq 0.001$ **$p \leq 0.01$; *$p \leq 0.05$.

oil favors the increase of lean mass (64). The underlying mechanism could be explained taking into account that saturated fatty acids contribute to the increase in ketone body levels that offset mitochondrial dysfunction and inefficient energy production, generating a positive impact on metabolism (65, 66) and facilitating energy bioavailability for muscle anabolic processes (67). The increase in muscle mass percentage the GCoco (Table 4; Figure 2) concurs with a previous study carried out by our research group on Multiple Sclerosis, where a sample of patients followed a Mediterranean Diet supplemented with coconut oil (68, 69). It should be added that adherence to a Mediterranean Diet is related to a good state of muscle mass, as this dietary pattern provides proteins necessary for the synthesis of muscle mass (70). On the contrary, GControl showed a decrease in muscle mass percentage (Table 4; Figure 2), a fact that may be due to the absence of a dietary plan and nutritional supplementation (71). Specifically, the GControl showed a worsening in body composition, manifested by an increase in fat mass and a decrease in muscle mass. These effects are typically associated with ALS progression. Indeed, the result observed in the body composition may serve as a prognostic factor and provide guidance for nutritional management in ALS patients (72).

Despite the absence of significant effects on body perimeters, it should be highlighted that the decrease in waist circumference is associated with less abdominal adiposity (Table 5). This decrease could be associated with the decrease observed in the abdominal skinfold (Figure 3), which presented the greatest number of significant effects, including a statistically significant decrease in GAx, GCoco, and GAx + coco, compared to GControl. Specifically, this anthropometric skinfold is measured in the abdomen, an area close to the waist. Consequently, the decrease observed in this skinfold would lead to a decrease in fat which could condition a decrease in volume manifested by a decrease in waist circumference. The accumulation of fat in this area has been reported to be associated with the production of proinflammatory cytokines leading to low-grade systemic inflammation (73), which has also been associated with neurodegeneration (74), decreased functional capacity (75) and cell apoptosis (76). Waist circumference is a marker of cardiovascular risk and insulin resistance (77), two factors that increase the risk of cardiovascular disease and diabetes, thus complicating patient prognosis.

All study groups presented a WHR greater than 0.5 (Table 5) in the pre-intervention assessment, a value considered unhealthy (78). The WHR continued to be greater than 0.5 in the post-intervention assessment (Table 5), but the decrease identified in the GAx, GCoco, and GAx + coco is related to a decrease in abdominal adiposity that results in a lower cardiovascular risk. It should be noted that the patients in this study had normal weight, low accumulation of adipose tissue in the abdominal region and slight variations in the hip

TABLE 5 Analysis of the variation of body perimeters, anthropometric indexes and ALSFRS-R depending on time and study group.

| Variable | Group (*n*) | Pre-intervention assessment Mean ± SD | Post-intervention assessment Mean ± SD | Post − Pre-intervention assessments Mean ± SD | *p*-value |
|---|---|---|---|---|---|
| Waist (cm) | GControl (10) | 84.50 ± 11.08 | 85.25 ± 11.36 | 0.75 ± 2.14 | 0.1266 |
| | GAx (11) | 88.82 ± 9.63 | 86.18 ± 9.94 | −2.64 ± 3.44 | |
| | GCoco (10) | 92.95 ± 9.30 | 92.40 ± 10.85 | −0.55 ± 3.89 | |
| | GAx + coco (9) | 89.61 ± 13.71 | 87.11 ± 10.55 | −2.5 ± 4.70 | |
| Hip (cm) | GControl (10) | 94.92 ± 5.12 | 95.56 ± 5.61 | 0.64 ± 1.08 | 0.3427 |
| | GAx (11) | 96.00 ± 5.80 | 96.00 ± 4.45 | 0.00 ± 2.65 | |
| | GCoco (10) | 101.50 ± 5.08 | 100.55 ± 4.74 | −0.95 ± 1.60 | |
| | GAx + coco (9) | 96.80 ± 3.70 | 96.22 ± 3.19 | −0.58 ± 2.42 | |
| BMI (kg/m$^2$) | GControl (10) | 23.61 ± 2.23 | 23.54 ± 2.37 | −0.07 ± 0.59 | 0.5703 |
| | GAx (11) | 23.60 ± 1.85 | 23.29 ± 1.60 | −0.31 ± 0.80 | |
| | GCoco (10) | 25.01 ± 2.66 | 24.95 ± 2.35 | −0.06 ± 0.63 | |
| | GAx + coco (9) | 24.44 ± 3.52 | 24.54 ± 3.44 | 0.10 ± 0.56 | |
| WHI | GControl (10) | 0.89 ± 0.11 | 0.89 ± 0.11 | 0.00 ± 0.02 | 0.1255 |
| | GAx (11) | 0.93 ± 0.13 | 0.90 ± 0.13 | −0.03 ± 0.03 | |
| | GCoco (10) | 0.92 ± 0.11 | 0.92 ± 0.13 | 0.00 ± 0.04 | |
| | GAx + coco (9) | 0.92 ± 0.12 | 0.90 ± 0.10 | −0.02 ± 0.04 | |
| WHR | GControl (10) | 0.51 ± 0.07 | 0.52 ± 0.07 | 0.01 ± 0.01 | 0.1300 |
| | GAx (11) | 0.52 ± 0.07 | 0.51 ± 0.06 | −0.01 ± 0.02 | |
| | GCoco (10) | 0.56 ± 0.04 | 0.55 ± 0.05 | −0.01 ± 0.02 | |
| | GAx + coco (9) | 0.53 ± 0.09 | 0.52 ± 0.07 | −0.01 ± 0.03 | |
| ALSFRS-R | GControl (10) | 40.30 ± 5.10 | 34.80 ± 3.00* | −5.50 ± 7.60 | |
| | GAx (11) | 39.10 ± 4.90 | 41.10 ± 2.90 | 2.00 ± 4.00 | |
| | GCoco (10) | 40.40 ± 5.20 | 39.90 ± 3.30 | −0.50 ± 2.40 | |
| | GAx + coco (9) | 40.70 ± 5.40 | 39.50 ± 4.10 | −1.20 ± 2.50 | |

GControl, Control group; GAx, Antioxidant group; GCoco, Coconut oil group; GAx + coco, Antioxidant group and coconut oil; BMI, body perimeters, Body Mass Index, WHI; Waste-to-Hip Index, WHR, Waist-Height Ratio; ALSFRS-R, revised ALS functional rating scale; SD, Standard deviation; n, sample number. Descriptive analysis values are shown as Mean ± SD. * $p \leq 0.05$.

circumference between the pre- and post-intervention assessments (Table 5). The above is probably why large changes in WHI were not observed.

In other clinical situations, anthropometric changes characterized by increased muscle mass and decreased fat mass are also accompanied by functional improvements. Specifically, it has been seen in women with breast cancer after a multidisciplinary rehabilitation program (79), in patients with cirrhosis after an exercise program (80) and in elderly women with sarcopenic obesity after a resistance training (81). However, in our study, with the exception of GControl which significantly worsened functional capacity after 4 months, the other 3 groups showed no change, with a worsening trend in the GAx + coco and GCoco groups and an improving trend in the GAx group (Table 5). These results suggest possible functional benefits of the interventions (greater in GAx) compared to the worsening observed in GControl.

However, it is important to note that the natural heterogeneity of the disease influences the interpretation of the evidences found in the present study and the limited sample size might be considered too small to confirm definitive conclusions. Besides, there is little available scientific evidence regarding the nutritional interventions used and their effect on anthropometric variables in humans affected by ALS, which makes consultation and direct comparison of results difficult. Moreover, each patient came from a different Spanish location and was attended by different health professionals depending on the correspondence hospital. Therefore, these professionals could have previously provided information on healthy nutritional habits that may influence the adherence to a dietary pattern. Specifically, the simultaneous prescription of a dietary plan together with nutritional supplementation does not allow to know which of the two strategies better contributes to the identified benefits or whether it is the sum of both. Added to this is the fact that ALS does not affect the limbs symmetrically, which is why different authors have suggested dual-energy X-ray absorptiometry (DEXA) or bone densitometry as a more precise methodology and one that could provide new findings in the study of ALS (82).

## 5. Conclusion

The Mediterranean Diet supplemented with NR and PTER and the Mediterranean Diet supplemented with coconut oil are the two nutritional interventions that seem to obtain greater anthropometric improvements in ALS patients. The limited sample size might preclude to reach definitive conclusions. Consequently, the preliminary data of this pilot study need to be implemented by a much larger clinical trial.

## 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 the University of Valencia Institutional Review Board on Human Studies and all the procedures related to the participants were approved by the University of Valencia Ethics Committee under reference number H1479983999044. 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

JE, MM, and ED conceived and designed the study. SC-J, MN, and MV-B performed the experiments. SC-J and MZ analyzed the data. JO supervised the study. MM and SC-J wrote the paper. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# A retrospective study on the physical growth of twins in the first year after birth

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**Objectives:** This study analyzed the physical growth of small for gestational age (SGA) and appropriate for gestational age (AGA) twins up to one year after birth.

**Methods:** Weight, length, and head circumference data of 0–1 year-old twins were collected from the Child Health Care System from 2010 to 2019. Physical data were presented as *Z*-scores. Five parameters – growth level of weight, body length, head circumference, growth velocity, and body proportion (weight for length) were compared in twins.

**Results:** A total of 3,909 cases were collected (22.61% SGA, 77.39% AGA). 1. In both groups, WAZ (Weight for age *z*-score), HCZ (Head circumference for age *z*-score), and LAZ (Length for age *z*-score) increased more rapidly in the first 6 months. By one year of age, WAZ, HCZ, and LAZ had reached the normal range, but none had reached the average level of normal singleton children. 2. The mean values of WAZ, HCZ, and LAZ in the AGA group were between –1 and 0, and between –2 and – 1 in the SGA group, in the first year after birth. The SGA group lagged significantly behind the AGA group. The LAZ score of SGA and AGA was lower than the WAZ and HCZ scores. 3. The proportion of preterm AGA was the largest in twins, and the growth rate of preterm AGA was the fastest. Preterm twins had greater growth potential than term twins. However, the growth level of preterm SGA was always low. 4. The WFLZ (Weight for length *z*-score) in each group was approximately close to 0. The WFLZ of SGA was smaller than that of AGA twins at most time points. After 4 months of age, the WFLZ of twins had a downward trend. The WFLZ of preterm SGA approached –1 at approximately 1 year old.

**Conclusion:** The physical growth of SGA and AGA in twins in the first year can reach the normal range but cannot reach the average level of normal singleton children. More attention should be paid to SGA in twins, especially preterm SGA. We should give proper nutritional guidance after 4 months of age to ensure the appropriate body proportion (weight for length) of SGA in twins.

**Clinical trial registration:** www.chictr.org.cn, CTR2000034761.

KEYWORDS

**appropriate for gestational age, catch up growth, growth and development, physical anthropology, small for gestational age**

# 1. Introduction

Small for gestational age (SGA) refers to children with birth weight or birth length below the 10th percentile for the same gestational age (GA) and sex. Some scholars have also defined SGA as less than P5 or P3 (1, 2). The International Society of Pediatric Endocrinology and the Growth Hormone Research Society jointly defined SGA as birth weight and/or birth length below mean-2SD for the same sex and the same gestational age (3). However, SGA in China is still determined as P10 with a birth weight below the same sex and the same gestational age (4). The incidence of SGA in China was 6.61% as of 2009 (5). The twin birth rate has increased in recent years, and the twin pregnancy rate in 2019 was 3.69%, according to the Special Committee on Twin Pregnancy of the Chinese Maternal and Child Health Association (6). There is a lack of relevant research on the physical growth and neuropsychological development of twins of appropriate for gestational age (AGA) and of small for gestational age (SGA), respectively.

Most SGA children will have catch-up growth, which can promote physical growth and neuropsychological development (7). The SGA children who fail to achieve catch-up growth are at risk for short stature, neuropsychological developmental problems, and behavioral problems in adulthood. However, excessive catch-up growth increases the risk of childhood overweight, obesity, hypertension (8), and metabolic syndrome in adulthood (9). Similar findings have been reported in twin studies (10, 11). In addition, catch-up growth is also observed in twins with AGA (12). How to balance the advantages and disadvantages of catch-up growth so that the SGA can reach the target height and weight without increasing the risk of metabolic syndrome in adulthood is a hot topic.

This study analyzed the physical growth of SGA and AGA in twins up to one year after birth, in order to provide a reference for promoting appropriate catch-up growth in twins.

# 2. Materials and methods

## 2.1. Data source

Study data were extracted from the Child Health Care System of the Children's Hospital of Chongqing Medical University for 9,688 visits between January 2010 and November 2019. The data included physical measurements (head circumference, body length, and body weight) and demographic information (sex, gestational age, birth length, and weight). The inclusion criteria were: (1) children were twins. (2) age 0–1 month and follow-up to 11 months. The exclusion criteria were: missing key information and being unable to be contacted by phone.

## 2.2. Research groups

According to the 2015 birth weight standards for newborns with different GA in China (7), children with birth weights between P10 and P90 of the same sex and GA were placed in the AGA group, and those with birth weights below P10 were placed in the SGA group. Preterm infants were those with 28 weeks ≤ GA < 37 weeks and term infants were those with 37 weeks ≤ GA < 42 weeks. Participants were divided into 12 age groups based on their age in months. If two or more visits were made to the same child in the same age group, the average was taken.

## 2.3. Physical index evaluation standard

The *Z*-scores of the anthropometric data were calculated using WHO Anthro (version 3.2.2) software and included the following indicators as growth levels: weight for age *Z*-score (WAZ), head circumference for age *Z*-score (HCZ), and length for age *Z*-score (LAZ). In addition, the weight for length *Z*-score (WFLZ) was used to measure body proportions. Due to the small number of preterm infants in some age groups, we worked with chronological age in premature newborns and did not calculate the corrected *Z*-score.

## 2.4. Statistical analysis

The data were analyzed with SAS 9.4 software (SAS Institute) and tested for normality. The measurement data were statistically described by $X \pm SD$. The difference between independent sample continuous variables was tested by an independent sample *T*-test. Multiple group comparisons were performed by Analysis of Variance (ANOVA). Counting data were analyzed using a Chi-squared test, and a non-parametric test was used for those variables that did not satisfy normal and equal variance. The growth trend of 0–to 11-month-old children was plotted using the hierarchical PROC SGPLOT (SAS 9.4) procedure. $p < 0.05$ indicated that the difference was statistically significant.

# 3. Results

A total of 3,909 cases of twins <1 year of age were enrolled. The data distribution is shown in Table 1. In the SGA group, 884 cases (22.61%) were enrolled, with 405 boys (10.36%) and 479 girls

TABLE 1 General characteristics of SGA and AGA.

| Variable | | Full-term | | Preterm | |
|---|---|---|---|---|---|
| | | AGA | SGA | AGA | SGA |
| Cases, *n* (%) | | 396 (10.13) | 378 (9.67) | 2,629 (67.26) | 506 (12.94) |
| Sex | Male infants, *n* (%) | 230 (29.72)[a] | 141 (18.22) | 1,347 (42.97)[b] | 264 (8.42) |
| | Female infants, *n* (%) | 166 (21.45) | 237 (30.62) | 1,282 (40.89) | 242 (7.72) |
| Birth weight (kg) | | 2.85 ± 0.26[c] | 2.28 ± 0.23 | 2.20 ± 0.44[c] | 1.79 ± 0.33 |
| Gestational age (weeks) | | 37.21 ± 0.52[c] | 37.44 ± 0.73 | 34.15 ± 1.97[c] | 35.01 ± 1.17 |

[a]Sex ratio of full-term AGA compared with full-term SGA, $p < 0.001$; [b]Sex ratio of preterm AGA compared with preterm SGA, $p = 0.7402$; [c]Compared with SGA, $p < 0.05$.

(12.25%). In the AGA group, there were 3,025 cases (77.39%), with 1,577 boys (40.34%) and 1,448 girls (37.04%). The proportion of preterm AGA (67.26%) was the highest. Birth weight in the SGA group was significantly lower than in the AGA group (2.00 ± 0.38 kg vs. 2.28 ± 0.48 kg, $p < 0.001$). The GA of the SGA group was significantly higher than that of the AGA group (36.05 ± 1.57 weeks vs. 34.54 ± 2.13 weeks, $p < 0.001$).

## 3.1. Growth level and growth rate of SGA and AGA twins

Table 2; Figure 1 show the mean and trend of WAZ, LAZ, HCZ of SGA, and AGA in twins from 0 to 11 months, which indicate: 1. The WAZ, LAZ, and HCZ of twins gradually increased within 1 year. The WAZ and LAZ of AGA twins within 6 months old and those indicators of SGA twins within 5 months old had a relatively rapid growth velocity, then those indicators of both two groups slowed down after 5-6 months. 2. Except for the age of 0 months, the WAZ, LAZ, and HCZ of SGA in twins were lower than those of AGA in twins at most time points ($p < 0.05$). LAZ was lower than WAZ and HCZ within 1 year after birth in all groups. 3. At the age of 11 months, the growth levels of AGA and SGA in twins were still lower than those of mean value of singleton children ($Z<0$) but still in the normal range ($Z > -2$); the WAZ, HCZ, and LAZ of the AGA group were > −1, and the WAZ, HCZ, and LAZ of the SGA group ranged from −2 to approximately −1.

## 3.2. Growth level of preterm and full-term SGA and AGA twins

Table 3 shows the changes in physical indicators in the full-term and preterm AGA groups. The number of preterm AGA infants was larger than that of full-term AGA twins. WAZ, LAZ, and HCZ gradually increased after birth in AGA twins. At most time points, the WAZ, HCZ, and LAZ of preterm AGA twins were smaller than those of full-term AGA subjects. There was no significant difference in the WAZ and HCZ at 7 months and in the WAZ, HCZ, and LAZ at 8–10 months between preterm AGA and full-term AGA twins. All the indicators were between −1 and 0 in both groups at 11 months.

Table 4 shows the changes in physical indicators in the full-term and preterm SGA groups. In both groups, there was an increasing trend in WAZ, LAZ, and HCZ. The indicators in the preterm SGA group were significantly smaller than those of the full-term SGA group at most time points, except that there was no significant difference in LAZ between the two groups at 9–11 months. All the indicators in preterm SGA were at a low level ($-2 < Z < -1$) at 11 months old.

Figure 2 shows the trends of WAZ, LAZ, and HCZ from 0 to 11 months in four groups. It can be seen that the trend of WAZ, LAZ, and HCZ is consistent. Preterm SGA and preterm AGA in twins grew rapidly after birth; the growth potential of preterm twins was greater than that of full-term twins. The growth velocity was faster before the age of 5–6 months, then slower. In preterm infants, there was a significant lag behind full-term infants in physical growth during the first year. Preterm SGA continuously had a lower growth level. The changes in WAZ, LAZ, and HCZ of full-term AGA and full-term SGA were slower in the first year after birth.

## 3.3. Body proportions of SGA and AGA twins

As shown in Table 5; Figure 3, the WFLZ were similar and the $Z$ scores were close to 0 in the first year; the WFLZ of SGA was smaller than that of AGA at most time points, showing a statistically significant difference at 3 months of age. The WFLZ of full-term SGA and preterm SGA did not increase significantly but decreased after 1 month of age, and WFLZ<0 after 4 months of age in full-term and preterm SGA, with the WFLZ of preterm SGA gradually approaching -1 It was suggested that after SGA experiences early accelerated catch-up growth, attention should be paid to nutritional intake after 4 months of age to ensure appropriate body proportions, especially in preterm SGA.

TABLE 2 WAZ, LAZ, and HCZ of SGA and AGA in twins under 1 year of age (X ± S).

| Age (m) | AGA | | | | SGA | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | WAZ | LAZ | HCZ | *n* | WAZ | LAZ | HCZ |
| 0 | 24 | −1.94 ± 1.18* | −2.14 ± 1.40* | −1.73 ± 1.23* | 4 | −2.59 ± 1.33 | −2.89 ± 0.89 | −1.57 ± 0.67 |
| 1 | 285 | −1.86 ± 1.20 | −2.26 ± 1.30 | −1.64 ± 1.17* | 81 | −2.39 ± 1.16 | −2.79 ± 1.22 | −1.82 ± 1.02 |
| 2 | 371 | −1.44 ± 1.35 | −2.11 ± 1.36 | −1.45 ± 1.27 | 87 | −1.92 ± 1.28 | −2.47 ± 1.29 | −1.79 ± 1.13 |
| 3 | 334 | −0.87 ± 1.26 | −1.65 ± 1.28 | −1.16 ± 1.23 | 111 | −1.58 ± 1.23 | −2.24 ± 1.21 | −1.49 ± 1.14 |
| 4 | 360 | −0.65 ± 1.19 | −1.44 ± 1.26 | −1.03 ± 1.21 | 95 | −1.53 ± 1.31 | −1.83 ± 1.29 | −1.50 ± 1.21 |
| 5 | 323 | −0.52 ± 1.18 | −1.22 ± 1.12 | −0.80 ± 1.16 | 105 | −1.22 ± 1.34 | −1.74 ± 1.08 | −1.19 ± 1.11 |
| 6 | 346 | −0.30 ± 1.14 | −0.94 ± 1.09 | −0.65 ± 1.10 | 105 | −1.22 ± 1.18 | −1.58 ± 1.05 | −1.20 ± 1.17 |
| 7 | 201 | −0.37 ± 1.11 | −0.90 ± 1.05 | −0.66 ± 1.13 | 74 | −1.35 ± 1.15 | −1.73 ± 1.14 | −1.21 ± 1.12 |
| 8 | 266 | −0.37 ± 1.15 | −0.92 ± 1.08 | −0.46 ± 1.15 | 70 | −1.23 ± 1.33 | −1.52 ± 1.21 | −1.28 ± 1.13 |
| 9 | 181 | −0.54 ± 1.16 | −1.14 ± 1.19 | −0.56 ± 1.28* | 51 | −1.28 ± 1.01 | −1.62 ± 0.92 | −0.89 ± 0.96 |
| 10 | 185 | −0.24 ± 1.14 | −0.79 ± 1.08 | −0.41 ± 1.06 | 50 | −0.97 ± 1.04 | −1.33 ± 0.95 | −0.93 ± 1.18 |
| 11 | 157 | −0.40 ± 1.12 | −0.86 ± 1.07 | −0.24 ± 1.12 | 52 | −1.26 ± 1.28 | −1.50 ± 1.27 | −1.06 ± 0.95 |

WAZ, weight for age *Z*-score; LAZ, length for age *Z*-score; HCZ, head circumference for age *Z*-score; *Compared with SGA group $p \geq 0.05$, others $p < 0.05$.

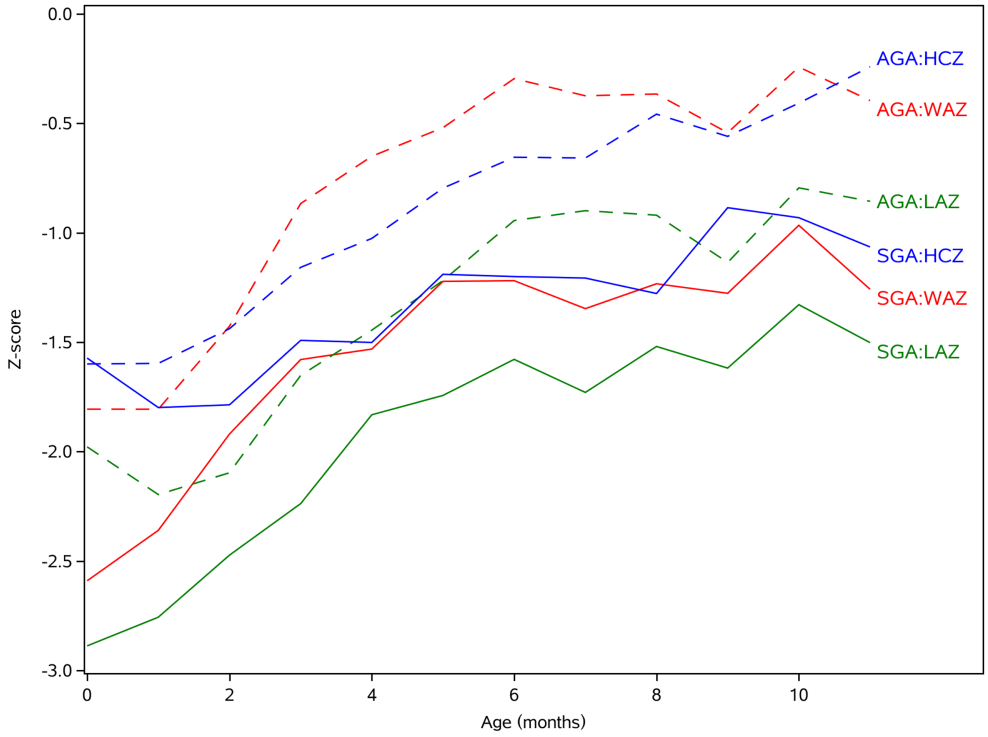



FIGURE 1
The *Z*-score of anthropometric parameters of SGA and AGA in twins under 1 year old. WAZ, weight for age *Z*-score; LAZ, length for age *Z*-score; HCZ, head circumference for age *Z*-score.

TABLE 3 WAZ, LAZ, HCZ of full-term and preterm AGA in twins under 1 year of age ($\bar{X} \pm S$).

| Age (m) | Full-term AGA | | | | Preterm AGA | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | WAZ | LAZ | HCZ | *n* | WAZ | LAZ | HCZ |
| 0 | 3 | −0.67 ± 0.14* | −1.27 ± 0.44 | −0.64 ± 0.82 | 22 | −2.12 ± 1.15 | −2.26 ± 1.45 | −1.88 ± 1.21 |
| 1 | 43 | −0.85 ± 0.89* | −1.29 ± 0.72* | −0.77 ± 1.05* | 247 | −2.03 ± 1.17 | −2.42 ± 1.30 | −1.79 ± 1.12 |
| 2 | 34 | −0.64 ± 1.10* | −1.13 ± 0.69* | −0.58 ± 0.94* | 338 | −1.52 ± 1.35 | −2.21 ± 1.37 | −1.54 ± 1.26 |
| 3 | 50 | −0.06 ± 0.82* | −0.74 ± 0.83* | −0.37 ± 0.89* | 284 | −1.02 ± 1.27 | −1.82 ± 1.28 | −1.30 ± 1.24 |
| 4 | 41 | −0.24 ± 1.05* | −0.75 ± 0.82* | −0.36 ± 0.92* | 319 | −0.70 ± 1.20 | −1.53 ± 1.28 | −1.11 ± 1.22 |
| 5 | 49 | 0.00 ± 1.10* | −0.51 ± 0.92* | −0.20 ± 0.80* | 274 | −0.61 ± 1.17 | −1.34 ± 1.11 | −0.90 ± 1.18 |
| 6 | 48 | 0.16 ± 0.90* | −0.37 ± 1.05* | −0.21 ± 0.91* | 298 | −0.37 ± 1.16 | −1.04 ± 1.07 | −0.73 ± 1.12 |
| 7 | 27 | −0.12 ± 1.07 | −0.26 ± 0.92* | −0.30 ± 0.94 | 174 | −0.41 ± 1.11 | −1.00 ± 1.04 | −0.71 ± 1.15 |
| 8 | 36 | −0.28 ± 1.18 | −0.79 ± 0.83 | −0.20 ± 1.17 | 230 | −0.37 ± 1.14 | −0.93 ± 1.12 | −0.50 ± 1.14 |
| 9 | 24 | −0.85 ± 1.39 | −1.10 ± 1.45 | −0.86 ± 1.24 | 157 | −0.50 ± 1.12 | −1.14 ± 1.15 | −0.51 ± 1.28 |
| 10 | 23 | −0.03 ± 0.98 | −0.51 ± 0.86 | −0.03 ± 1.14 | 162 | −0.27 ± 1.15 | −0.83 ± 1.10 | −0.46 ± 1.04 |
| 11 | 19 | 0.02 ± 1.10* | −0.15 ± 1.00* | −0.23 ± 1.17 | 138 | −0.45 ± 1.12 | −0.95 ± 1.05 | −0.24 ± 1.12 |

*Compared to preterm AGA, $p < 0.05$.

## 4. Discussion

The main conclusions of this study are as follows: 1. At approximately 1 year of age, the growth level of twins could reach the normal range but did not reach the average level of singleton children. The growth level of SGA in twins lagged behind that of AGA within 1 year of birth. The LAZ of SGA and AGA was lower than that of WAZ and HCZ. 2. The proportion of preterm AGA was the largest in twins, and the growth rate was the fastest. Preterm twins had greater growth potential than term twins. However, the growth level of preterm SGA was always low. 3. The WFLZ in each group was approximately close to 0. The WFLZ of SGA is smaller than that of AGA at most time points. After reaching 4 months of age, the WFLZ of twins had a downward

TABLE 4 WAZ, LAZ, and HCZ of full-term and preterm SGA in twins under 1 year of age (X ± S).

| Age (m) | Full-term SGA | | | | Preterm SGA | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | WAZ | LAZ | HCZ | *n* | WAZ | LAZ | HCZ |
| 0 | 1 | −0.61 ± 0.00 | −1.73 ± 0.00 | −0.64 ± 0.00 | 3 | −3.25 ± 0.22 | −3.27 ± 0.54 | −1.88 ± 0.29 |
| 1 | 34 | −1.81 ± 1.05* | −2.23 ± 1.15* | −1.23 ± 1.00* | 48 | −2.80 ± 1.05 | −3.20 ± 1.12 | −2.23 ± 0.82 |
| 2 | 34 | 1.42 ± 0.95 | −1.82 ± 0.93 | −1.18 ± 0.74 | 53 | −2.23 ± 1.37 | −2.87 ± 1.33 | −2.16 ± 1.17 |
| 3 | 50 | −1.00 ± 0.92* | −1.67 ± 0.83* | −0.94 ± 0.78* | 61 | −2.05 ± 1.25 | −2.70 ± 1.28 | −1.94 ± 1.20 |
| 4 | 42 | −1.12 ± 1.18* | −1.26 ± 0.90* | −1.13 ± 1.17* | 53 | −1.86 ± 1.32 | −2.28 ± 1.38 | −1.80 ± 1.16 |
| 5 | 52 | 0.65 ± 1.25 | −1.27 ± 0.92 | −0.7 ± 0.78 | 53 | −1.78 ± 1.18 | −2.2 ± 1.02 | −1.67 ± 1.18 |
| 6 | 48 | −0.81 ± 1.10* | −1.17 ± 0.84* | −0.85 ± 0.92* | 57 | −1.56 ± 1.14 | −1.92 ± 1.09 | −1.50 ± 1.27 |
| 7 | 31 | −0.83 ± 1.11* | −1.08 ± 1.00* | −0.75 ± 0.88* | 43 | −1.72 ± 1.03 | −2.20 ± 1.02 | −1.54 ± 1.17 |
| 8 | 28 | −0.87 ± 1.34 | −1.27 ± 1.16 | −1.00 ± 1.37 | 42 | −1.48 ± 1.28 | −1.68 ± 1.24 | −1.46 ± 0.91 |
| 9 | 15 | −0.71 ± 1.04* | −1.28 ± 0.94 | −0.49 ± 0.78 | 36 | −1.51 ± 0.91 | −1.76 ± 0.89 | −1.05 ± 0.99 |
| 10 | 22 | −0.58 ± 1.13* | −1.06 ± 1.02 | −0.38 ± 1.09* | 28 | −1.27 ± 0.85 | −1.54 ± 0.86 | −1.36 ± 1.08 |
| 11 | 22 | −0.81 ± 0.99* | −1.16 ± 0.96 | −0.71 ± 0.78* | 30 | −1.59 ± 1.39 | −1.75 ± 1.42 | −1.32 ± 1.00 |

*Compared to preterm SGA, $p < 0.05$.

trend. The WFLZ of preterm SGA approached −1 at about 1 year of age.

## 4.1. Comparing SGA and AGA growth velocity

### 4.1.1. Comparison of AGA and SGA

In the present study, we found that the physical indices of twins increased significantly but were still lower than the average level of singleton children at 11 months. This may be related to the low birth weight of twins. A study (13) on the physical growth of twins aged 0–4 years with birth weight discordance in twins showed that the growth level of low birth weight twins lagged behind that of normal birth weight twins. A study (11) of monozygotic twins suggested that birth weight affects not only recent physical growth and development, but also further secondary development at puberty, and hence final height. Another study (14) has shown that catch-up growth after birth is not associated with birth weight but with intrauterine growth restriction (IUGR), especially when IUGR happens at 20-32 weeks of gestational age. A study (15) on singletons showed that the mean body weight and length of AGA with IUGR were lower than those of regular AGA and that the gap was not significant at 4 months of age. This suggests that fetuses with IUGR may develop better catch-up growth after birth, especially in AGA. which may be related to higher insulin sensitivity, lower leptin levels, and lower body fat percentage (16).

This study found that the growth level of SGA twins was always lower than that of AGA twins, which is the same as that found in another study on singletons (14).In addition, this study also found that all groups had a smaller LAZ than WAZ and HCZ, suggesting that it takes a longer time to achieve length catch-up. A nationwide Japanese (17) population-based study showed that 15% of 32,533 full-term SGA twins did not show catch-up growth in height until 2 years of age, which is the same conclusion as previous singleton studies (14, 18). A Dutch study (19) showed a faster growth rate in twins after birth, although they did not reach the same height and weight until 2.5 years of age. A study (18) of 9 cities in China found that the growth patterns of infants aged 1 to 12 months under different feeding patterns were very similar, which revealed that the growth differences of infants under different feeding patterns were much smaller than the growth differences of infants under different ethnic and region. That is, recent nutrition has less impact on length catch-up than long-term nutrition and genetic factors.

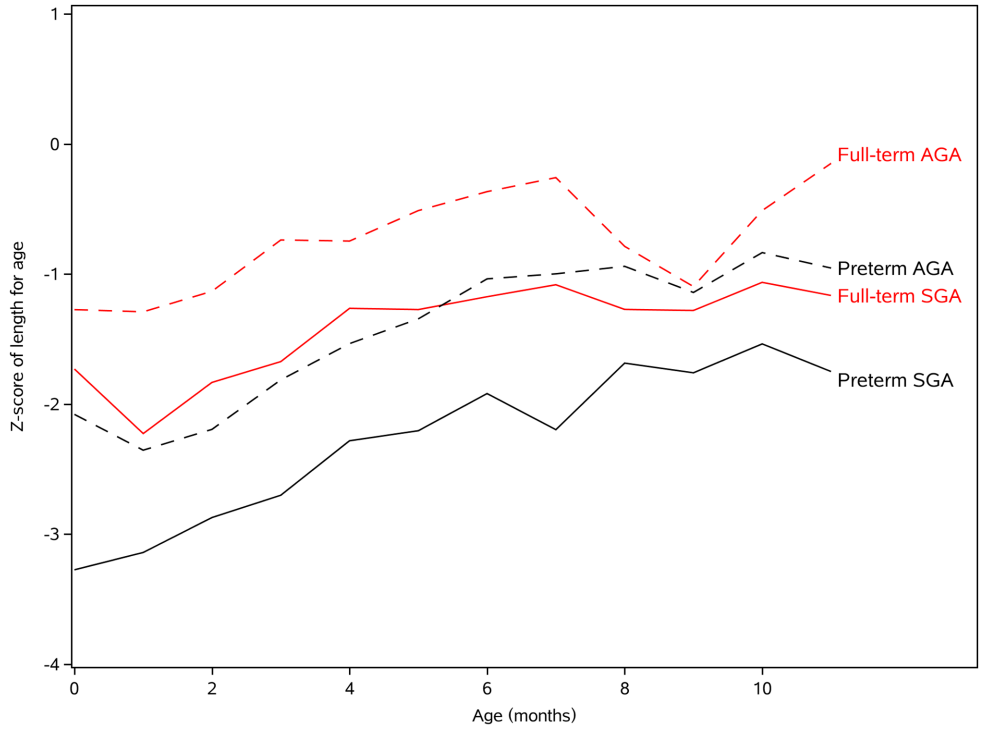
### 4.1.2. Comparison of full-term and preterm twins

In this study, the proportion of premature AGA twins was the highest and their growth velocity was the fastest. It is suggested that better catch-up growth occurs in premature AGA. The results are consistent with Anchieta et al. (20), who concluded that catch-up growth in preterm infants after delivery is closely related to birth weight. EJ McLaughlin et al. (15) showed that, compared with AGA with regular intrauterine growth rate, AGA with growth restriction had lower *Z*-scores in body weight, body length, and BMI; the difference was not significant at 4 months of age. This suggests that preterm AGA subjects may achieve catch-up growth earlier and faster than SGA infants.

On the other hand, preterm SGA has always had a lower growth level. In a singleton children study, Nagasaka et al. (21) found that preterm infants were twice as likely as full-term infants to have short stature at 3 years of age, while preterm SGA infants were 4.5 times more likely to be of short stature than full-term infants. This may be related to the risk of gastrointestinal disorders such as necrotizing enterocolitis and food allergy in premature infants. In addition, the rapid transition to breast milk after birth may result in an insufficient supply of protein and energy; the introduction time and quantity of supplementary foods and the high incidence of feeding intolerance may also lead to decreased growth in premature infants. Full-term twins will more easily achieve catch-up growth than normal singleton children due to more mature organs, phylogeny, and better nutrient uptake.

## 4.2. Body proportion is an important indicator of having appropriate catch-up growth or not

Another issue that needs to be addressed is the prevention of excessive catch-up growth to reduce the risk of childhood excess weight, obesity, hypertension, and the risk of developing type 2 diabetes, cardiovascular disease, and metabolic syndrome in adulthood. Therefore, we need to pay attention to the change in body proportion (expressed as WFLZ in this study). In this study, the WFLZ values in the early postnatal period were similar and in the normal range (close to 0) in all groups. In singleton studies, BMI increased faster at 0 to 3 months after birth for



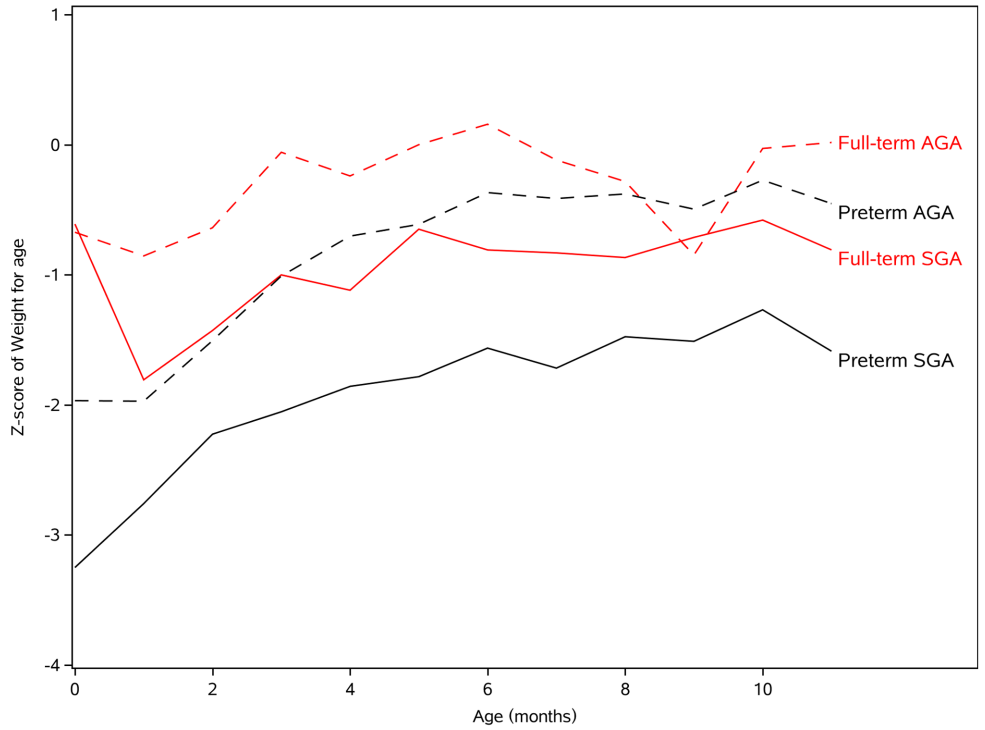




FIGURE 2 (Continued)

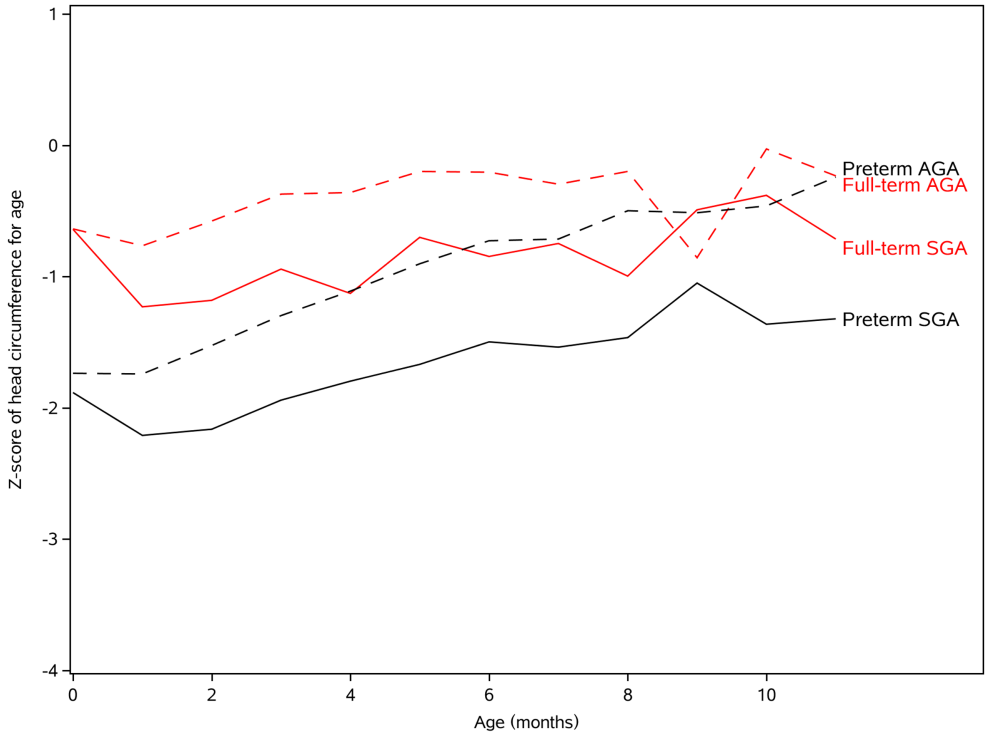



FIGURE 2
The WAZ, LAZ, and HCZ of preterm AGA, full-term AGA, preterm SGA, and full-term SGA in Twins.

TABLE 5 WFLZ of preterm AGA, full-term AGA, preterm SGA, and full-term SGA in twins ($\bar{X} \pm S$).

| Age (m) | Full-term AGA | Preterm AGA | Full-term SGA | Preterm SGA | *p* |
|---|---|---|---|---|---|
| 0 | 0.69 ± 0.63 | 0.06 ± 2.50 | 1.43 ± 0.00 | −0.87 ± 0.44 | 0.1416 |
| 1 | 0.49 ± 0.96 | 0.43 ± 1.67 | 0.35 ± 0.97 | 0.21 ± 1.74 | 0.1165 |
| 2 | 0.51 ± 1.19 | 0.71 ± 1.16 | 0.27 ± 0.99 | 0.54 ± 1.29 | 0.1861 |
| 3 | 0.70 ± 0.90 | 0.67 ± 0.93 | 0.48 ± 0.96 | 0.29 ± 0.93 | 0.0192 |
| 4 | 0.40 ± 1.04 | 0.65 ± 0.96 | −0.27 ± 1.22 | −0.07 ± 0.82 | <0.001 |
| 5 | 0.50 ± 1.00 | 0.46 ± 1.05 | 0.30 ± 1.2 | −0.3 ± 1.06 | <0.001 |
| 6 | 0.61 ± 0.72 | 0.44 ± 1.07 | −0.04 ± 1.06 | −0.37 ± 1.10 | <0.001 |
| 7 | 0.12 ± 0.96 | 0.31 ± 1.07 | −0.19 ± 0.94 | −0.26 ± 0.99 | <0.05 |
| 8 | 0.26 ± 1.14 | 0.27 ± 1.02 | −0.18 ± 1.19 | −0.61 ± 1.20 | <0.001 |
| 9 | −0.06 ± 0.97 | 0.21 ± 0.96 | 0.01 ± 1.00 | −0.69 ± 0.96 | <0.001 |
| 10 | 0.33 ± 0.94 | 0.25 ± 1.04 | −0.01 ± 1.01 | −0.62 ± 0.80 | <0.001 |
| 11 | 0.13 ± 0.97 | 0.04 ± 1.03 | −0.31 ± 1.04 | −0.92 ± 1.11 | <0.001 |

*p* is the comparison among the four groups by Analysis of Variance (ANOVA).

preterm SGA than for full-term SGA and AGA twins; it increased with age but decreased after 8 months of age (22, 23). In the present study, the WFLZ of SGA decreased gradually after 4 months of age. It is suggested that nutritional intake after 4 months of age should receive more attention so as to ensure body shape proportion after early accelerated catch-up growth of SGA, especially for premature SGA infants.

The 2019 Infant Feeding and Nutrition Guidelines (24) state that breastfeeding should be the first choice for SGA feeding and that the choice of feeding method should be based on gestational age rather than birth weight. For full-term SGA, regular use of the preterm formula is not recommended to promote better growth. However, this study suggests that for twins with SGA, close monitoring of growth and individualized nutritional guidance are necessary if intensive feeding is required. For twins with AGA, attention should be paid to monitoring physical growth to avoid adverse long-term outcomes caused by overfeeding.

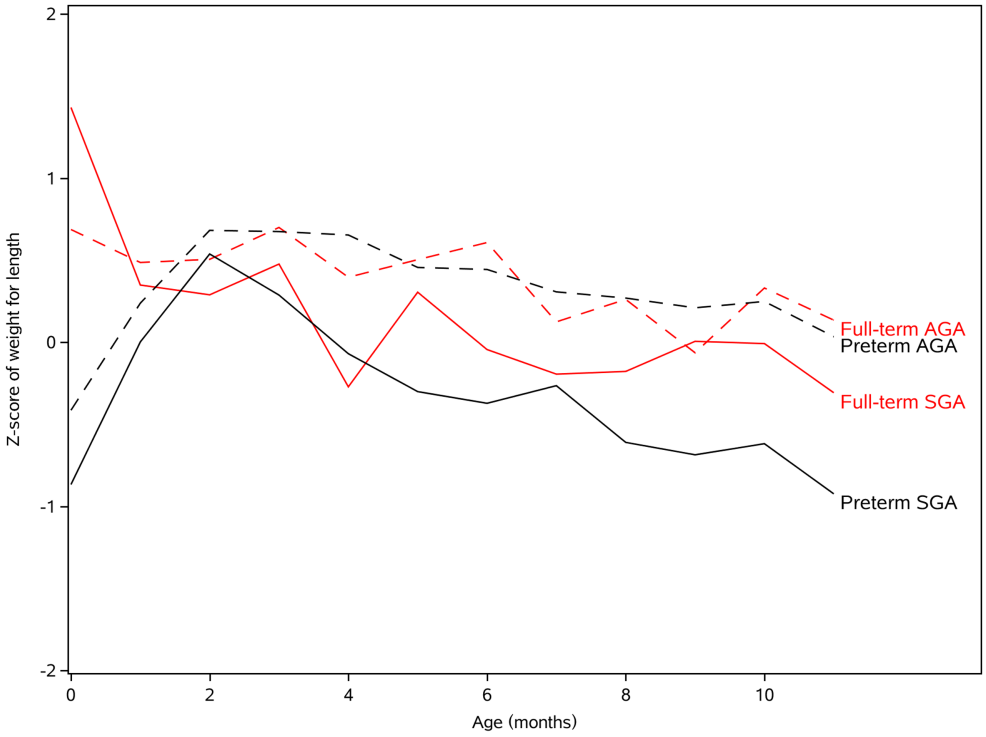



FIGURE 3
The *Z*-score of weight for length (WFLZ) of preterm AGA, full-term AGA, preterm SGA, and full-term SGA in twins.

## 5. Conclusion

In summary, the physical growth of twins during the first year of life may be more complex than that of singletons. Twins can achieve normal range, which is above mean-2SD in the first year after birth but may not reach the average level of singleton children of the same age. The growth level of twins with SGA lags behind that of AGA, especially preterm SGA, so more attention should be paid to SGA in twins. After achieving catch-up growth in the early stage of SGA, we should give proper nutritional guidance after 4 months of age to ensure the appropriate body proportion of SGA twins. Although the number of participants in the study was relatively large, there were only a few participants in some age groups, particularly in the case of SGA and full-term AGA children. More children should be enrolled and followed up regularly in future studies.

## Data availability statement

The datasets generated and analyzed during the current study are not publicly available due to patients' privacy concerns but are available from the corresponding author upon reasonable request.

## Ethics statement

The studies involving humans were approved by the Institutional Review Board of Children's Hospital of Chongqing Medical University (CHCMU). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because The present study was an observational and retrospective study, it did not need to use human biological specimens. We applied for the exemption from the need for informed consent and was reviewed and approved by the Institutional Review Board of Children's Hospital of Chongqing Medical University (CHCMU). The Institutional Review Board of CHCMU waived the need for informed consent.

## Author contributions

XZ conceptualized and designed the study, acquired funding, conducted the data analysis, and reviewed and revised the manuscript. TP and YrH drafted the initial manuscript and revised it. QCg, LC, YH, YD, XL, ZJ, YZ, ZZ, QC, and QZ acquired the data and were responsible for the follow-up of these children. All authors approved the final version of this manuscript and agreed to its publication.

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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



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# Comparison of three malnutrition screening tools prior to allogeneic hematopoietic stem-cell transplantation

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**Background:** Previous studies have shown that malnutrition before hematopoietic stem cell transplantation (HSCT) is associated with poor patient prognoses. There is inconsistency among studies on which nutritional status screening tool is appropriate for malnutrition diagnosis before allo-HSCT. The present study aimed to compare nutritional screening tools in patients with leukemia before allo-HSCT.

**Methods:** An observational, cross-sectional, and single-center study was conducted in Tehran, Iran. One hundred four adults allo-HSCT candidates aged 18-55 years with leukemia were selected sequentially. Malnutrition assessment was done using three tools, the Global Leadership Initiative on Malnutrition (GLIM), nutritional risk screening 2002 (NRS-2002) and European Society for Clinical Nutrition and Metabolism (ESPEN) criteria. The agreement between malnutrition assessment tools was evaluated with Cohen's kappa.

**Results:** The agreement between GLIM and NRS-2002 was perfect ($\kappa$ =0.817, $p$ <0.001), while the agreement between GLIM and ESPEN was fair ($\kappa$ =0.362, $p$ <0.001). The agreement between NRS-2002 and ESPEN was fair ($\kappa$ =0.262, $p$ <0.001). We also found a moderate agreement for all tools ($\kappa$ =0.489, $p$ <0.001).

**Conclusion:** NRS-2002 is an accepted tool for screening malnutrition in hospitalized patients. In the current study, the GLIM criterion perfectly agreed with the NRS-2002. Further studies in the HSCT setting are needed to introduce a valid tool.

KEYWORDS

**hematopoietic stem cell transplantation, leukemia, malnutrition, global leadership initiative on malnutrition, GLIM**

# Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a usual treatment for hematological diseases like leukemia (1). Even though life expectancy is incremented, treatment is related to a range of complications, among which changes in nutritional status (inadequate consumption or uptake of nutrients) have been shown as the most frequent (2, 3). Due to the disease, patients experience metabolic and endocrine alterations, which could provoke catabolic and inflammatory processes (4, 5). Furthermore, the nutritional status of patients may be affected due to gastrointestinal dysfunctions as a side effect of receiving various high-dose systematic radiation and/or chemical therapies before transplantation (6). Poor nutritional status increases the risk of emerging complications, including mucositis or fungal infections, higher mortality rate, and longer lengths of hospital stay (7, 8). Therefore, evaluating the nutritional status of HSCT patients with leukemia, providing nutritional support in advance, and maintaining patients in a well-nourished state are prominent for bone marrow and immune rebuilding (6, 9).

Few studies demonstrated nutritional screening tools to diagnose malnutrition in patients with hematological malignancies prior to HSCT, and none has presented conclusive evidence that verified which tool is obviously superior (10, 11). Among these tools, the European Society for Clinical Nutrition and Metabolism (ESPEN) (12) and nutritional risk screening 2002 (NRS-2002) criteria (13) have been widely used in oncology patients.

Notably, the Global Leadership Initiative on Malnutrition (GLIM) criteria were suggested by nutritional scientific societies in 2019 for diagnosing malnutrition (14). It consists of some phenotypic criteria (weight loss, decreases in body mass index (BMI), or loss of muscle reserve) and etiological criteria (decreased intake, acute or chronic stress) being prominent to recognize a minimum of one of each to be considered malnourished. Although GLIM criteria have been used in a few oncology studies, some showed that GLIM is sensitive and recommended for diagnosing malnutrition in hospitalized patients with cancer (15).

Until now, no study evaluates the malnutrition status of patients with leukemia who are candidates for allo-HSCT with GLIM criteria. A few studies compare the GLIM criteria with other previously utilized criteria, including NRS-2002 and ESPEN. We explained that NRS-2002 offers a holistic assessment, ESPEN's evidence-based nature ensures a comprehensive framework, and GLIM criteria incorporate the latest advancements. This comparison enables us to identify the most appropriate criteria in the clinical setting. Therefore, this study aimed to compare the diagnostic test accuracy of the GLIM, NRS-2002, and ESPEN criteria for malnutrition diagnosis before allo-HSCT in patients with leukemia. This combination of tools ensures a thorough evaluation of nutritional risk in the context of allo-HSCT.

# Materials and methods

## Design and sample

An observational, cross-sectional, and single-center study was conducted in the Hematology Center of Shariati Hospital, Tehran, Iran. One hundred four adult allo-HSCT candidates aged 18–55 years with leukemia hospitalized in bone marrow transplant wards from November 2021 to December 2022 were selected sequentially. Patients with leukemia were eligible for inclusion if they were aged between 18 and 55 and candidates for allo-HSCT.

The exclusion criteria were refusal to be involved in this study, and patients who were candidates for autologous transplantation.

## Demographic and clinical assessments

Demographic variables such as age, sex (male or female), and clinical variables of the patients, which included the type of malignancy (acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL)), complete remission (CR) status (CR = 1, CR = 2, CR = 3), and risk status (favorable, intermediate, and adverse) were extracted from the patient's medical records.

## Functional status assessment

The functional status of patients was assessed based on the Karnofsky functional status index, which includes a score from 0 (dead) to 100 (normal) with 10-point intervals (16). A score of 80 (the patient can perform normal activities with effort) was considered the cut-off, and the patients were subdivided into two groups, >80 and ≤80.

## Anthropometric and body composition assessment

Body weight was measured using a digital scale (Seca, Hamburg, Germany) with an accuracy of 0.1 kg. Height was assessed using a tape measure attached to the wall and an accuracy of 0.5 cm. BMI was calculated by dividing weight (kg) by the square of height ($m^2$).

The Tanita (BC-418's) device was used to evaluate body composition during fasting conditions, with minimal water consumption and little exercise before the test and after defecation. This device offers independent analysis for various organs (right and left hand and right and left foot) and the trunk due to employing eight electrodes (two beneath the right foot and two in the right and left hand). Before the assessment, all the anthropometric devices were calibrated.

## Dietary assessment

Daily calorie intake and consumption of macronutrients (carbohydrate, protein, and fat) of all patients was checked by a trained dietitian with 3-day 24-h dietary recalls (2 non-consecutive normal days and 1 day off). The recorded amount of each food using the scale guide for Iranian households was converted to grams (17), and analyzed using the United States Department of Agriculture food composition database (18).

## Malnutrition assessment

Nutritional assessment was conducted by a trained evaluator who remained blinded during the initial 48 h of hospitalization. Three tools were utilized for this purpose: the NRS-2002 for nutritional screening to identify patients at risk, and the GLIM and ESPEN criteria for diagnosing malnutrition. The GLIM criteria requires at least one

phenotypic and etiological criteria for malnutrition diagnosis (14). Phenotypic criteria include unwanted weight loss (weight loss of 5–10% in 6 months or 10–20% in more than 6 months), age-related BMI (>20 kg/m$^2$ for <70 years and < 22 kg/m$^2$ for ≥70 years) and reduced muscle mass. In the current study, the reduction of muscle mass was considered based on Appendicular Skeletal Muscle Index (ASMI, kg/m2) <7 for men and ASMI <5.7 for women. Etiological criteria include reduced energy expenditure, chronic gastrointestinal status, disease burden, and inflammatory conditions. According to the definition of GLIM criteria, disease burden, and inflammation were considered positive in all patients in the current study.

Assessment of nutritional status based on NRS-2002 is done using a questionnaire. The main components of this questionnaire were: 1) the severity of the impact of the primary disease on the nutritional status; 2) recent changes in body weight (during the last one to 3 months); 3) Change in food intake during the last week; 4) BMI; If the evaluated person is 70 years old or more, one point will be added to the sum of her points. NRS score equal to 3 and more than 3 is defined as a nutritional risk (13).

The ESPEN criteria have proposed two methods to diagnose malnutrition. The first method is BMI <18.5, and the second method is a combination of unwanted weight loss (more than 10% of normal weight in an unlimited time or more than 5% in 3 months) along with low BMI (<22 kg/m$^2$ for patients ≥70 years old and < 20 kg/m$^2$ for <70 years) or low fat-free mass index (FFMI) (<15 kg/m$^2$ in women and < 17 kg/m$^2$ in men) (19).

## Calculation of sample size

According to a previous study comparing NRS2002 and GLIM (20) with area under the curve (AUC) of 0.896, considering alpha = 0.05, power = 80%, and precision of 10%, the minimum required sample size was estimated to be 94 patients using PASS 2023 Power Analysis and Sample Size Software (2023). NCSS, LLC. Kaysville, Utah, United States, ncss.com/software/pass. Therefore, taking into account 10% drop-out rate, the sample size was finally determined to be 104 patients (21).

## Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the normality of continuous variables. Demographic, clinical, and anthropometric variables, as well as dietary intakes of patients in accordance with malnutrition status (defined by GLIM, NRS-2002, and ESPEN), were evaluated by independent sample t-test or Mann–Whitney test and Chi-squared or Fisher's exact test for continuous and categorical variables, respectively. The agreement between the two malnutrition assessment tools was evaluated with Cohen's kappa (22). Fleiss' kappa was used to assess the agreement between three malnutrition screening tools (23). The agreement of the instruments in subgroups, including sex, type of leukemia, CR, and risk status, were also examined. The Kappa value varies from 0 to 1, and its interpretation is as follows: <0.2 is weak, 0.2–0.4 is fair, 0.4–0.6 is moderate, 0.6–0.8 is substantial, and > 0.8 is perfect. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to assess the effectiveness of diagnostic tests. $p$ value <0.05 was considered significant. Statistical analysis was performed with SPSS (version 24.0 Armonk, New York, NY, United States).

## Ethical considerations

The ethics committee of Tehran University of Medical Sciences evaluated and approved this project (Ethics code: IR.TUMS.MEDICINE.REC.1400.1089). A signed consent form was obtained from all the participants.

# Results

Table 1 presents demographic and clinical variables according to the GLIM, NRS-2002, and ESPEN criteria. In total, 104 patients (41.3% female) were recruited. The mean ± SD age of the patients was 35.5 ± 10.4 years (median = 38 years, range = 19–55). AML was the most frequent type of leukemia ($n$ = 67, 64.4%). The GLIM and NRS-2002 indicated the highest percentage of patients with malnutrition (26 and 33.6%), and the ESPEN criteria indicated the lowest percentage of patients with malnutrition (8.65%). Patients without malnutrition were more prone to be in the first CR for all tools (all $p$ < 0.05). The NRS-2002 showed that patients without malnutrition were more prone to AML than ALL ($p$ = 0.049); however, the adverse risk of disease was higher ($p$ = 0.012).

Anthropometric variables of patients according to the GLIM, NRS-2002, and ESPEN criteria are summarized in Table 2. According to three screening tools, patients not suffering from malnutrition were more prone to having higher weight, BMI, FFMI, and ASM than those with malnutrition (all $p$ < 0.05). Although GLIM and ESPEN criteria indicated that FM was significantly higher in patients without malnutrition, this relation was insignificant based on NRN-2002. No significant difference was observed between malnourished and well-nourished groups for all tools regarding BF (all $p$ > 0.05).

The detailed results of the sensitivity, specificity, positive and negative predictive values for all patients and according to sex, type of leukemia, CR, and risk of disease are available in Table 3. All findings were subdivided based on the two comparisons: 1) GLIM vs. NRS-2002, 2) GLIM vs. ESPEN, and 3) ESPEN vs. NRS-2002.

## Results for all patients

GLIM indicated sensitivity and specificity of 100 and 77.14% when comparing the GLIM with NRS-2002 as a reference tool, and 80 and 88.89% when comparing the GLIM with ESPEN as reference tool, the agreement between GLIM and NRS-2002 was perfect (κ = 0.817, $p$ < 0.001), while the agreement between GLIM and ESPEN was fair (κ = 0.362, $p$ < 0.001). Moreover, when comparing the ESPEN with NRS-2002 as a reference tool, ESPEN showed a sensitivity of 93.55%, while the specificity was 22.86%. The agreement between these two instruments was fair (κ = 0.262, $p$ < 0.001). We also found a moderate agreement between GLIM, NRS-2002, and ESPEN (κ = 0.489, $p$ < 0.001) (Table 3).

## Results per gender

In male patients, the agreement between GLIM and NRS-2002 was perfect (κ = 0.915, $p$ < 0.001); however, the agreement between GLIM and ESPEN (κ = 0.274, $p$ = 0.002), and between ESPEN and

TABLE 1 Demographic and clinical variables according to the GLIM criteria, NRS-2002, and ESPEN criteria.

| Variables | Total ($n$ = 104) | GLIM criteria | | $p$-value | NRS-2002 | | $p$-value | ESPEN criteria | | $p$-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No malnutrition ($n$ = 77) | Malnutrition ($n$ = 27) | | No malnutrition ($n$ = 69) | Malnutrition ($n$ = 35) | | No malnutrition ($n$ = 95) | Malnutrition ($n$ = 9) | |
| *Gender, n (%)* | | | | | | | | | | |
| Male | 61 (58.7) | 46 (59.7) | 15 (55.6) | 0.704 | 44 (63.8) | 17 (48.6) | 0.137 | 37 (38.9) | 6 (66.7) | 0.157[a] |
| Female | 43 (41.3) | 31 (40.3) | 12 (44.4) | | 25 (36.2) | 18 (51.4) | | 58 (61.1) | 3 (33.3) | |
| *Age (years)* | 35.50 ± 10.37 | 38.61 ± 10.75 | 38.19 ± 38 | 0.856 | 39.03 ± 10.87 | 37.46 ± 9.38 | 0.468 | 38.95 ± 10.56 | 33.78 ± 6.83 | 0.154 |
| *Type of leukemia, n (%)* | | | | | | | | | | |
| AML | 67 (64.4) | 53 (68.8) | 14 (51.9) | 0.113 | 49 (71.0) | 18 (51.4) | **0.049** | 64 (67,4) | 3 (33.3) | 0.065[a] |
| ALL | 37 (35.6) | 24 (31.2) | 13 (48.1) | | 20 (29.0) | 17 (48.6) | | 31 (32.6) | 6 (66.7%) | |
| *CR, n (%)* | | | | | | | | | | |
| CR = 1 | 79 (76.0) | 63 (81.8) | 16 (59.3) | **0.008** | 58 (84.1) | 21 (60.0) | **0.011** | 73 (76.8) | 6 (66.7) | **<0.001** |
| CR = 2 | 20 (19.2) | 13 (16.9) | 7 (25.9) | | 10 (14.5) | 10 (28.6) | | 20 (21.1) | 0 (0) | |
| CR = 3 | 5 (4.8) | 1 (1.3) | 4 (14.8) | | 1 (1.4) | 4 (11.4) | | 2 (2.1) | 3 (33.3) | |
| *Risk status, n (%)* | | | | | | | | | | |
| Favorable | 3 (2.9) | 2 (3.1) | 1 (3.7) | 0.054 | 2 (3.6) | 1 (2.9) | **0.012** | 2 (2.4) | 1 (11.1) | 0.202 |
| Intermediate | 12 (11.5) | 12 (18.8) | 0 (0) | | 12 (21.4) | 0 (0) | | 12 (14.6) | 0 (0) | |
| Adverse | 76 (83.5) | 50 (78.1) | 26 (96.3) | | 42 (75) | 34 (97.1) | | 68 (82.9) | 8 (88.9) | |
| *Functional status, n (%)* | | | | | | | | | | |
| >80 | 101 (97.1) | 76 (98.7) | 25 (92.6) | 0.164[a] | 68 (98.6) | 33 (94.3) | 0.26[a] | 94 (98.9) | 7 (77.8) | **0.019**[a] |
| ≤80 | 3 (2.9) | 1 (1.3) | 2 (7.4) | | 1 (1.4) | 2 (5.7) | | 1 (1.1) | 2 (22.2) | |

AML, Acute myeloid leukemia; ALL, Acute lymphocytic leukemia; CR, complete remission; GLIM, Global Leadership Initiative on Malnutrition; NRS-2002, Nutrition Risk Screening 2002.
The data are presented as mean ± standard deviation (SD) or percent.[a]Calculated by Fisher test. We meant to use bold to show statistical significance ($p < 0.05$).





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TABLE 2 Anthropometric variables according to the GLIM criteria, NRS-2002, and ESPEN criteria.

| Variable | Total ($n$ = 104) | GLIM criteria | | $p$-value | NRS-2002 | | $p$-value | ESPEN criteria | | $p$-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No malnutrition ($n$ = 77) | Malnutrition ($n$ = 27) | | No malnutrition ($n$ = 69) | Malnutrition ($n$ = 35) | | No malnutrition ($n$ = 95) | Malnutrition ($n$ = 9) | |
| Anthropometric variables | | | | | | | | | | |
| Weight (kg) | 78.87 ± 15.49 | 81.95 ± 14.33 | 70.11 ± 15.58 | **<0.001** | 81.88 ± 14.79 | 72.96 ± 15.37 | **0.005** | 81.10 ± 14.10 | 55.40 ± 8.68 | **<0.001** |
| BMI (kg/m$^2$) | 26.49 ± 4.35 | 27.51 ± 3.61 | 23.58 ± 5.01 | **<0.001** | 27.37 ± 3.61 | 24.76 ± 5.17 | **0.010** | 27.19 ± 3.81 | 19.10 ± 2.45 | **<0.001** |
| FFM (kg) | 57.97 ± 13.11 | 59.53 ± 12.87 | 53.51 ± 13.01 | **0.043**[a] | 60.29 ± 12.86 | 53.39 ± 12.56 | **0.012**[a] | 59.34 ± 12.58 | 43.41 ± 9.62 | **0.001**[a] |
| FM (kg) | 20.91 ± 8.98 | 22.41 ± 8.37 | 16.61 ± 9.44 | **0.003**[a] | 21.59 ± 8.21 | 19.56 ± 10.35 | 0.294[a] | 21.75 ± 8.72 | 11.98 ± 6.95 | **0.003**[a] |
| BF (%) | 26.33 ± 9.64 | 27.40 ± 9.04 | 23.29 ± 10.79 | 0.056 | 26.39 ± 8.59 | 26.22 ± 11.58 | 0.942 | 26.78 ± 9.41 | 21.57 ± 11.36 | 0.122 |
| ASM (kg) | 25.84 ± 6.38 | 26.65 ± 6.27 | 23.52 ± 6.24 | **0.027**[a] | 27.01 ± 6.22 | 23.53 ± 6.14 | **0.008** | 26.52 ± 6.12 | 18.62 ± 4.52 | **<0.001**[a] |

BF, body fat; BMI, body mass index; FFM, fat free mass; FM, fat mass; ASM, Appendicular Skeletal Muscle; GLIM, Global Leadership Initiative on Malnutrition; NRS-2002, Nutrition Risk Screening 2002; SMM, skeletal muscle mass.
The data are presented as mean ± standard deviation (SD). [a]Calculated by Mann–Whitney test. We meant to use bold to show statistical significance ($p < 0.05$).

NRS-2002 (κ = 0.236, $p$ = 0.004) were fair. We also found a moderate agreement between GLIM, NRS-2002, and ESPEN (κ = 0.505, $p$ < 0.001). In female patients, the agreement between GLIM and NRS-2002 was substantial (κ = 0.699, $p$ < 0.001), and the agreement between GLIM and ESPEN was moderate (κ = 454, $p$ = 0.001). However, the agreement between ESPEN and NRS-2002 was fair (κ = 0.262, $p$ = 0.026). We also found a moderate agreement between GLIM, NRS-2002, and ESPEN (κ = 0.461, $p$ < 0.001) (Table 3).

## Results per type of leukemia

In AML patients, the agreement between GLIM and NRS-2002 was perfect (κ = 0.837, $p$ < 0.001), while the agreement between GLIM and ESPEN was slight (κ = 0.174, $p$ = 0.046). There was no significant agreement between ESPEN and NRS-2002. We observed a fair deal between these three tools (κ = 0.400, $p$ = 0.008). In ALL patients, our results indicated substantial agreement between GLIM and NRS-2002 (κ = 0.778, $p$ < 0.001) and moderate agreement between GLIM and ESPEN (κ = 0.527, p < 0.001). Nevertheless, there was a fair agreement between ESPEN and NRS-2002 (κ = 0.371, $p$ = 0.004). Also, the agreement between these three tools was moderate (κ = 0.496, $p$ < 0.001) (Table 3).

## Results per complete remission

In patients in the first CR, the agreement between GLIM and NRS-2002 was perfect (κ = 0.825, $p$ < 0.001), while the agreement between GLIM and ESPEN (κ = 0.387, $p$ < 0.001) and between ESPEN and NRS-2002 (κ = 0.286, $p$ = 0.001) were fair. We found a moderate agreement between all three mentioned tools (κ = 0.517, $p$ < 0.001). In patients who achieved a second CR, the agreement between GLIM and NRS-2002 was substantial (κ = 0.700, $p$ = 0.001). The agreement between GLIM, ESPEN, and NRS-2002 was not significant. In patients in the third CR, the agreement between GLIM and NRS-2002 was perfect (κ = 1.000, $p$ = 0.025), while the agreement between GLIM and ESPEN and between ESPEN and NRS-2002 were insignificant. We found a substantial agreement between these three tools (κ = 0.659, $p$ = 0.011) (Table 3).

## Results per risk status

In patients with a favorable risk of disease, although we observed no significant agreement between tools when comparing them two by two, a perfect agreement between GLIM, ESPEN, and NRS-2002 was seen (κ = 1.000, $p$ = 0.003). In patients with adverse risk of disease, the agreement between GLIM and NRS-2002 was substantial (κ = 0.782, $p$ < 0.001); however, the agreement between GLIM and ESPEN (κ = 0.299, $p$ = 0.001) and ESPEN and NRS-2002 (κ = 0.196, $p$ = 0.010) were fair and slight, respectively. We also found a moderate agreement between these three tools (κ = 0.413, $p$ < 0.001) (Table 3).

# Discussion

This study is one of the first to compare different tools for evaluating malnutrition in patients with leukemia who are also

TABLE 3 Statistical results comparing GLIM criteria, NRS-2002, and ESPEN criteria in all patients and according to sex, type of leukemia, CR, and risk of disease.

| Tools | Sensitivity % (95% CI) | Specificity % (95% CI) | Positive predictive value % (95% CI) | Negative predictive value % (95% CI) | kappa value (P) | Kappa Fleiss (P)[a] |
|---|---|---|---|---|---|---|
| **All patients** | | | | | | 0.489 (<**0.001**) |
| GLIM vs. NRS-2002 | 100 (94.79 to 100) | 77.14 (59.86 to 89.58) | 89.61 (82.43 to 94.07) | 100 (NA) | 0.817 (<**0.001**) | |
| GLIM vs. ESPEN | 80 (70.54 to 87.51) | 88.89 (51.75 to 99.72) | 98.70 (92.27 to 99.79) | 29.63 (20.94 to 40.10) | 0.362 (<**0.001**) | |
| ESPEN vs. NRS-2002 | 93.55 (92.19 to 99.96) | 22.86 (10.42 to 40.14) | 71.58 (67.72 to 75.14) | 88.89 (51.02 to 98.40) | 0.262 (<**0.001**) | |
| **Sex** | | | | | | |
| *Male* | | | | | | 0.505 (<**0.001**) |
| GLIM vs. NRS-2002 | 100 (91.96 to 100) | 88.24 (63.56 to 98.54) | 95.65 (85.68 to 98.78) | 100 (NA) | 0.915 (<**0.001**) | |
| GLIM vs. ESPEN | 79.31 (66.65 to 88.83) | 100 (29.24 to 100) | 100 | 20 (13.12 to 29.27) | 0.274 (**0.002**) | |
| ESPEN vs. NRS-2002 | 100 (91.96 to 100) | 17.65 (3.80 to 43.43) | 75.86 (71.61 to 79.66) | 100 (NA) | 0.236 (**0.004**) | |
| *Female* | | | | | | 0.461 (<**0.001**) |
| GLIM vs. NRS-2002 | 100 (86.28 to 100) | 66.67 (40.99 to 100) | 80.65 (68.43 to 88.90) | 100 (NA) | 0.699 (<**0.001**) | |
| GLIM vs. ESPEN | 81.08 (64.84 to 92.04) | 83.33 (35.88 to 99.58) | 96.77 (83.27 to 99.45) | 41.67 (25.10 to 60.36) | 0.454 (**0.001**) | |
| ESPEN vs. NRS-2002 | 96 (79.65 to 99.90) | 27.78 (9.69 to 53.48) | 64.86 (57.83 to 71.31) | 83.33 (38.93 to 97.51) | 0.262 (**0.026**) | |
| **Type of leukemia** | | | | | | |
| *AML* | | | | | | 0.400 (**0.008**) |
| GLIM vs. NRS-2002 | 100 (92.75 to 100) | 77.78 (52.36 to 93.59) | 92.45 (83.77 to 96.67) | 100 (NA) | 0.837 (<**0.001**) | |
| GLIM vs. ESPEN | 81.25 (69.54 to 89.92) | 66.67 (9.43 to 99.16) | 98.11 (91.27 to 99.62) | 14.29 (6.06 to 30.09) | 0.174 (**0.046**) | |
| ESPEN vs. NRS-2002 | 97.96 (89.15 to 99.95) | 11.11 (1.38 to 34.71) | 75.0 (71.71 to 78.02) | 66.67 (16.17 to 95.40) | 0.123 (0.112) | |
| *ALL* | | | | | | 0.4969 (<0.001) |
| GLIM vs. NRS-2002 | 100 (83.16 to 100) | 76.47 (50.10 to 93.19) | 83.33 (67.97 to 92.18) | 100 (NA) | 0.778 (<0.001) | |
| GLIM vs. ESPEN | 77.42 (58.90 to 90.41) | 100 (54.07 to 100) | 100 (NA) | 46.15 (30.87 to 62.19) | 0.527 (<0.001) | |
| ESPEN vs. NRS-2002 | 100 (83.16 to 100) | 35.29 (14.21 to 61.67) | 64.52 (56.14 to 72.09) | 100 (NA) | 0.371 (0.004) | |
| **CR** | | | | | | |
| *CR = 1* | | | | | | 0.517 (<**0.001**) |
| GLIM vs. NRS-2002 | 100 (93.84 to 100) | 76.19 (52.83 to 91.78) | 92.06 (84.37 to 96.14) | 100 (NA) | 0.825 (<**0.001**) | |
| GLIM vs. ESPEN | 84.93 (74.64 to 92.23) | 83.33 (35.88 to 99.58) | 98.41 (91.18 to 99.73) | 31.25 (19,15 to 46.59) | 0.387 (<**0.001**) | |
| ESPEN vs. NRS-2002 | 98.28 (90.76 to 99.96) | 23.81 (8.22 to 47.17) | 78.08 (73.67 to 81.94) | 83.33 (38.25 to 97.58) | 0.286 (**0.001**) | |
| *CR = 2* | | | | | | 0.179 (0.432) |
| GLIM vs. NRS-2002 | 100 (69.15 to 100) | 70.0 (34.75 to 93.33) | 76.92 (56.39 to 89.57) | 100 (NA) | 0.700 (**0.001**) | |
| GLIM vs. ESPEN | – | – | – | – | – | |
| ESPEN vs. NRS-2002 | – | – | – | – | – | |
| *CR = 3* | | | | | | 0.659 (**0.011**) |
| GLIM vs. NRS-2002 | 100 (2.5 to 100) | 100 (39.76 to 100) | 100 (NA) | 100 (NA) | 1.000 (**0.025**) | |
| GLIM vs. ESPEN | 50 (1.26 to 98.74) | 100 (29.24 to 100) | 100 (NA) | 75.0 (42.87 to 92.31) | 0.545 (0.171) | |
| ESPEN vs. NRS-2002 | 100 (2.50 to 100) | 75.0 (19.41 to 99.37) | 50.0 (15.48 to 84.52) | 100 (NA) | 0.545 (0.171) | |
| **Risk status** | | | | | | |
| *Favorable* | | | | | | 1.000 (**0.003**) |
| GLIM vs. NRS-2002 | 100 (15.18 to 100) | 100 (2.50 to 100) | 100 (NA) | 100 (NA) | 1.000 (0.083) | |
| GLIM vs. ESPEN | 100 (15.81 to 100) | 100 (2.50 to 100) | 100 (NA) | 100 (NA) | 1.000 (0.083) | |
| ESPEN vs. NRS-2002 | 100 (15.81 to 100) | 100 (2.50 to 100) | 100 (NA) | 100 (NA) | 1.000 (0.083) | |

*(Continued)*

TABLE 3 (Continued)

| Tools | Sensitivity % (95% CI) | Specificity % (95% CI) | Positive predictive value % (95% CI) | Negative predictive value % (95% CI) | kappa value (P) | Kappa Fleiss (P)[a] |
|---|---|---|---|---|---|---|
| **Adverse** | | | | | | 0.413 (<**0.001**) |
| GLIM vs. NRS-2002 | 100 (91.59 to 100) | 76.47 (58.83 to 89.25) | 84.0 (74.12 to 90.59) | 100 (NA) | 0.782 (<**0.001**) | |
| GLIM vs. ESPEN | 72.06 (59.85 to 82.27) | 87.50 (47.35 to 99.68) | 98.0 (88.62 to 99.68) | 26.92 (18.82 to 36.92) | 0.299 (**0.001**) | |
| ESPEN vs. NRS-2002 | 97.92 (88.93 to 99.95) | 20.59 (8.70 to 37.90) | 63.51 (59.35 to 67.49) | 87.50 (47.43 to 98.19) | 0.196 (**0.010**) | |

AML, Acute myeloid leukemia; ALL, Acute lymphocytic leukemia; CR, complete remission; CI, confidence interval; NA, not applicable. [a]Indicating the agreement between the three instruments. We meant to use bold to show statistical significance ($p < 0.05$).

candidates for allo-HSCT. According to NRS-2002, GLIM, and ESPEN criteria, the results showed that 33.6, 26, and 8.6% of the patients were malnourished, respectively. Regardless of gender, type of leukemia, CR status, and risk status, GLIM and NRS-2002 instruments had a perfect agreement in diagnosing malnutrition; however, the ESPEN criterion showed fair agreement with the other two instruments (GLIM and NRS-2002). In all patients, we obtained a moderate agreement for all tools. In general, these results were maintained in subgroup analyses.

Although malnutrition caused by disease is known as a serious problem, a gold standard for its diagnosis has not been introduced so far. While Peng et al. introduced the NRS-2002 as the first choice for assessing malnutrition before HSCT (24), studies have shown contradictions (10, 25). In 2017, the ESPEN guideline published a lack of consensus on the appropriate malnutrition screening method in patients with cancer (12). The GLIM criterion was developed in 2019 and now has a global consensus and has been evaluated in various diseases in recent years (14).

Most previous studies evaluated malnutrition in patients with solid tumors, and studies in HSCT candidate patients are limited. However, the nutritional status of patients with hematologic malignancies is not vastly different from general oncology patients (26). Various screening tools have led to different results in the prevalence of malnutrition in patients with hematological malignancies. For example, the prevalence of malnutrition using Subjective Global Assessment (SGA), Malnutrition Screening Tool (MST), Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA), Patient-Generated Subjective Global Assessment (PG-SGA), and BMI tools varied from 13 to 41.3% (27–29).

The prevalence of malnutrition in this study based on the GLIM criteria was 26%, which was in line with previous studies in cancer patients. Previous studies have reported that the rate of malnutrition was 32% in head and neck cancer (30), 24% in lung cancer (31), and 72.2–80% in advanced stages of cancer based on GLIM criteria (32). In studies that included all types of cancer with larger sample sizes (637 and 2,794 patients), malnutrition was between 26 and 31% (20, 33). The current study's results were consistent with previous studies in patients with hematological malignancies. In a study that examined 120 leukemia, lymphoma, and myeloma patients, the prevalence of malnutrition based on the GLIM criteria was 25.8%, which was 29.7% in leukemia patients (34). In lymphoma and leukemia patients, the prevalence of malnutrition significantly differs between different types of blood malignancies (28, 35). In China, Guo et al. (36) evaluated the prevalence of malnutrition based on the GLIM criteria in 98 HSCT candidate patients, which was 80.6%. One of the possible reasons for the difference in the results of the current study with the results of Guo et al.'s (35) study was the difference in the ethnicity of the study cohort. Guo et al. considered the difference in muscle tissue in the Chinese population with other races as the reason for this difference. They proposed the GILM criterion without reduced muscle tissue for the Chinese people.

In this study, our choice of comparing these tools stemmed from a prior investigation that pitted the NRS-2002 against the SGA. The findings revealed a high degree of concordance, with NRS-2002 exhibiting a specificity of 94.81% in identifying severe malnutrition. This strong agreement might be attributed to NRS-2002's balanced consideration of both nutritional status and disease severity. It implies that NRS-2002 could categorize patients as high-risk primarily due to the severity of their illness (37).

Hence, the primary objective of our study was to assess NRS-2002 against alternative tools like the GLIM criteria, focusing on their specificity and sensitivity. While the PG-SGA is widely regarded as the gold standard for cancer patients, our study specifically aimed to compare screening and assessment tools commonly used in the pre-transplant setting. The choice of which method to employ depends on factors such as available infrastructure, resources, automation feasibility, and the healthcare environment (38).

Moreover, previous research has indicated that GLIM criteria demonstrate 'moderate agreement' (kappa = 0.426) when compared to SGA. This suggests that GLIM criteria can effectively assess the nutritional status of cancer patients even without considering SGA, a recommendation supported by existing literature (15, 39). Additionally, large-scale prospective research by Tan et al. indicated that GLIM criteria demonstrated "moderate agreement" (kappa = 0.76) and good reliability with SGA. Prediction of nutritional and functional status, cancer-associated symptoms and quality of life can be done by applying GLIM (40). In addition, a cross-sectional study among colorectal cancer patients showed that malnutrition frequency according to GLIM criteria can be recorded with/without considering the screening tools (41). Another survey among esophageal cancer patients indicated that between GLIM, SGA, and ESPEN criteria, the GLIM indicated a greater malnutrition prevalence rate and seemed to be the optimal framework for predicting post-surgery complications (42). We might conclude that the implication of criteria with higher sensitivity, including the GLIM criteria, might assist early diagnosis and, therefore, early intervention in patients with cancer.

The results of our study determined that the GLIM and ESPEN criteria have a fair agreement in diagnosing malnutrition in leukemia patients who are candidates for HSCT. In the subgroup analysis, the agreement ranged from weak to moderate; however, in the group of patients with favorable risk at the beginning of transplantation, a perfect agreement was shown, but because only three patients were in that

group, the clinical significance of the result is reduced, and further studies are needed. The results of our study were consistent with previous studies; for example, Ruiz et al. determined the prevalence of malnutrition in outpatient cancer patients based on the GLIM criteria, 46.7%, and based on the ESPEN criteria, 17.6% (39). The kappa value between the two instruments was 0.34, which indicates a fair agreement. A fair agreement between the GLIM and the ESPEN criterion has been reported in studies with a population of various cancers and esophageal cancer [35; 44]. In general, the amount of malnutrition based on the ESPEN criteria is estimated to be lower than the GLIM criteria.

One of the important reasons for the difference in the prevalence of malnutrition obtained with the above two tools is the reduction of the BMI cut-off required to diagnose malnutrition in the ESPEN criteria. In addition to all the parameters for diagnosing malnutrition based on ESPEN, the GLIM criterion also has a series of etiological criteria that can be effective in the high prevalence of malnutrition compared to the ESPEN criterion.

The NRS-2002 and GLIM criteria perfectly agreed in diagnosing malnutrition in this study. In the subgroup analysis, the agreement ranged from substantial to perfect. 33.6% of patients in the current research based on NRS-2002 were recognized as being at nutritional risk, comparable to previous studies in patients with cancer and candidates for HSCT (10, 20). Among 637 patients with cancer, the GLIM criterion had the best agreement with the NRS-2002 instrument compared to several other questionnaires (20). The higher agreement between NRS-2002 and GLIM criteria in this study and previous studies is most likely due to the similarity of NRS-2002 measures (weight, BMI, food intake, and disease severity) to determine malnutrition with GLIM criteria.

Malnutrition assessment is important because its early diagnosis leads to better and more effective interventions in the hospital. Early intervention prevents the progression of malnutrition to cancer cachexia (43). Various classifications have been proposed for cancer cachexia, but they all have the exact definition and introduce cachexia as an irreversible stage in that even the use of some nutritional supplements or drugs can be a moral conflict (44). Cachexia has three stages: pre-cachexia, cachexia, and refractory cachexia. The stage of pre-cachexia refers to weight loss below 5%; Cachexia includes BMI <20, weight loss of more than 5% in the last 6 months, or sarcopenia. BMI <20 is similar to the BMI cut-off in the ESPEN criteria. Therefore, the ESPEN criterion may have problems diagnosing patients in the stage of pre-cachexia. Diagnosing the stage of pre-cachexia leads to a better effect of nutritional treatment.

## Strengths and limitations

One of the strengths of this study was that the total population was patients with leukemia who were candidates for allo-HSCT, which had low heterogeneity. The number of participants in the project was greater than in similar studies because other hematological malignancies and autologous HSCT candidates were omitted. Additionally, three separate days were used for the collection of dietary data. As a result, individual variation could more effectively be detected. Despite the strengths, there were also limitations. The cross-sectional design makes the cause-and-effect relationship between the diagnosis of malnutrition and post-transplant outcomes unclear. Considering the differences in ethnicity within other studies and its effect on some parameters for determining malnutrition, such as BMI, FFMI and ASMI, it is necessary to conduct similar studies in different populations in different countries to obtain results with higher clinical significance. While our study aimed to compare the performance of three tools, namely NRS-2002, ESPEN criteria, and GLIM criteria, it is important to acknowledge that these tools serve distinct roles in the nutritional assessment process. NRS-2002 is a recognized screening tool designed to identify patients at risk of malnutrition (13), whereas ESPEN criteria and GLIM criteria are assessments used for diagnosing and stratifying malnutrition (45). We recognize the conceptual challenge in directly comparing screening and assessment tools. However, our study's scope was tailored to the pre-allo-HSCT context, where early detection of nutritional risk is crucial. As such, these tools were chosen considering their relevance to this specific setting.

## Conclusion

This study demonstrates that the GLIM criterion perfectly agreed with the NRS-2002. The ESPEN criterion had a fair agreement with other two instruments, and it has problems in early diagnosis of malnutrition, especially in the pre-cachexia stage. The agreement of the three tools with each other was also moderate. In the future, it is imperative to undertake rigorous scientific investigations focused on discerning the optimal diagnostic modality for malnutrition and fostering consensus in this regard.

## 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 Tehran University of Medical Sciences ethics committee. 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

RK and HM designed the study. SM, MB, and AR did data collection. ES did the analysis. HI, SZ-M, and RK wrote the article. SW provided additional scientific analysis and reviewed and edited the manuscript. Finally, HM and SW carefully read the text and tables and made the necessary edits. All authors contributed to the article and approved the submitted version.

## 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



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# Mid-upper arm circumference as a screening tool for identifying underweight adolescents

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**Background:** Mid-upper arm circumference (MUAC) is a potentially credible alternative method for body mass index (BMI) to assess nutritional status. We aimed to assess the correlation between MUAC and BMI- Z-score and to identify a reliable MUAC cut-off point to detect underweight (BMI- Z-score of < −2 standard deviation) Sudanese adolescents.

**Methods:** A cross-sectional study was conducted in eastern Sudan. After obtaining adolescents' age and sex, their weight, height, and MUAC were measured using the standard procedures. The MUAC (cm) cut-off corresponding to underweight was calculated using receiver operating characteristic (ROC) curve analysis.

**Results:** In total, 390 adolescents were enrolled in the study and 205 (52.6%) of them were females. The median (interquartile range, IQR) age was 15.1 (14.0–16.3) years. The medians (IQR) of MUAC and BMI- Z-score were 22.0 (20.0–24.0) cm and – 0.62 (–1.5–0.3), respectively. MUAC was positively correlated with BMI Z-score in all participants ($r = 0.534$, $p < 0.001$), in females ($r = 0.715$, $p < 0.001$), and in males ($r = 0.404$, $p < 0.001$). Of the 390 enrolled adolescents, 61(15.6%) were underweight. The MUAC cut-off for underweight was ≤21.2 cm in all participants (Youden's Index, YI = 0.50; sensitivity = 82.0%; specificity = 68.0%, AUROCC = 0.78), in females (YI = 0.66, sensitivity = 86.0%, specificity = 80.0%, AUROCC = 0.87), and in males (YI = 0.32, sensitivity = 80.0%, specificity = 52.0%, AUROCC = 0.69).

**Conclusion:** MUAC has good accuracy results and can be adopted for community-based screening of underweight adolescents.

KEYWORDS

**body mass index, Z-score, mid-upper arm circumference, underweight, adolescents**

## Introduction

Adolescence is defined by "The World Health Organization (WHO)" as an age between 10 and 19 years. Adolescents constitute 16% of the global population and the majority (90%) live in low-and middle-income countries (1, 2). Adolescence represents the period of development that starts at puberty and ends at adulthood, which reflects the physiological pattern (3). Adolescents are vulnerable to several risk factors for adult non-communicable diseases, communicable diseases, nutritional diseases, and malnutrition (4). Malnutrition among adolescents is associated with several medical problems such as increased risk of contracting

communicable diseases, delayed growth, lower intellectual quotient, impaired cognitive maturation, and behavioral problems (5). Undernutrition is associated with poverty, violence, food insecurity, impaired sexual and reproductive health, and risk of contracting communicable and non-communicable diseases (3). Recent data showed that children and adolescents were at risk of malnutrition globally, and it was among the main causes of mortality: 225,906 deaths in 2013 (approximately 34 deaths per 100,000) which significantly varied between developing and developed countries with 38.5 per 100,000 and 0.2 per 100,000, respectively, (2).

Several anthropometric measurements such as weight, height, weight for height, head circumference, body mass index (BMI), mid-upper arm circumference (MUAC), and triceps skinfold thickness have been proposed to assess nutritional status (6). BMI may be affected by fluid overload, edemas, and muscle mass (7). However, the MAUC is a practical and cheap method. It is a simple measurement as it does not require difficult tools or expert frontline professionals compared to the requirements for measuring BMI (8). MAUC may be useful instead of BMI in different medical problems such as cancer, growth failure (9), among pregnant adolescents (10), and cerebral palsy (11). MUAC could be used as an alternative to BMI to evaluate nutritional status among adolescents in different countries, especially in countries with low resources (8, 12–14).

Malnutrition is a significant health problem in Sudan and it has economic, educational, and productivity impacts (15). There are no published data on the reliability of MUAC measurement in detecting the nutritional status of Sudanese adolescents. Thus, obtaining specific MUAC cut-offs for certain populations of adolescents could be an important method in countries with fewer resources like Sudan. Moreover, Sudan has suffered and is still suffering from civil war, tribal tension, famines, displaced people, and refugee crises, and thus requires a practical, simple, and cheap method to assess nutrition status. We aimed to assess the correlation between MUAC and BMI-*Z*-score and to identify a reliable MUAC cut-off point to detect underweight (BMI- *Z*-score of < −2 standard deviation) Sudanese adolescents.

# Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standard checklists were followed (16). The methods followed in this study have been previously described in our previous work among adults with the same objectives. In summary: a multistage sampling study was conducted in eastern Sudan (New Halfa) during the period of January to February 2021. Four out of seven sectors, which are the lowest administrative units, were selected using a simple random method. The total sample size of 390 participants (both males and females) was distributed between the selected four sectors according to the size of the sector itself. Then, adolescents (10–19 years of age) and their parents in households were selected via a lottery method. If there was no adolescent in the selected household or they refused to participate or had met one of the exclusion criteria, the next household was chosen.

## Inclusion criteria

Apparently healthy adolescent males and females who were residents in the area of the study, whose age was (≥10 years – ≤19 years), and who had signed consent by their guardians for participation.

## Exclusion criteria

Age below 10 years and above 19 years; adolescent pregnant women; adolescents with chronic diseases such as diabetes, thyroid diseases, and heart failure; critically ill patients with severe acute illness; athletes; those on hormonal medication; those who had any apparent congenital dysmorphism; adolescents on chronic medications; and those who refused to participate.

The eligible adolescents were interviewed and their sex and birth dates (confirmed from identity cards) were recorded. Anthropometric measures (weight, height, and MUAC) were taken twice and the mean of measurements was taken. The measurements followed the standard procedures using calibrated instruments. A third measurement was performed in case of considerable variation between the first two readings (differences of >100.0 g for weight, 0.5 cm for height, and 0.2 cm for MUAC). After taking off their shoes and removing heavy clothing and objects from their pockets, the participants were then weighed (to the nearest 10.0 g). Their standing height was measured (to the nearest 1 mm) by a stadiometer with their feet positioned together at the heels with the back of the heels. MUAC was measured (to the nearest 1 mm) in sitting or standing posture using a non-stretchable MUAC measuring tape which was placed at mid between the olecranon process of the left ulna and the acromion process of the left scapula. BMI was computed as weight in kg/height in $m^2$ (17). Thereafter, BMI Z-scores were calculated using the WHO international growth reference data for children and adolescents (18).

## Sample size calculation

A sample of 390 adolescents was calculated to obtain the significant minimum difference in the correlation ($r = 0.15$) between BMI Z-scores and MUAC. The sample (390 adolescents) had an 80% power and a difference of 5% at $\alpha = 0.05$ (19).

## Statistical analysis

Data were analyzed using IBM SPSS version 25. Shapiro–Wilk tests were used to check the normality of the continuous data. A non-parametric Mann–Whitney *U* test was used to assess the difference in variables between the groups (males and females). Scatterplots with fitted linear regression lines were computed to

Abbreviations: AUROCC, Area Under the Receiver Operating Characteristics Curve; BAZ, BMI-for-age Z-score; BMI, Body mass index; CI, Confidence interval; cm, centimeter; IQR, Interquartile range; kg, kilogram; ROC, receiver operating characteristic curve; m, meter; MUAC, mid-upper arm circumference; YI, Youden's Index; SPSS, Statistical Package for the Social Sciences; STROBE, The Strengthening the Reporting of Observational Studies in Epidemiology; WHO, The World Health Organization.

evaluate the association between MUAC and BMI z-score for all adolescents and for each sex separately. The sensitivity and the specificity were computed and Youden's Index (YI) was calculated as YI = sensitivity + specificity-1. The MUAC cut-off with the highest YI-value represented the optimal statistically-derived cut-off (20). The area under the receiver operating characteristic curve (AUROCC) was obtained for all adolescents and for females and males separately. A value of $p$ less than 0.05 was considered statistically significant.

## Results

In total, 390 adolescents were enrolled in the study and 205 (52.6%) of them were females. The median (IQR) age was 15.1 (14.0–16.3) years. The medians (IQR) of MUAC and BMI- Z-score were 22.0 (20.0–24.0) cm and −0.62 (−1.5–0.3), respectively. Compared with males, females were significantly older, taller, and had higher MAUC and BMI Z-scores (Table 1).

There was a significant positive correlation between MUAC and BMI Z-score ($r = 0.534$ ($p < 0.001$) in all participants, in females [$r = 0.715$ ($p < 0.001$)], and in males [$r = 0.404$ ($p < 0.001$; Figure 1)].

Of the 390 enrolled participants, 61(15.6%) were underweight. The best statistically derived MUAC cut-off based on BMI z-scores for underweight was ≤21.25 cm in all participants (YI = 0.50; sensitivity = 82.0%; specificity = 68.0%) with a good predictive value (AUROCC = 0.78, 95.0% CI = 0.73–0.84), in females (YI = 0.66, sensitivity = 86.0%, specificity = 80.0%), (AUROCC = 0.87, 95.0% CI = 0.79–0.95), and in males (YI = 0.32, sensitivity = 80.0%, specificity = 52.0%), with a good predictive value (AUROCC = 0.69, 95.0% CI = 0.60–0.77; Table 2; Figure 2).

## Discussion

Our study showed a positive correlation between BMI Z-scores and MUAC in all adolescents and in each sex separately. This goes with similar previous findings reported among adolescents in Ethiopia ($r = 0.81$) (13) and in Tanzania [females ($R = 0.846$) versus males ($r = 0.459$)] (21).

The best statistically derived MUAC cut-off for underweight adolescents in this study was ≤21.2 cm which showed similar results in females and males separately. The MUAC cut-off observed in our results to detect underweight adolescents was almost similar to that obtained in Tanzania in adolescents (18.5–22.0 cm, sensitivity = 40.0%, specificity = 92.5%) aged 15–17 years old (21) and in India (≤21.6 cm, sensitivity = 75.4%, specificity = 87.1%, and AUROCC = 0.91; age 15–19 years) (12). In Tanzania (21), they enrolled adolescents aged 15–17 years old and we enrolled adolescents aged ≥10 years –≤19 years and this could explain the difference in our results and the results from Tanzania. However, the MUAC cut-off which is proposed to detect underweight in the current study is slighter higher than that reported in Turkey for males (≤20.50 cm sensitivity = 60.9%, specificity = 87.4%, and AUROCC = 0.791) and females (≤20.50 cm sensitivity = 45.0.8%, specificity = 87.8%, and AUROCC = 0.748) (22), in India (≤19.4 cm sensitivity = 84.0%, specificity = 81.4% and AUROCC = 0.86) for females aged 10–14 years (12) and in another study for males (≤19.2 cm sensitivity = 82.2%, specificity = 68.9% and AUROCC = 0.77) and females (≤19.4 cm sensitivity = 87.7%, specificity = 70.9% and AUROCC =0.79) aged 10–14 years (14). Additionally, a markedly higher MUAC cut-off of more than 21.25 cm was reported among adolescents in Ethiopia (≤23.3 cm, sensitivity = 87.9%, specificity = 75.9% and AUROCC = 0.90) for males and (≤22.6 cm, sensitivity = 100% specificity = 88.2% and AUROCC = 0.97) for females (13), in India (≤22.0 cm sensitivity = 77.0%, specificity = 79.6% and AUROCC =) in adolescents aged 15–19 years (8), and in males (≤22.9 cm sensitivity = 81.9%, specificity = 75.1% and AUROCC = 0.82) and females (≤21.7 cm sensitivity = 87.9%, specificity = 77.8% and AUROCC = 0.84) aged 10–14 years (14). The different MUAC cut-off points for different populations are summarized in Table 3. The variation in MUAC cut-offs in different studies may be explained by the difference in adipose tissue as well as in skeletal muscle mass observed in some children which could be due to differences in ethnicity (23). Moreover, a significant difference according to sex and age in undernutrition was observed in some studies (24–26). Hence, no universal agreement on the MUAC cut-off point to screen malnutrition among children and adolescents (27, 28). Therefore, adopting local references of MUAC for epidemiological and anthropological studies is recommended (29). Several previous studies reported that MUAC could be an alternative tool to detect underweight/thinness among adolescents (8, 13, 21, 27–29). MAUC is useful in different clinical situations, e.g., in cases of adolescents who have edema (7), chronic disorders and growth failure (9, 30, 31), cerebral palsy (11) severe learning disabilities (32), and anorexia nervosa (33, 34). Additionally, MUAC has also been adopted for many years for assessing nutritional status in certain conditions, like famines or refugee crises, where ordinary methods for height and weight measurements are difficult to perform (35). Furthermore, adopting a restricted MUAC cut-off for discharging children from severe acute malnutrition treatment can predict and prevent relapses and hospital readmission (36). Likewise, it has been shown to predict the worsening of nutritional status in low-income countries with laboratory indicators for hemoglobin, ferritin, zinc, serum albumin, and plasma retinol concentrations as dependent variables (37). Moreover, MUAC has emerged as the measurement that was most preferred by participants because it is less distressing than routinely used measurement techniques for weight and skin fold (34). Interestingly a simplified method of MAUC-based weight estimation can be used for the administration of many drugs and fluid regimens in emergency

TABLE 1 Comparing medians (interquartile range) of anthropometric profile between adolescent boys and girls in eastern Sudan, 2021.

| | Total (number = 338) | Female (number = 205) | Male (number = 184) | $p$ |
|---|---|---|---|---|
| Age, years | 15.1 (14.0–16.3) | 15.6 (14.4–16.5) | 14.5 (13.7–15.6) | 0.031 |
| Body mass index, Z score | −0.62 (−1.5–0.3) | −0.5 (−1.3–0.0.2) | −0.8 (−1.8–0.6) | 0.617 |
| Mid-upper arm circumference, cm | 22.0 (20.0–24.0) | 23.0 (21.0–25.0) | 21.0 (19.0–23.0) | < 0.001 |

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TABLE 2 Mid-upper arm circumference cut-off points for the diagnosis of underweight adolescents in eastern Sudan, 2021.

| Variables | All participants | Females | Males |
|---|---|---|---|
| Mid-upper arm circumference cut-off | ≤21.2 cm | ≤21.2 cm | ≤21.2 cm |
| Area under the curve (95.0% confidence interval) | 0.78 (0.73–0.84) | 0.87 (0.79–0.95) | 0.69 (0.77–0.88) |
| Youden's index | 0.50 | 0.66 | 0.32 |
| Sensitivity | 82.0% | 86.0% | 80% |
| Specificity | 68.0% | 80.0% | 52.0% |

TABLE 3 Specificity, correlation coefficients and the area under the receiver operating characteristic curve (AUROC) from different studies on underweight adolescents using mid-upper arm circumference and body mass index Z-scores.

| Study years/ country | Total | Male | Female | Age | MUAC cut-off, cm | Youden's Index | Sensitivity | Specificity | AUROCC | *r* |
|---|---|---|---|---|---|---|---|---|---|---|
| (11) (Ethiopia) | 851 | 456 | 395 | 15–19 | M 23.3<br>F 22.6 | M 0.64<br>F 0.88 | M 87.9<br>F 100.0 | M 75.9<br>F 88·2 | M = 0.90<br>F = 0·97 | 0.81 |
| (21) (Tanzania) | 154 | 62 | 92 | 10–14<br>15–17 | 16.0–18.5<br>18.5–22.0 | | 40.0 | 92.5 | | M = 0.459<br>F = 0.846 |
| (8) (India) | 106,208 | 14,893 | 91,315 | 15–19 | ≤22.00 | | 6.6 | 99.1 | | M = 0.54<br>F = 0.55 |
| (12) (India) | 2,492 | | 2,492 | 10–14 | ≤19.4 | 0·59 | 84·0 | 75·4 | 0·86 | 0·780 |
| (12) (India) | 2,136 | | 2,136 | 15–19 | ≤21.6 | 0·68 | 81·4 | 87·1 | 0·91 | 0·780 |
| (14) (India) | 31,471 | 16,158 | 15,313 | 10–19 | M 21.9<br>F 20.4 | – | – | – | – | 0.810 |
| | | | | 10–14 | M 19.2<br>F 19.4 | M 0.51<br>F 0.59 | M 82.2<br>F 87.7 | M 68.9<br>F 70.9 | M 0.77<br>F 0.79 | |
| | | | | 15–19 | M 22.9<br>F 21.7 | M 0.57<br>F 0.66 | M 81.9<br>F 87.9 | M 75.1<br>F 77.8 | M 0.82<br>F 0.84 | |
| (22) (Turkey) | 626 | 307 | 319 | 10–13 | M 20.50<br>F 20.50 | | M 60.9<br>F 45.8 | M 87.4<br>F 87.8 | M 0.791<br>F 0.748 | |

M, males; F, female; MUAC, mid upper arm circumference; AUROCC, Area Under the Receiver Operating Characteristics Curve; YI, Youden's Index; *r*, correlation coefficient.

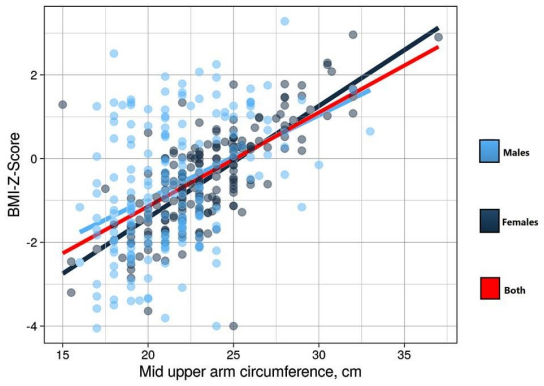


FIGURE 1
Curve estimation for assessing the linear relationship between mid-upper arm circumference and body mass index Z-score in adolescents in eastern Sudan 2021.

medicine that are weight-dependent in patients and when no standard adult weight estimation tools exist or are difficult to perform (27, 38, 39).

Our study is a community-based study and enrolled both males and females and these are strengths of this study. One limitation of the present study is that the data for MUAC cut-off from this area might be different from other areas in Sudan. Moreover, height, weight, and MUAC are all measurements that are subjected to measurement error due to inter-observer differences in measurement or miscalculation error (40). A larger sample size might have strengthened the prevalence of the outcome and the analysis.

## Conclusion

Our study proposes the cut-offs based on MUAC (≤22.5 cm) as an alternative for BMI for community-based screening of underweight adolescents.

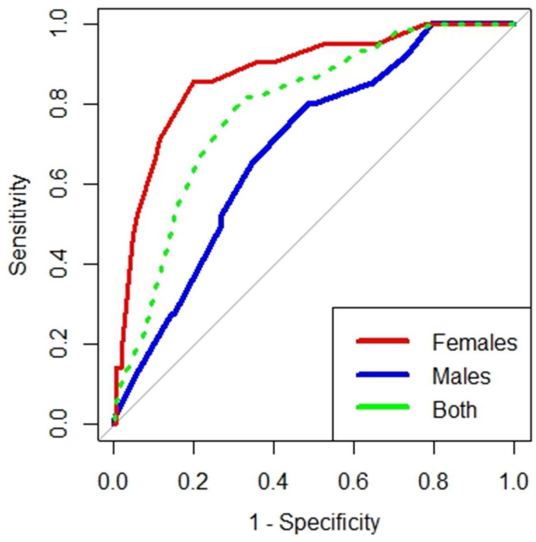


FIGURE 2
Receiver operating curve of mid-upper arm circumference for diagnosing underweight adolescents in eastern Sudan 2021.

## 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 this study complies with the Declaration of Helsinki. Ethics approval was obtained from the Ethics Committee of the Faculty of Medicine of Gadarif University, Sudan (Reference number #2021.03). Written informed consent was collected from each participant. 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

IM and SO conceived the study and supervised data collection. AA, AA-N, and IA supervised the work, guided the analysis, critically reviewed the manuscript, prepared the analysis plan, performed the data analysis, and wrote the first draft of the paper. All authors reviewed and approved the final manuscript.

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## Conflict of interest

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

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# Measurement of body composition by deuterium oxide dilution technique and development of a predictive equation for body fat mass among severe neurologically impaired children

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**Introduction:** Neurologically impaired (NI) children are at risk of malnutrition, which consequently impacts their health and quality of life. Accurate nutrition assessment is an important step in guiding appropriate nutrition support. Conventional anthropometric measurements among NI children have some limitations. Determining body composition requires more complex equipment, which is not routinely performed. This study was conducted to evaluate the association between anthropometric parameters and body composition assessed using the deuterium dilution technique (DDT) in NI children.

**Methods:** A cross-sectional study enrolled severe NI children aged 1–20 years who received home enteral nutrition for at least 3 months. Weight, length, and 4-site skinfold thickness were measured. Body composition was determined using DDT following the International Atomic Energy Agency (IAEA) protocol.

**Results:** A total of 37 NI children (56.76% male, median age 7.2 years) were enrolled. The prevalence of underweight, stunting, and overweight were 22, 38, and 35%, respectively. Body composition analysis showed the mean (SD) of total body water (TBW) and fat mass (FM) were 10.52 (4.51) kg and 9.51 (6.04) kg, respectively. Multivariate GLM analysis showed that the factors associated with FM were age (β = 0.07 [0.05,0.08]; $p < 0.001$), body mass index (BMI) (β = 0.82 [0.52, 1.12]; $p < 0.001$), biceps skinfold thickness (BSF) (β = 0.49 [0.23,0.75]; $p = 0.001$), and subscapular skinfold thickness (SSF) (β = −0.24 [−0.46,0.03]; $p = 0.030$). A predictive equation for FM was constructed.

**Conclusion:** A high prevalence of malnutrition was found among severe NI children despite enteral nutrition support. Our findings showed that age, BMI, BSF, and SSF were associated with FM. The predictive equation of FM was proposed and needed to be further validated and applied to clinical practice.

KEYWORDS

**deuterium oxide dilution technique, body composition, anthropometric measurement, neurologically impaired children, home enteral feeding**

## Introduction

Neurological impairment (NI) in children affects their development and cognitive function, which also impacts oral motor function and feeding development (1). Malnutrition is commonly found in children with NI, with a reported prevalence of 46–90% from previous studies (2–4). Malnutrition causes muscle weakness, impaired immune function, and prolonged hospitalization in children with NI. Several factors, including the types and severity of underlying diseases, ambulatory and cognitive status, and medication use, contribute to the risk of malnutrition (5). In addition, 90% of NI children are affected by gastrointestinal disorders such as oropharyngeal dysphagia and gastroesophageal reflux disease (GERD) (5), which are associated with inadequate diet intake and respiratory complications. Some children with severe NI need enteral nutrition support due to inadequate nutrient intake via oral route or having contraindications to oral feeding (3). Overweight and obesity may be found in NI children with enteral nutrition support (6).

Accurate nutrition assessment, including medical and dietary history, anthropometric measurements and growth assessment, physical examination, and specific investigations, is essential for providing appropriate nutrition support to NI children. Frequently, routine anthropometric measurements such as weight and height/length are inaccurately assessed in NI children due to limitations such as bedridden status, joint contractions, and deformities. In addition, growth assessment of NI children is difficult because of the limited information on the disease-specific growth curve. A single anthropometric parameter such as body mass index (BMI), weight, or length is not an optimal indicator of nutrition status among NI children (7–9). Body composition is also an essential parameter for monitoring nutrition status, but the assessment is more complicated. NI children have a different proportion of fat and muscle than normal children, depending on their underlying diseases and severity. Consequently, some proposed estimations of fat mass (FM) or fat-free mass (FFM) from anthropometric parameters in normal children could not accurately determine the body composition of NI children. Measurement of body composition among NI children using standard techniques, including whole-body dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and isotope dilution technique, has some limitations. DXA is costly and requires more complex equipment. The isotope dilution technique provides accurate information but is usually performed in research rather than clinical practice due to its sophisticated processes and cost. BIAs are widely used in clinical practice, but more advanced equipment is needed when performing the measurement in NI children who cannot stand or cooperate with the assessment process. The equipment for BIA measurements in the supine position is not available in some areas.

In Thailand, information regarding nutrition status and management in NI children is scarce. Many NI children suffer from malnutrition and feeding problems, and some of them need enteral nutrition support. Nutrition assessment is comprehensively performed in NI children, but there are some limitations to demonstrating their accurate nutrition status. Body composition could not be routinely assessed by the standard method due to limited resources. Therefore, this study aimed to investigate the association between anthropometric parameters and the body composition of children with severe NI who depended on enteral nutrition support. We also aimed to develop a predictive equation that may help estimate body composition based on the bedside anthropometric parameters.

## Materials and methods

A cross-sectional study was performed from June 2021 to March 2022 at the Nutrition Clinic, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. NI children, aged 1–20 years, with home enteral nutrition support for at least 3 months were enrolled. Children who had abnormal hydration status (either dehydration or edema, by history and physical examination), acute illness, or active infection, and who were unable to be fed on sampling day, were excluded from this study. The study protocol was approved by the Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (Protocol No. COA. MURA2021/390). The detailed study protocol was explained to parents or legal guardians, and informed consent was obtained before enrollment. The study was performed in accordance with the Declaration of Helsinki.

In this study, we used the deuterium oxide dilution technique (DDT) to determine body composition in NI children. The sample size for a single mean estimation was calculated by STATA version 16.1. Following the standard method described by Rieken et al. (10), the mean (SD) of total body water (TBW) determined using DDT in NI children with gastrostomy tubes, which was 10.3 (3.8) kg, was used to estimate the sample size in this study. With a level of confidence of 95% and a power of 80%, the calculated sample size for our study was 45.

### Baseline characteristics

Baseline characteristics, including age, sex, underlying neurological diseases, presence of seizures, and feeding methods (enteral feeding with/without oral route), were reviewed from the medical record. The severity of NI was assessed by motor mobility using the Gross Motor Functional Classification System (GMFCS), from the less severe or ability to walk without restrictions (level I) to the most severe or limited voluntary movement and the ability to maintain antigravity in the head and trunk (level V) (11). The characteristics of NI were classified as spasticity, dyskinesia, and hypotonia by researchers or pediatric neurologists. Pubertal development was assessed using Tanner staging (Tanner stages I–V) by the researchers.

### Anthropometric assessments

Anthropometric measurements, including weight, length, mid-upper arm circumference (MUAC), and skinfold thickness, were performed by the researchers on the day of data collection.

Body weight while wearing a light cloth or naked without a diaper was obtained using a standard digital scale to the nearest 0.1 kg. Children aged less than 24 months were weighed on a pan-type digital scale (Seca® 374, Seca Corporation, Hamburg, Germany). Children aged older than 24 months who could stand without assistance were weighed on a platform digital scale (Seca® 284, Seca Corporation, Hamburg, Germany), whereas those who were unable to stand were weighed by subtracting their parents' weight after being weighed together while holding their child.

Length was measured to the nearest 0.1 cm using an infantometer (Seca® 416, Seca Corporation, Hamburg, Germany). Because an infantometer is limited to 100 cm, the researchers used a self-made measuring instrument for children over 100 cm. The instrument was made with a 150 cm flexible, non-stretchable tape attached to a head and foot plastic board, routinely used in our nutrition clinic for length assessment of NI children. Length could not be accurately measured in some NI children with scoliosis or joint contraction. Instead, length was estimated from knee height by a predictive equation developed by Stevenson (12). Knee height was assessed using a flexible, non-stretchable tape that measured from heel to the anterior surface of the thigh, approximately 3 cm above the patella, with a 90 degree angle between thigh to leg and leg to foot (13).

MUAC was measured at the midway point between the uppermost edge of the posterior border of the acromion process and the olecranon process of both arms using a flexible, non-stretchable tape when the arm was hanging loosely. Skinfold thickness was measured to the nearest 0.1 mm at four different sites, i.e., biceps (BSF), triceps (TSF), subscapular (SSF), and suprailiac (SiSF) skinfold, both right and left sides, using Holtain caliper (Holtain Ltd., Crymych, United Kingdom), following the standard method described by Lee and Nieman (14).

All anthropometric parameters were assessed following the standard method by trained dietitians, nurses, and researchers. The measurements of length, knee height, MUAC, and skinfold thickness were repeated three times. The represented values were determined by the average of the three values from each measurement. Anthropometric parameters were calculated using Z-scores, including length-for-age Z-score (LAZ), weight-for-length Z-score (WLZ), weight-for-age Z-score (WAZ), BMI-for-age Z-score (BMIZ), MUAC-for-age Z-score, TSF-for-age Z-score, and SSF-for-age Z-score, were calculated using the WHO Anthro software (15) for children aged 0–60 months and the WHO AnthroPlus software (16) for children aged 5–19 years.

## Body composition assessment

Body composition was assessed using DDT. The principle of this technique is to assess TBW with deuterium oxide ($D_2O$), and then calculate FFM from TBW. The DDT was performed according to the protocol proposed by the International Atomic Energy Agency (IAEA) (17). In brief, the appropriate amount of $D_2O$, according to the participant's weight, was fed via a feeding tube, followed by 10 mL of sterile water. $D_2O$ was traced from its concentration in saliva to its equilibrium. At least 2 mL of saliva was collected before $D_2O$ dosing, then repeated at 3 and 4 h post-dosing. The researchers collected saliva samples by putting a cotton swab into the mouth of each participant and extracted the saliva into microtubes using a syringe plugger. The samples were then kept frozen until analysis of $D_2O$ enrichment using Fourier transform infrared (FTIR) spectroscopy at the Institute of Nutrition Mahidol University (INMU). TBW was calculated using the information of the initial dose and enrichment of $D_2O$ at equilibrium. Once TBW was calculated, FFM was determined based on the value of TBW using the FFM hydration factors suggested in the IAEA protocol, which vary by age and sex (13). Then, FM was calculated by subtracting FFM from body weight.

In addition to DDT, FM was determined by predictive equations using the variables from bedside anthropometric measurements. We calculated body FM percentage based on the predictive equations proposed by previous studies and compared it with the value of body FM percentage obtained from DDT. These predictive equations were the following:

1) The Baton Rouge Children's Study (18) suggested the equation to determine body FM percentage using the data of 4-site skinfold thickness as

$$\mathrm{FM}(\%) = 8.71 + 0.19(\mathrm{SSF}) + 0.76(\mathrm{BSF}) + 0.18(\mathrm{SiSF}) + 0.33(\mathrm{TSF})$$

2) Modified Slaughter equations, which were modified from the original Slaughter equations by additional correction factors for children with cerebral palsy (19).

## Statistical analysis

Statistical analysis was performed using STATA version 16.1 for Windows (StataCorp LLC, Texas, United States). Calculated probabilities ($p$-value) < 0.05 were considered statistically significant. Descriptive data were tested for normality using the Shapiro–Wilk test. Normal distributed data were presented as mean and standard deviation (SD), and non-normal distributed data were presented as median and interquartile range. A comparison of FM from predictive equations and DDT used paired $t$-tests and Bland–Altman analysis. Associations between body composition parameters (TBW and FM) from DDT and anthropometric parameters were analyzed using a univariate generalized linear model (GLM). Variables with significant associations ($p$-value <0.05) were assessed by multivariate GLM using backward elimination, log-likelihood, and likelihood ratio tests to obtain minimum variables that preserve the power of the model. The model was presented as a calibration plot of prediction model performance by adjusted R-square. The concordance correlation coefficient was analyzed by Lin's approach (20). Testing of multicollinearity was performed with variance inflation factor (VIF) heteroskedasticity using the Breusch-Pagan/Cook-Weisberg test (21). If VIF was less than 5, the model was accepted (22).

# Results

Thirty-seven NI children were enrolled in this study. The baseline characteristics of participants are shown in Table 1. The median (IQR) age was 7.42 (3.67, 10.42) years. Spasticity was the most common type of NI. All participants were classified in GMFCS IV-V. All baseline characteristics were not different in the subgroup analysis, either by type or etiology of NI (asphyxia vs. non-asphyxia).

## Anthropometric assessments and body composition

Anthropometric parameters are presented in Table 2. The proportions of participants with underweight (WAZ < -2), stunting

TABLE 1 Baseline characteristics of study participants ($n = 37$).

| Characteristics | Number (%) |
|---|---|
| Sex, *n* (%) | |
| Male | 21 (56.76) |
| Female | 16 (43.24) |
| Sexual maturation, *n* (%) | |
| Prepuberty | 26 (70.27) |
| Puberty | 11 (29.73) |
| Types of NI, *n* (%) | |
| Dyskinesia | 6 (16.22) |
| Hypotonia | 6 (16.22) |
| Spasticity | 25 (67.57) |
| Etiology of NI, *n* (%) | |
| Asphyxia | 9 (24.32) |
| Brain malformation | 6 (16.22) |
| CNS infection | 1 (2.70) |
| Epilepsy | 2 (5.41) |
| Genetic disease | 9 (24.32) |
| Inflammation | 1 (2.70) |
| Stroke | 6 (16.22) |
| Toxic or metabolic disease | 3 (8.11) |
| Severity, *n* (%) | |
| GMFCS IV-V | 37 (100) |
| Presence of seizure, *n* (%) | |
| No | 16 (43.24) |
| Yes | 21 (56.76) |
| Oral intake, *n* (%) | |
| No | 36 (97.30) |
| Yes | 1 (2.70) |

NI, neurologically impairment; GMFCS, gross motor functional classification system.

TABLE 2 Anthropometric parameters of study participants.

| Parameters | Represented value |
|---|---|
| Weight-for-age Z-score; WAZ ($n = 27$)[a] | |
| WAZ, median (IQR) | −0.73 (−1.83, 1.08) |
| WAZ classification, *n* (%) | |
| <−2 | 6 (22.22) |
| −2 to 2 | 19 (70.37) |
| >2 | 2 (7.41) |
| Length-for-age Z-score; LAZ ($n = 37$) | |
| LAZ, median (IQR) | −1.79 (−3.23, −0.59) |
| LAZ classification, *n* (%) | |
| <−2 | 14 (37.84) |
| ≥−2 | 23 (62.16) |
| BMI Z-score; BMIZ ($n = 37$) | |
| BMIZ, median (IQR) | 0.36 (−1.08, 2.06) |
| BMIZ classification, *n* (%) | |
| <−2 | 8 (21.62) |
| −2 to 2 | 16 (43.24) |
| >2 | 13 (35.14) |
| Mid-upper arm circumference (MUAC) Z-score ($n = 13$)[b] | |
| MUAC Z-score, mean (SD) | 0.99 (2.57) |
| MUAC Z-score, *n* (%) | |
| <−2 | 3 (23.08) |
| ≥−2 | 10 (76.92) |
| Triceps skinfold thickness (TSF) Z-score ($n = 13$)[b] | |
| TSF Z-score, mean (SD) | 2.98 (1.68) |
| Subscapular skinfold thickness (SSF) Z-score ($n = 13$)[b] | |
| SSF Z-score, mean (SD) | 3.70 (2.94) |

[a]WAZ was assessed in children aged under 10 years.
[b]MUAC, TSF, and SSF Z-score were assessed in children aged under 5 years. BMI, body mass index.

(LAZ < -2), and wasting (BMIZ <-2) were 22, 38, and 22%, respectively. Meanwhile, 35% of participants were overweight (BMIZ >2). The mean (SD) of FM and TBW from DDT were 9.51 kg (6.04) and 10.52 kg (4.51), respectively. Anthropometric parameters and body composition were not different between types or etiologies of NI.

Body FM percentage obtained from DDT was significantly lower than that estimated by Baton's equation (mean difference −12.72 [−17.24, −8.20]; $p < 0.001$), but tended to be higher than that estimated by modified Slaughter equation without statistical significance (mean difference 3.02 [−2.00, 8.04]; $p = 0.229$), as shown in Table 3. The Bland–Altman analysis showing the agreement of body FM percentage calculated from previous predictive equations and DDT is presented in Figures 1A,B. The body FM percentage calculated using DDT was 13% lower than that calculated using Baton's equation. While comparing with the modified Slaughter equation, the analysis showed a wide limit of agreement. Body FM percentage tended to have a negative bias toward small values but a positive bias when the mean body FM percentage using both methods was over 30%.

## Association between anthropometric parameters and body composition

The linear relationships between FM and TBW with participants' age and anthropometric parameters evaluated using univariate GLM analysis are shown in Table 4. The variables with significant associations were included in the multivariate GLM analysis. The factors associated with FM from multivariate GLM analysis were age in months (β = 0.07 [0.05, 0.08]; $p < 0.001$), BMI (β = 0.82 [0.52, 1.12]; $p < 0.001$), BSF (β = 0.49 [0.23, 0.75]; $p = 0.001$), and SSF (β = −0.24 [−0.46,0.03]; $p < 0.030$). From these associations, we constructed the predictive equation to estimate FM as.

$$\mathrm{FM\,(kg)} = \left[0.07^{*}\,\mathrm{age\,(months)}\right] + \left[0.82^{*}\,\mathrm{BMI}\left(\mathrm{kg/m^2}\right)\right] + \left[0.49^{*}\,\mathrm{BSF\,(mm)}\right] - \left[0.24^{*}\,\mathrm{SSF\,(mm)}\right] - 13.84$$

TABLE 3 Comparison of body fat mass percentage estimated using deuterium dilution technique (DDT) and predictive equations.

| Estimation methods | Body fat mass percentage mean (SD) | Mean difference (95% CI) | *p*-value |
|---|---|---|---|
| The Baton Rouge Children's study (18) | 43.10 (12.28) | −12.72 (−17.24, −8.20) | <0.001 |
| DDT | 30.38 (17.34) | | |
| Modified Slaughter equation (19) | 27.34 (9.96) | 3.02 (−2.00, 8.04) | 0.229 |
| DDT | 30.38 (17.34) | | |

The model analysis showed adjusted $R^2 = 0.906$. Figure 2 shows the explanatory power of the predictive equation. Validation of the equation showed that factors in this newly developed equation had no multicollinearity; VIF for age, BMI, BSF, and SSF were 1.32, 2.41, 4.70, and 4.23, respectively. The concordance correlation coefficient was 0.984. This equation showed no heteroskedasticity ($p = 0.090$). The mean absolute percentage error (MAPE) was 23.53%, and the greater of two *p*-values from the one-side test for equivalent (TOST) was 0.009. The Bland–Altman analysis between FM estimated by the newly developed equation and DDT is presented in Figure 1C.

## Discussion

Our study presented a comprehensive assessment of the nutrition status of severe NI children with home-based nutritional support. Body composition was evaluated using DDT, and the association between anthropometric parameters and FM in NI children was demonstrated. Malnutrition, including wasting, stunting, and overweight, was found in more than half of the study participants.

Our study found a lower prevalence of undernutrition (wasting and stunting) and a higher prevalence of overweight among NI children compared to previous studies (2, 23). Our center provides a home-based nutrition program aiming to promote good nutrition status among children receiving home-based nutrition. Their feeding and growth are regularly monitored by nutritionists and pediatricians. Therefore, the study participants had received nutrition support and improved their nutrition status before study enrollment. However, one-third of the participants were overweight or obese. We found that it is difficult to determine the appropriate energy intake for children with severe NI as they have limited physical activity and might have a lower basal metabolic rate compared to children with normal development (24).

A previous study found that FM was varied by the age of children and severity. Our study also showed that the age of children was one of the factors associated with FM. The mean body FM percentage in our study populations was lower than the finding from a study by Rieken et al. (10), which enrolled NI children with a higher mean age compared to our study. FM is also affected by the severity of NI assessed by GMFCS and the presence of enteral feeding via gastrostomy tube (10, 19). In contrast, our study did not find this association due to the limited number of study participants and no variation in disease severity. While comparing with healthy children, we found that NI children had higher FM than healthy children (25, 26). Limited physical activity in NI children causes higher FM compared to healthy children. This is a challenging issue in monitoring nutrition status in NI children, as normal weight or BMI may reflect low muscle mass and high FM.

We compared the body FM percentage calculated from DDT and predictive equations that were previously developed (18, 19). Our result demonstrated an overestimation of FM percentage among children with NI by the equation developed from the data of healthy children (the Baton Rouge study) (18). In contrast, the body FM percentage from DDT was similar to the value obtained from the Slaughter equations with correction factors for NI children. A previous study showed an underestimation of FM percentage when using modified Slaughter equations compared to DXA among children with cerebral palsy, but the difference was lower among children with more severe disease (19). Another study found that children with cerebral palsy who had a similar FM percentage to healthy children assessed by DXA had a lower Z-score for anthropometric parameters (27). The authors hypothesized that NI children had relatively more internal fat than peripheral fat distribution. Using parameters of peripheral fat deposit, such as TSF, in a predictive equation could cause an underestimation of body FM percentage. A recent study reported a difference in glucose metabolism and insulin resistance between children with NI and healthy children (28), which may be due to different patterns of body fat distribution and physical activity. Our result showed a trend in overestimation of FM percentage by Baton Rouge and modified Slaughter equation among children with a higher FM percentage, as shown in the Bland–Altman plot (Figure 1). We assumed that fat distribution may be different between NI children with undernutrition and overweight, which needed to be explored in further study. Another factor influencing body FM percentage in children is the pubertal stage, and some studies integrated pubertal status into the predictive equations. Most of our study participants (70%) were in the pre-pubertal stage, and we could not find an association between FM parameters and pubertal status.

FM was recommended to be assessed as a part of nutrition monitoring in NI children (9); however, a single anthropometric parameter is a poor indicator of body FM. Kuperminc et al. (27) demonstrated that a single parameter, including BMI, MUAC, TSF, and upper arm fat area, had poor predictive ability to estimate FM among children with cerebral palsy. Many previous studies, both in healthy and NI children, used the multiple-site skinfold thickness as a predictor for FM. Rieken et al. (10) used the sum of four-site skinfold thickness measurements to predict FM among children with NI. A study in premenarcheal girls by Scerpella et al. (29) also showed that adding BSF to age, weight, and height parameters could improve the accuracy of FM prediction. The addition of TSF and SSF to a model containing BMI was found to reduce the prediction error by 20–30% compared to using BMI alone to predict FM in healthy children (30). Our findings showed that BMI, BSF, and SSF were associated with FM and were included in the proposed predictive equation.

The strength of this study is the assessment of the body composition of NI children receiving home enteral nutrition support

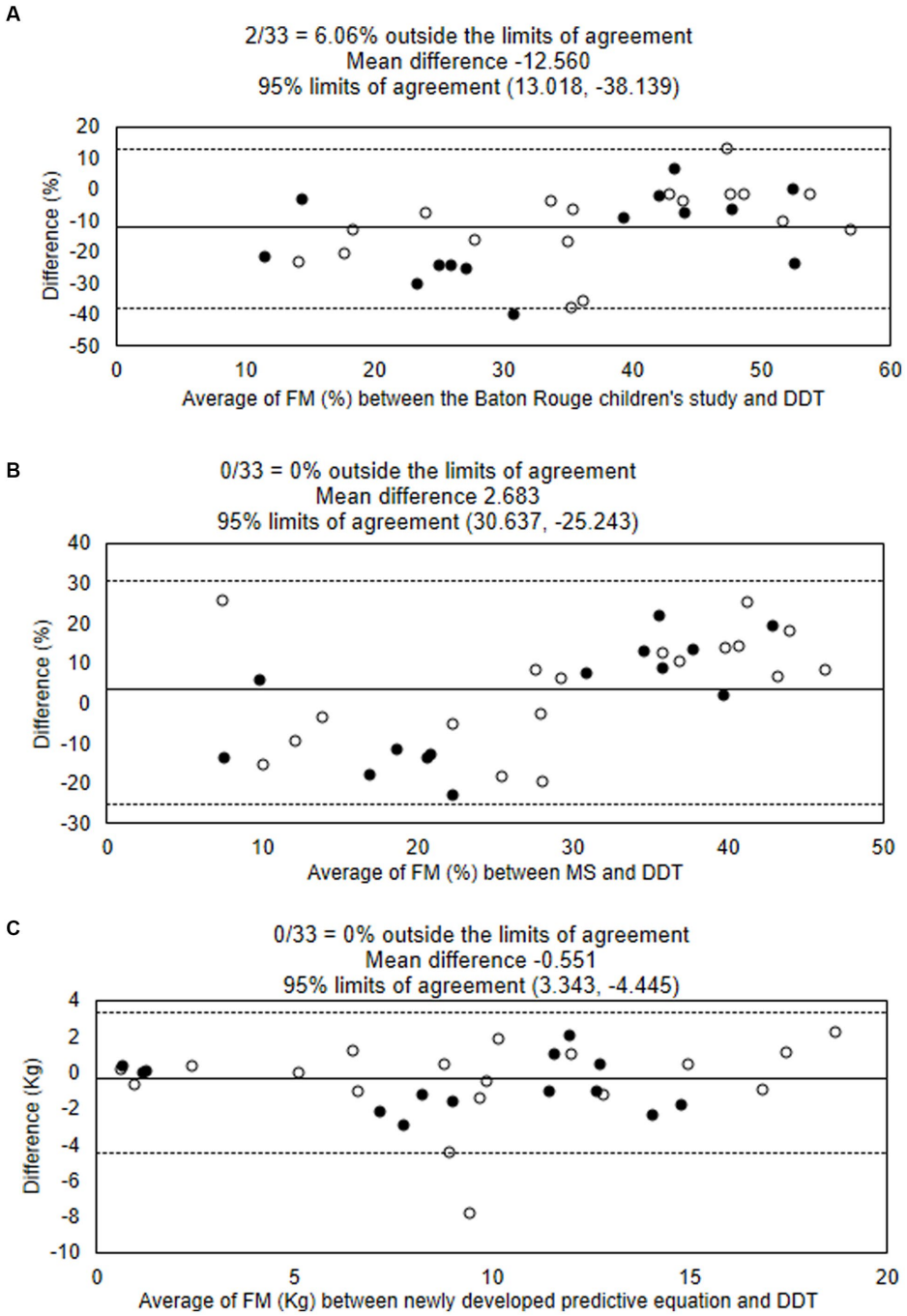


FIGURE 1
Bland–Altman analysis showing the agreement of body fat mass percentages estimated using the deuterium oxide dilution technique (DDT), the Baton Rouge study's equation **(A)**, and Modified Slaughter equation **(B)**. The agreement of fat mass (kg) estimated using DDT and the newly developed equation is shown **(C)**. Solid lines show means, and dotted lines show limits of agreement. ○ male ● female. DDT, deuterium oxide dilution technique; FM, fat mass; MS, Modified Slaughter equation.

by the gold standard technique, which reveals the association of body composition with bedside anthropometric measurements. The predictive model to determine FM in NI children was developed based on the findings of our study. The predictive model of FM may be useful, especially in resource-limited settings where the equipment for body composition assessment is not available. With the information about body composition, we can provide a more appropriate nutrition management plan and better nutrition support to NI children. Consequently, they can recover from malnutrition and improve their quality of life. However, the application of predictive models in clinical practice should be further evaluated. There are some limitations to this study. First, the determination of malnutrition was performed using criteria for children with normal development because the data for growth assessment in NI children is limited. Second, the number of participants was lower than the expected sample size. As the study was performed during the COVID-19

TABLE 4 Univariate generalized linear model between body composition and variable parameters.

| Variable parameters | FM (kg) | | TBW (kg) | |
|---|---|---|---|---|
| | β (95% CI) | *p*-value | β (95% CI) | *p*-value |
| Age (months) | 0.08 (0.05, 0.11) | <0.001 | 0.07 (0.06, 0.09) | <0.001 |
| BMI (kg/m$^2$) | 1.39 (0.96, 1.82) | 0.001 | 0.45 (−0.01, 0.91) | 0.054 |
| WAZ | 1.43 (0.87, 1.97) | <0.001 | 0.62 (0.12, 1.12) | 0.015 |
| LAZ | 0.00 (−0.68, 0.68) | 0.993 | 0.00 (−0.51, 0.51) | 0.998 |
| WLZ | 1.21 (0.85, 1.58) | <0.001 | 0.42 (0.25, 0.59) | <0.001 |
| BMI z-score | 1.34 (0.51, 2.17) | 0.002 | 0.09 (−0.63, 0.80) | 0.813 |
| MUAC (mm) | 1.15 (0.84, 1.46) | <0.001 | 0.65 (0.35, 0.96) | <0.001 |
| MUAC z-score | 1.23 (0.76, 1.70) | <0.001 | 0.47 (0.30, 0.63) | <0.001 |
| BSF (mm) | 0.67 (0.33, 1.00) | <0.001 | 0.12 (−0.19, 0.42) | 0.451 |
| TSF (mm) | 0.66 (0.40, 0.92) | <0.001 | 0.15 (−0.10, 0.41) | 0.234 |
| TSF z-score | 1.43 (0.41, 2,46) | 0.006 | 0.50 (0.10, 0.90) | 0.014 |
| SSF (mm) | 0.53 (0.25, 0.80) | <0.001 | 0.22 (−0.01, 0.46) | 0.064 |
| SSF z-score | 1.30 (0.57, 2.04) | 0.001 | 0.48 (0.20, 0.76) | 0.001 |
| SiSF (mm) | 0.50 (0.25, 0.75) | <0.001 | 0.16 (−0.07, 0.38) | 0.168 |

BMI, body mass index; BSF, biceps skinfold thickness; FM, fat mass; LAZ, length-for-age Z-score; MUAC, mid-upper arm circumference; SiSF, suprailiac skinfold thickness; SSF, subscapular skinfold thickness; TBW, total body water; TSF, triceps skinfold thickness; WAZ, weight-for-age Z-score.

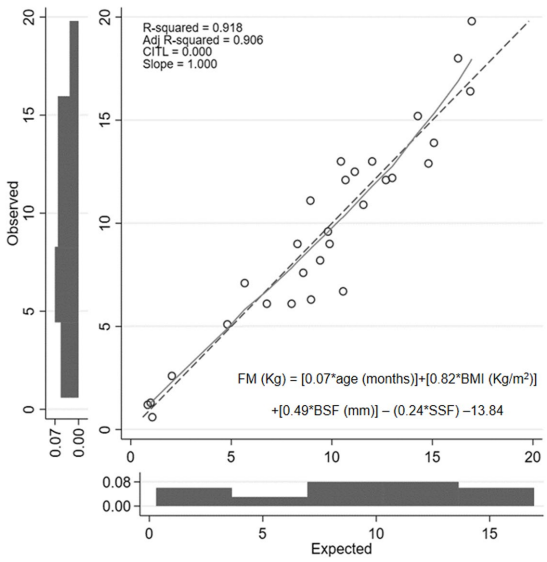


FIGURE 2
Calibration plot of fat mass value obtained from newly developed predictive equation compared with the value determined using the deuterium dilution technique. FM, fat mass; BMI, body mass index; BSF, biceps skinfold thickness; SSF, subscapular skinfold thickness.

pandemic, some families of eligible NI children were unwilling to visit the hospital and spent 4–5 h to complete the study. In addition to the number of participants we were able to enroll, 4 of 37 saliva samplings were errors in the DDT analysis. The reduced number of participants from the number expected by the sample size calculation causes a reduction in study power from 80 to 65%.

This predictive equation for the determination of FM in NI children using anthropometric parameters and age is a simple equation that may be implicated for routine use. Precise body composition determination in NI children leads to an appropriate nutrition intervention to diminish malnutrition. Further studies to validate this new predictive equation with standard methods, compare anthropometric parameters in NI children with different types of etiologies, and determine body composition in NI children with lower severity are needed.

## Conclusion

Malnutrition is common among severe NI children with home enteral nutrition, both undernutrition and overweight. Our study found that FM determined using DDT was associated with age, BMI, SSF and BSF, and we proposed a predictive equation for FM that should be further validated in clinical practice. Assessment of FM together with routine anthropometric measurements provides more effective nutrition monitoring and guides appropriate nutrition support for children with NI.

## 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 Human Research Ethic Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (Protocol No. was COA. MURA2021/390). 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

WS: principal investigator, conceptualization, methodology, data collection and analysis, and writing – original draft. OD: conceptualization, methodology, data analysis, revised and finalized manuscript, and supervision. JP and SS: conceptualization, methodology, and revised manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Impact of food-based fortification on nutritional outcomes and acceptability in older adults: systematic literature review

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**Background:** "Do it yourself" (DIY) food-based fortification involves adding fortificants into everyday foods. It is a flexible solution that allows older people with reduced appetite to meet their nutritional needs.

**Objectives:** The aims of the systematic review are (a) to describe DIY fortified recipes, (b) to evaluate their acceptability, and (c) to evaluate whether they are effective levers to improve nutritional outcomes in older people.

**Methods:** A systematic search of 3 databases (Web of Science, PubMed, Scopus, last searched on January 2022) was undertaken. Main eligibility criteria include older adults aged ≥60 years living at home, in an institution or in hospital. Studies carried out for a specific medical condition or targeting only micronutrient fortification were excluded. After reviewing all titles/abstracts then full-text papers, key data were extracted and synthesized narratively. The quality of included studies was assessed using Kmet et al.

**Results:** Of 21,493 papers extracted, 44 original studies were included (3,384 participants), with 31 reporting nutritional outcomes, 3 reporting acceptability outcomes and 10 reporting both nutritional and acceptability outcomes. The review highlighted a wide variety of DIY fortified recipes, with additional energy ranging from 23 to 850 kcal/d ($M = 403$; SE = 62) and/or protein ranging from 4 to 40 g/d ($M = 19$; SE = 2). Compared to a standard diet, DIY fortification seems to be a valuable strategy for increasing energy and protein intake in older people. However, no strong evidence was observed on the nutritional status.

**Implication for future:** Further acceptability studies are crucial to ensure that DIY fortified foods are palatable and thus have a significant impact on the nutritional status. In addition, it would be useful for studies to better describe DIY recipes. This information would result in a better understanding of the factors that maximize the impact of DIY fortification on nutritional outcomes. Study registration: PROSPERO no. CRD42021244689.

**Systematic review registration:** PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021244689.

KEYWORDS

**elderly, enrichment, supplementation, food-first, malnutrition, intake, body weight, acceptability**

## 1. Introduction

Contrary to common beliefs, our nutritional needs decrease little with age and are sometimes higher in late adulthood than in early adulthood. With regard to caloric intake, the European Food Safety Authority (1) recommends a daily allowance from 2000 to 2,500 Kcal for people aged 50 to 59 and from 1800 to 2,300 Kcal for people aged 70 to 79. More recently Volkert et al. (2) established that recommended energy intake should reach 30 Kcal per kg of body weight per day. With regard to protein intake, recent works carried out by the PROT-AGE consortium (3) and by the European Society for Clinical Nutrition and Metabolism (EPSEN) (4) show that older people need to ingest more protein than younger people to stay healthy, to maintain their abilities and to fight infections. As a result, the daily protein intake should be 1 to 1.2 g protein per kg of body weight per day for a healthy person over 60 versus 0.8 to 1 g per kg of body weight in younger adults. The literature review by Shad et al. (5) highlighted the importance of a constant distribution of protein intake over the main meals of the day at amounts of 25–30 g/meal to avoid catabolic protein status [see also (3, 6)].

At the same time, a decline in appetite can appear with aging (7). Various studies have reported that 31 to 56% of the aged population are "small eaters" (8–10). Small eaters are characterized by a low consumption of every food category compared to the overall population – they eat foods in small or even very small amounts (8–11). A recent French survey carried out by CREDOC ("Centre de Recherche pour l'Observation et les Conditions de Vie") showed that 87% of adults aged 18–54 met the recommendations for protein intake compared with only 56% of those over 65 (12). This situation is even worse when older adults are frail and dependent. In an aged population receiving a Home-Delivery Meal (HDM) service or living in nursing homes, Sulmont-Rossé and Van Wymelbeke (13) observed that 7–8 out of 10 people did not meet their energy and/or protein needs. This study also showed that 55% of home-delivery meal recipients and 46% of people living in nursing homes had energy and/or protein intake lower than 2/3 of the recommendations. In addition to age, many factors can be at the origin of this decline in appetite, such as physiological changes, sensory decline and eating/swallowing difficulties, which appear during aging. It also can be related to "life-breaking moments" (e.g., widowhood, illness, dependence) that can amplify iatrogenic factors correlated with medications and affect sociological/psychological aspects (13). Thus, poor appetite in older adults leads to a decrease in food and nutrient intake, which increases the risk of undernutrition (14, 15). Undernutrition, a recognized pathology in the older population, corresponds to an imbalance between nutritional intake and the body's needs. This imbalance leads to weight loss, a decrease in muscle reserves and an alteration of the body's defences. In older people, undernutrition increases the risk of falls and therefore fractures. It contributes to the increase in infectious morbidity (16), nosocomial infections (17) and the appearance of pressure ulcers (18). If left untreated, undernutrition can induce or aggravate a state of fragility and dependence, which affects the quality of life and life expectancy of our elders (16, 19).

Understanding the factors responsible for appetite decline is certainly important, but a major challenge is to get older people with reduced appetite to fulfill their nutritional needs in order to prevent undernutrition and the associated consequences. Food-based fortification, which consists in incorporating ingredients of nutritional interest (namely "fortificants") in commonly consumed foods (20) in order to deliberately increasing the content of an essential nutrient in a diet without increasing (too much) the volume to be ingested, is acknowledged to be a relevant approach for older adults with reduced appetite (21). Fortificants can be: (a) regular food products (e.g., semolina, oils, butter, cream, pureed nuts, egg), or (b) macronutrients extracts (e.g., whey protein isolate, milk protein concentrate, caseinate, maltodextrin) (22, 23). Besides the numerous fortified foods developed and marketed by the food industry, "do it yourself" (DIY) fortification recipes empower older adults and their carers to take a personalized approach to their nutrition and current diet. DIY fortification is a flexible strategy that may fit better with older people's food habits and preferences: older people (or their carers) add fortificants to the food they usually eat, during the preparation of daily meals. This constitutes a significant advantage in the older population, which is often reluctant to change their consumption habits. However, DIY fortification remains largely unknown and underused by older adults as well as by caregivers and healthcare professionals although it is now known to be a relevant approach to counterbalance appetite decline and to adjust to nutritional needs (24).

The goal of the present study was to conduct a systematic review of all studies related to the nutritional and acceptability aspects of DIY food-based fortification in older people. The aims of this review are (a) to describe the DIY food-based fortification solutions and recipes that have been developed, (b) to evaluate the acceptability of these solutions in older people, and (c) to evaluate whether these solutions can be relevant and effective levers to preserve or improve nutritional outcomes in older people.

## 2. Materials and methods

The present systematic review followed the approach proposed by Xiao and Watson (25), which summarizes the evidence available on a topic to convey the breadth and depth of that topic. The protocol was written using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P, (26), see Supplementary material). The protocol was deposited on the HAL website[1] and on PROSPERO with the registration number CRD42021244689. The PRISMA checklist is available on the Supplementary material.

### 2.1. Research question

The research question is: "What are the objectives, characteristics and results of existing research conducted on the nutritional issues and/or on acceptability among older people receiving DIY fortified foods?"

1 https://hal.archives-ouvertes.fr/hal-03180038

## 2.2. Inclusion and exclusion criteria

The PICOS (Population, Intervention, Comparator, Outcome, Study design) eligibility criteria was as follows (27):

*Population:* Any studies focusing on adults aged 60 years and older living either at home, in an institution or in hospital was eligible for inclusion. Older adults of all nutritional status, cognitive status and oral ability (e.g., chewing, swallowing) were eligible for inclusion. Studies carried out in the context of a specific medical condition (e.g., cardiac rehabilitation, renal failure, cancers, diabetes) were excluded.

*Intervention:* Any DIY food-based fortification intervention was eligible for inclusion (e.g., incorporating ingredients of nutritional interest in food products). Fortification in energy and/or macronutrients was eligible for inclusion. Studies without an intervention (e.g., observational studies) were relevant for inclusion. Were excluded from the review: (a) studies targeting only micronutrient fortification, non-food dietary supplement or bio-fortification (genetically modified crop), (b) studies using only fortified food developed and marketed by the Food Industry, and (c) interventions targeting artificial nutrition (e.g., tube feeding, parenteral feeding, enteral feeding).

*Comparators:* As the present review aimed at compiling DIY food-based fortification recipes and reporting their acceptability, any comparator was eligible for inclusion (e.g., studies comparing food-based fortification versus Oral Nutritional Supplements (ONS), or studies comparing two types of fortified food). In addition, studies without a comparator were eligible for inclusion.

*Outcomes:* Three categories of outcomes were considered: (a) characterization of the nutritional intake (e.g., dietary pattern, nutrient intake), (b) characterization of the nutritional status (e.g., body mass index (BMI), weight, undernutrition) and (c) characterization of the acceptability (e.g., liking, preference, pleasure).

*Study design:* All types of study design including interventional and observational design were eligible. All period of times and duration of follow-up were eligible.

*Other:* No restriction was set for the publication date. Only publications written in English were included because of the uncertainty surrounding the words used to refer to the concept of "DIY food-based fortification" in foreign languages. Narrative review, conference abstracts, editorials, and grey literature were excluded.

## 2.3. Information sources and search strategy

A search strategy with both thesaurus and free-text terms was developed – after repeated attempts and adjustments – to retrieve relevant articles in the following databases: Web of Science (WOS), PubMed and Scopus (Supplementary material). Separate title, abstract and keywords searches were conducted for older people, food-based fortification and outcomes in February 2021. An update was performed in January 2022. The results for the three separate search strings were combined to identify relevant articles. Afterwards, for further screening, references from selected articles and systematic reviews were checked manually in case they were not identified during the whole search process. After duplicates removal, titles and abstracts in the first step and full texts in a second step were screened by two independent reviewers (AG and MP) according to the agreed inclusion and exclusion criteria. For each screening level, a training exercise was conducted before the starting of the screening process on a random sample of 100 titles and abstracts and 10 full texts to ensure high inter-reviewer reliability. Disagreements between reviewers were resolved by consensus or by consulting a third reviewer (CSR or VVW). The reasons for exclusion were recorded at the full-text stage (the list of excluded studies at the full-text stage and the reasons of exclusion are presented on Supplementary material).

## 2.4. Charting the data

A standardized data summarization form was developed *a priori* and revised, as needed, after the completion of a training exercise completed on a sample of 5 articles. All included studies were summarized by two reviewers (AG and MP), independently, with conflicts resolved by a third reviewer (CSR or VVW). The data summarization included the following items:

- Article identifiers (authors, year of publication)
- Study identifiers (objective, design, country)
- Population (age, gender, sample size, inclusion and exclusion criteria)
- Intervention (description of the DIY fortification recipes)
- Comparator (if applicable)
- Outcomes (endpoints, measurement method, main results)

## 2.5. Quality assessments

All included studies were independently assessed for quality by two reviewers (AG and MP); conflicts were resolved by consensus. The articles' quality was assessed with the quality assessment criteria developed by Kmet et al. (28). The criteria are presented in Supplementary material. In addition, the description quality of the DIY fortification recipes (fortificants, food matrices, concentration) was assessed (but not included in the quality score).

## 2.6. Collating, summarizing and reporting the results

A descriptive numerical summary of the characteristics of the included studies was performed. Tables and graphs were created to reflect the number of studies included, study designs and settings, publication years, the characteristics of the study populations, the outcomes reported, and the countries where the studies were conducted. In line with systematic literature review guidelines, the quality of the included studies was assessed (25, 29).

# 3. Results

## 3.1. Characteristics of the included studies

On the 21,493 articles retrieved, 253 records were kept for full text screening and 49 studies were included in the systematic review: 44 original studies (Figure 1; 3,384 participants) and 5 systematic

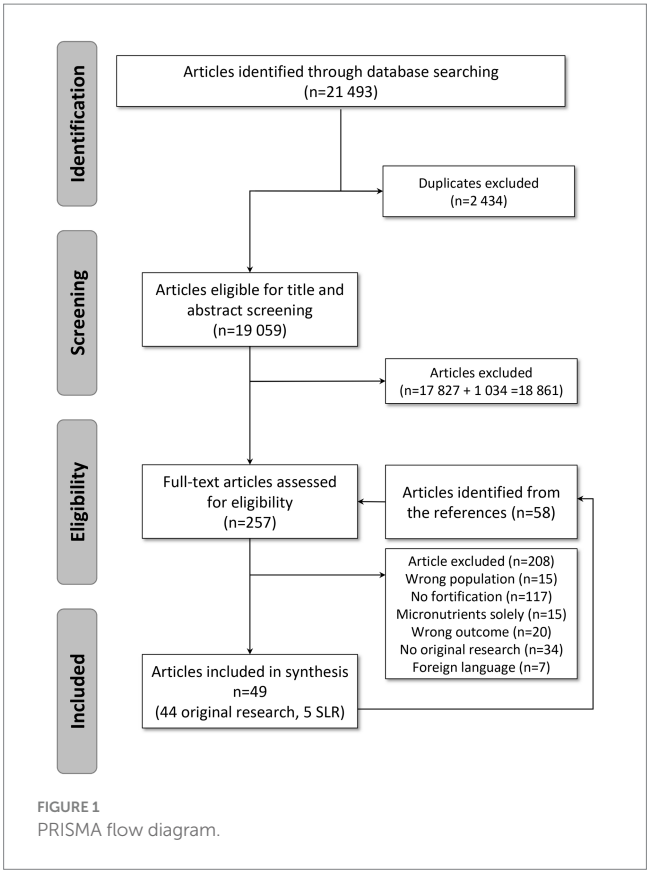


FIGURE 1
PRISMA flow diagram.

literature reviews (21–24, 30). The reasons for excluding papers were: no original research ($n = 18$), wrong population ($n = 18$), no DIY food-based fortification ($n = 135$), fortification with micronutrients only ($n = 15$), wrong outcomes ($n = 18$). Wrong outcomes included functional outcomes (muscle strength), gastric emptying, glycemia, gut hormones, bone mineral density, quality of life. Two articles (31, 32) were excluded because they did not provide enough information about the nutritional strategy used.

The included articles were published between 1996 and 2021, and most were published after 2011 ($n = 34$) (Table 1). The studies mainly took place in Europe ($n = 33$). The rest took place in Australia ($n = 4$), North America ($n = 4$) or Asia ($n = 3$). The setting was most often the hospital ($n = 20$) followed by nursing homes ($n = 13$) and home setting ($n = 13$). Twenty-seven studies of the selection were longitudinal with follow-up times between 10 days to 12 months and 16 studies were cross-sectional (Table 1). In addition, 30 studies used a between-subject design while 13 studies used a within-subject design; only 1 study was observational. Finally, sample sizes varied (ranging from 7 to 320 participants), but most studies recruited 20 to 49 subjects ($n = 17$).

Among the 44 original research studies, 3 were fully focused on the acceptability outcome (33–35). Among the 41 remaining articles, the majority ($n = 31$) were entirely dedicated to nutritional outcomes. Finally, 10 articles were "mixed" and assessed both nutritional and acceptability outcomes.

A descriptive summary of the included studies yielded the four following topics:

- Description of DIY fortification recipes: which types of food are fortified? Which nutrients are added? In what form? At which concentration?

TABLE 1 Characteristics of the systematic literature review articles.

| | Nb | % |
|---|---|---|
| Year of publication | | |
| 1990–2000 | 3 | 6.8% |
| 2001–2010 | 7 | 15.9% |
| 2011–2021 | 34 | 77.3% |
| Design | | |
| Longitudinal study | 27 | 62.8% |
| Of which < 1 month | 7 | 16.3% |
| Of which 1–3 months | 15 | 34.9% |
| Of which > 3 months | 5 | 11.6% |
| Cross-sectional survey | 16 | 37.2% |
| Between-subject | 30 | 68.2% |
| Within-subject | 13 | 29.5% |
| Observational | 1 | 2.3% |
| Country | | |
| Australia | 4 | 9.1% |
| Belgium | 1 | 2.3% |
| Canada | 2 | 4.5% |
| Denmark | 5 | 11.4% |
| Finland | 3 | 6.8% |
| France | 2 | 4.5% |
| Germany | 3 | 6.8% |
| Japan | 1 | 2.3% |
| Korea | 1 | 2.3% |
| Netherlands | 8 | 18.2% |
| Sweden | 4 | 9.1% |
| Switzerland | 1 | 2.3% |
| Taiwan | 1 | 2.3% |
| UK | 6 | 13.6% |
| USA | 2 | 4.5% |
| Setting | | |
| Home | 13 | 28.3% |
| Of which home care | 2 | 4.3% |
| Of which HDM | 2 | 4.3% |
| Hospital | 20 | 43.5% |
| Nursing home | 13 | 28.3% |
| Nb participants | | |
| >200 | 2 | 4.4% |
| 100–200 | 8 | 17.8% |
| 50–99 | 14 | 31.1% |
| 20–49 | 17 | 37.8% |
| <20 | 4 | 8.9% |

HDM, home-delivery meal.

- Assessment of DIY fortified foods acceptability: to which extent do older people like fortified food? Do the sensory characteristics of fortified foods fulfil older people' sensory expectations and preferences?

- Assessment of the nutritional impact of DIY food-based fortification: did older people who received fortified food improve their nutritional intake and nutritional status compared to a standard diet?
- Comparison of DIY food-based fortification with other alternatives (e.g., dietary counseling, Oral Nutritional Supplement – ONS): is fortified food more acceptable and/or does it provide a nutritional benefit compared to other alternatives?

## 3.2. Quality assessment

A quality assessment was performed for each outcome, i.e., nutritional outcome and acceptability outcome (Supplementary material). In fact, in mixed articles, different panels and designs were often used for nutritional and acceptability outcomes.

Regarding nutritional outcomes, the methodological quality of the studies was in general good with an average quality score of 0.92 (standard deviation: 0.09) ranging from 0.62 (36) to 1 (37–54) (Supplementary material). Overall, recruitment of participants was the variable that was the most poorly rated in the selected studies. This was because the majority of studies did not detail the recruitment procedure nor the precise localization where the study took place. Sample size and control for confounding factors were badly rated because a large number of studies did not reach an appropriate sample size or did not consider confounding variables (e.g., age, gender, Body Mass Index (BMI), weight, nutrition status) in data analysis. Study design and subject description factors were moderately rated due to insufficient/incoherent information preventing clear understanding of concerned articles.

The methodological quality of the 13 studies related to acceptability outcomes was on the whole lower than for the nutritional outcomes, with an average quality score of 0.75 (standard deviation: 0.23) ranging from 0.33 (37) to 1 (33, 43, 44) (Supplementary material). Usually, recruitment of participants, sample size, analytic methods and results were the lowest rated factors. As for the nutritional quality assessment, the majority of studies did not detail the recruitment procedure nor the precise localization where the study took place. Moreover, most studies did not clearly describe the analytic method used when it was mentioned. For 4 criteria (sample size, results, outcomes measures and study design) the poor quality is related to the fact that the acceptability measure was not the main outcome of the article.

Finally, the description of the DIY fortification recipes was also poorly rated: very few studies provided precise information about food matrices, fortificants and recipes.

## 3.3. Description of DIY fortified recipes

Table 2 shows the description of the DIY fortified recipes. On the whole, 7 articles implemented energy fortification, 18 implemented

TABLE 2 Description of DIY fortified recipes.

| Author(s) (year), Country | Population | Type of fortification | Matrices | Fortificants | Target meal | Additional supply from fortification | Detailed recipe given? |
|---|---|---|---|---|---|---|---|
| Allepaerts et al. (2020) (53), Belgium | Hospital ($n$ = 78)<br>85 y<br>77% of women | Energy | Homemade cream snack, soup | Not specified | Snack, lunch and dinner | + 540 kcal/d<br>+ 24 g proteins/d | No |
| Arjuna et al. (2018) (48), Australia | Home with HDM ($n$ = 29)<br>83 y<br>55% of women | Protein & Energy | Soup, dessert Sauces | + Skim-milk protein or cream or custard<br>+ Extra cheese or margarine or oil | Lunch | + 550 kcal/d<br>+ 30 g proteins/d | No |
| Barton et al. (2000) (55), UK | Hospital ($n$ = 35)<br>77 y<br>63% of women | Energy | Meals | + Fats (butter, cream and cheese)<br>+ Carbohydrates (glucose polymers) | Day | + 200 kcal/d<br>- 5 g proteins/d<br>- 20% portion size/ meal | No |
| Beelen et al. (2017a) (45), Netherlands | Hospital and nursing home ($n$ = 22)<br>83 y<br>59% of women | Protein | Bread, soup, fruit juice, mashed potatoes | + Soy or dairy proteins | Day | Not specified | No |
| Beelen et al. (2017b) (56), Netherlands | Home ($n$ = 75)<br>77 y<br>56% of women | Protein | Bread, meatballs, dairy dessert | Not specified | Day | Not specified | No |
| Beelen et al. (2018) (57), Netherlands | Hospital ($n$ = 147)<br>79 y<br>55% of women | Protein | Bread, soup, beverages, beef, mashed potatoes, ice cream | Not specified | Day | Not specified | No |

*(Continued)*

TABLE 2 (Continued)

| Author(s) (year), Country | Population | Type of fortification | Matrices | Fortificants | Target meal | Additional supply from fortification | Detailed recipe given? |
|---|---|---|---|---|---|---|---|
| Beermann et al. (2016) (42), Denmark | Hospital ($n = 62$)<br>69 y<br>Not specified | Protein | Skyr<br>Yoghurt, oatmeal<br>Omelet | + Cream<br>+ WPI<br>+ Cheese, ham | Breakfast | Maximum intake: 20 g proteins/ breakfast | No |
| Björkman et al. (2012) (39), Finland | Nursing home ($n = 99$)<br>84 y<br>76% of women | Protein | Fruit juice | + Whey protein | Day | + 20 g proteins/d | Yes |
| Bonnefoy et al. (2010) (58), France | Hospital ($n = 26$)<br>81 y<br>58% of women | Protein | Liquid food, semi-liquid food | + Hyperprotidine powder (BCAAs) | Lunch and dinner | + 11–18 g proteins/d (of which 47.5% BCAAs) | No |
| Castellanos et al. (2009) (59), USA | Nursing home ($n = 26$)<br>87 y<br>70% of women | Protein & Energy | Oatmeal<br>Soup<br>Potato side dish | + Fats + Sugar<br>+ Fats + Starchy ingredients<br>+ Fats<br>Fats (margarine, high-fat dairy products and kosher non-dairy substitute…) Proteins (dairy or eggs) | Breakfast and lunch | + 4.17 kcal/g food<br>+ 0.06 g protein/g food | No |
| Evans et al. (2017) (46), Canada | Home ($n = 41$)<br>60 y<br>64% of women | Protein | Orange juice | + L-carnitine combination sachet or + L-carnitine sachet | Breakfast | + 1.5–6.5 g proteins/d | Yes |
| Gall et al. (1998) (60), UK | Hospital ($n = 143$)<br>67 y<br>66% of women | Protein & Energy | Dessert<br>Soup | + Double cream<br>+ Dried skimmed-milk or milk powder | Lunch and dinner | Not specified | No |
| Hashimoto et al. (2015) (61), Japan | Hospital ($n = 28$)<br>74 y<br>57% of women | Protein | Meals | + Casein powder or + Soy protein isolate | Lunch | + 7.1–7.5 g proteins/d | No |
| Irvine et al. (2004) (36), France | Hospital ($n = 12$)<br>84 y<br>33% of women | Protein & Energy | Semi-skimmed milk | + Fresh cream, sugar, dextrin maltose or + Protifar protein powder, sugar, dextrin maltose | Breakfast | + 250 kcal/d<br>+ 3.5–20 g proteins/d | No |
| Iuliano et al. (2013) (62), Australia | Nursing home ($n = 130$)<br>88 y<br>78% of women | Protein & Energy | Soup<br>Vegetables | + Milk powder or evaporated milk or cheese<br>+ Cheese-based sauces | Day | Not specified | No |
| Lee et al. (2013) (40), Taiwan | Nursing home ($n = 83$)<br>80 y<br>58% of women | Protein | Warm drink | + Soy powder | Snack | + 250 kcal/d<br>+ 9.5 g proteins/d | No |
| Leslie et al. (2013) (63), UK | Nursing home ($n = 31$)<br>91 y<br>88% of women | Energy | Cereal, porridge, soup, dessert<br>Potatoes<br>Malted milk snack | + Double cream<br>+ Butter<br>Replace water by whole milk | Day | + 400 kcal/d | No |

*(Continued)*

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TABLE 2 (Continued)

| Author(s) (year), Country | Population | Type of fortification | Matrices | Fortificants | Target meal | Additional supply from fortification | Detailed recipe given? |
|---|---|---|---|---|---|---|---|
| Lorefält et al. (2005) (64), Sweden | Hospital ($n = 10$)<br>82 y<br>60% of women | Protein & Energy | Meals | + Fats: cream, butter, mono and poly unsaturated oils<br>+ Proteins: gruels of maize | Lunch and dinner | + 0 kcal/d<br>+ 0 g proteins/d<br>– 50% portion size | No |
| Mertz et al. (2021) (65), Denmark | Home ($n = 184$)<br>70 y<br>46% of women | Protein | Fluids | + Protein powder (whey or collagen) | Breakfast and lunch | + 40 g protein/d | No |
| Mortensen et al. (2019) (51), Denmark | Hospital ($n = 92$)<br>69 y<br>56% of women | Protein | Milkshake, chocolate cake, pizza bun, fruit salad, bun, cheese crackers, sandwich, jelly | + Egg or shun<br>+ Whey protein or gelatine or pea protein | Snack | 18–27 kcal/d<br>15–23 g proteins/d | No |
| Munk et al. (2013) (66), Denmark | Hospital ($n = 79$)<br>73 y<br>75% of women | Energy | Meat, fish, egg, vegetables, soup, cereal, pulse, bread, dairy, beverage, dessert | + Fats (butter, cream, oil…) | Day | Not specified | No |
| Munk et al. (2014) (41), Denmark | Hospital ($n = 78$)<br>75 y<br>58% of women | Protein & Energy | Meat, fish, egg, vegetables, soup, cereal, dessert | + Natural energy-dense ingredients<br>+ High-quality protein powder GlanPro | Day | + 0.6–4.7 kcal/g food<br>+ 6.1–11.5 g proteins/serving | No |
| Neelemaat et al. (2012) (67), Netherlands | Hospital + Home ($n = 150$)<br>75 y<br>55% of women | Protein & Energy | Oatmeal, desserts Dishes | + Cream, maltodextrin<br>+ Milk products or butter or margarine | Day | + 750 kcal/d<br>+ 30 g proteins/d | No |
| Niccoli et al. (2017) (47), Canada | Hospital ($n = 47$)<br>81 y<br>68% of women | Protein | Porridge, milk based-drink | + Whey protein | Day | + 24 g proteins/d | No |
| Norton et al. (2020) (33), UK | Home ($n = 32$)<br>75 y<br>56% of women | Protein | Cupcakes | + WPC or WPe | Snack | + 6 g proteins/100 g | Yes |
| | Home ($n = 42$)<br>74 y<br>55% of women | Protein | Cake, biscuits | + WPI | Snack | Cake: + 6 g proteins/100 g<br>Biscuit: + 10 g proteins/100 g | Yes |
| Nykänen et al. (2019) (52), Finland | Home with home care ($n = 85$)<br>83 y<br>72% of women | Energy | Berry purée | + Sugar, rapeseed oil | Snack | Not specified | No |
| Ödlund Olin (2003) (69), Sweden | Nursing home ($n = 35$)<br>82 y<br>51% of women | Energy | Beef in horseradish sauce<br>Fruit syrup dessert<br>Oven-baked sausage<br>Mashed potatoes, boiled broccoli | Whipping cream instead of milk<br>+ Hydrolysed starch, cream instead of milk<br>+ Cheese<br>+ Margarine | Lunch and dinner | + 500 kcal/d | No |

*(Continued)*

TABLE 2 (Continued)

| Author(s) (year), Country | Population | Type of fortification | Matrices | Fortificants | Target meal | Additional supply from fortification | Detailed recipe given? |
|---|---|---|---|---|---|---|---|
| Ödlund Olin et al. (1996) (70), Sweden | Hospital ($n = 36$)<br>82 y<br>67% of women | Energy | Vegetable casserole<br>Rosehip soup<br>Fish quenelle<br>Fish soup, pancake with jam<br>Ragout with liver<br>Potatoes<br>Beans | + Oil, cream<br>+ Almond biscuit<br>+ Sour cream<br>+ Cream<br>+ Sour cream<br>+ Milk<br>+ Margarine | Lunch and dinner | + 850 kcal/d | No |
| Ott et al. (2019) (71), Germany | Nursing home ($n = 16$)<br>87 y<br>88% of women | Protein & Energy | Cream, mousse<br>Vegetable<br>Meat, fish, smoothie | + Whey protein<br>+ Rapeseed oil<br>+ Rapeseed oil, whey protein | Day | + 600 kcal/d<br>+ 30 g proteins/d | No |
| Park et al. (2018) (49), Korea | Home ($n = 99$)<br>77 y<br>65% of women | Protein | Corn silk tea | + Whey protein | Snack | + 0.4–0.7 g proteins/kg/d | Yes |
| Polonen et al. (2017) (72), Finland | Home with home care ($n = 227$)<br>84 y<br>71% of women | Protein & Energy | Food<br>Bread | + Oils<br>+ Margarine or cheese | Day | Not specified | No |
| Seemer et al. (2021) (54), Germany | Nursing home ($n = 50$)<br>84 y<br>74% of women | Protein | Cream (sweet or savory version) | + Whey protein | Lunch | + 125–250 kcal/d<br>+ 10–20 g protein/d | Yes |
| Silver et al. (2008) (37), USA | Home with HDM ($n = 45$)<br>84 y<br>69% of women | Protein & Energy | Mashed potatoes<br>Broccoli casserole | + Eggs and replacing water by non-dairy kosher creamer<br>+ Almonds, mayonnaise | Lunch | + 300 kcal/d<br>+ 10 g proteins/serving | No |
| Smoliner et al. (2008) (73), Germany | Nursing home ($n = 52$)<br>83 y<br>73% of women | Protein & Energy | Soups<br>Sauces<br>Milk basis snack | + Hydrolyzed milk, heavy cream<br>+ Hydrolyzed milk, rapeseed oil<br>+ Hydrolyzed milk | Day | Not specified | Yes |
| Sossen et al. (2020) (74), Australia | Nursing home ($n = 122$)<br>88 y<br>76% of women | Protein & Energy | Milkshake, fruit juice, milk, porridge<br>Meals | Not specified<br>+ Butter | Day | + 701 kcal/d<br>+ 27 g proteins/d | No |
| Starke et al. (2011) (38), Switzerland | Hospital ($n = 132$)<br>73 y<br>Not specified | Protein & Energy | Meal | + Maltodextrin<br>+ Rapeseed oil<br>+ Cream and/or protein powder | Day | Not specified | No |
| Stelten et al. (2015) (75), Netherlands | Hospital ($n = 47$)<br>80 y<br>55% of women | Protein | Drinking yoghurt | + WPC | Day | + 13 g proteins/serving (*ad libitum*) | No |
| Stow et al. (2015) (76), UK | Nursing home ($n = 67$)<br>Not specified<br>82% of women | Protein & Energy | Fruit, dessert, dairy, beverage | + Milk powder, cream | Day | + 600 kcal/d<br>+ 20–25 g proteins/d | No |

*(Continued)*

TABLE 2 (Continued)

| Author(s) (year), Country | Population | Type of fortification | Matrices | Fortificants | Target meal | Additional supply from fortification | Detailed recipe given? |
|---|---|---|---|---|---|---|---|
| Tsikritzi et al. (2015) (34), UK | Home ($n$ = 67)<br>71 y<br>Not specified | Protein & Energy | Sauces | + Unsalted butter<br>or + Double cream<br>or + WPI, maltodextrin<br>or + Whole milk, double cream<br>or + Double cream, vegetable oil, unsalted butter | Sauce | + 69–150 kcal/100 g<br>+ 0.0–1.3 g proteins/100 g | Yes |
| Van Til et al. (2015) (77), Netherlands | Hospital ($n$ = 34)<br>78 y<br>68% of women | Protein | Drinking yoghurt | + WPC | Day | + 25 g proteins/d | No |
| Wendin et al. (2017) (35), Sweden | Home ($n$ = 7)<br>60–69 y<br>71% of women | Protein | Muffin | + Almond flour<br>or + Soy flour<br>or + Whey protein | Snack | + 3–7.7 g proteins/100 g muffin | Yes |
| Young et al. (2018) (50), Australia | Hospital ($n$ = 320)<br>81 y<br>53% of women | Protein & Energy | Porridge, sauces, Soups, Desserts | Not specified | Day | Maximum intake:<br>2030 kcal/d<br>77 g proteins/d | No |
| Ziylan et al. (2016) (43), Netherlands | Home ($n$ = 120)<br>71 y<br>54% of women | Protein & Energy | Sauce, mashed potatoes<br>Creamed spinach | Replacing water with milk powder + cooking cream<br>+ Milk powder, cooking cream | Lunch | + 45–90 kcal/d<br>+ 5 g proteins/d | No |
| Ziylan et al. (2017) (44), Netherlands | Nursing home ($n$ = 42)<br>74 y<br>67% of women | Protein | Meal | Replacing low protein density ingredients (water, carrots, potatoes, sauce) by high protein density ingredient (milk powder, peas, meat) | Lunch or diner | + 90 kcal/d<br>+ 8 g proteins/d | No |

y, years old; d, day; WPI, whey protein isolate; WPC, whey protein concentrate; Wpe, whey permeate.

protein fortification and 19 implemented a combination of protein and energy fortification. It should be noted that 10 articles did not specify the nature of food matrices (38, 44, 55, 58, 61, 64, 65, 67, 72, 74) and 5 articles did not specify the nature of the fortificants (50, 53, 56, 57, 74). Only 8 articles provided enough details about the recipes for them to be reproduced by a third party (33–35, 39, 46, 49, 54, 73).

Overall, 137 DIY fortified recipes were listed: 75 savory and 62 sweet. Among these recipes, 64 were meant to be eaten cold and 67 were meant to be eaten hot (6 can be eaten cold or hot). The food matrices included desserts ($n$ = 20 articles; mousse, pie, muffin, cake, biscuit, ice-cream…), meat and fish dishes ($n$ = 18; meatball, chicken sticks, marinated duck, baked salmon…), side dishes ($n$ = 17; purée, sautéed vegetables), dairy products ($n$ = 17; milk, yoghurt, cream), soups ($n$ = 14), carbohydrate-based dishes ($n$ = 14; oatmeal, cereal, risotto, pancake), beverages ($n$ = 9; fruit juice, tea), sauces ($n$ = 9), breads ($n$ = 8), fruits ($n$ = 7; compote/purée, salad, smoothie), eggs dishes ($n$ = 3; omelet) and pulse-based dishes ($n$ = 1). It is interesting to note that food matrices included both liquids (milk, soup, fruit juice…), semi-liquid foods (purée, yoghurt…) and solid foods (cake, chicken sticks, bread). There was a large variability in the number of matrices used for fortification in the articles. Twelve articles used one only matrix category to be fortified (33–36, 39, 40, 46, 49, 52, 54, 75, 77). Munk et al. (66) developed 36 fortified dishes in collaboration with dietitians, chefs and patients from a hospital. These dishes covered a large range of different food types (soup, meat and fish dishes, vegetable dishes, bread, dessert, beverages).

Twenty different fortificants were identified across all the studies, including 10 regular food ingredients and 10 macronutrient isolates or concentrates. Four articles (38, 45, 59, 66) did not provide enough details about fortificants ("high fat dairy food," "dairy," "non-dairy substitute," "natural energy-dense ingredient," "protein powder," "soy origin"), thus they could not be classified. Seven fortificants targeted energy fortification, 8 targeted protein fortification and 5 targeted both. Most of the fortificants were powdered ($n$ = 11). Other fortificants were solid ($n$ = 4), semi-liquid ($n$ = 3) or liquid ($n$ = 2). Energy fortificants included cream ($n$ = 20 articles), butter/margarine ($n$ = 13), oils ($n$ = 10), carbohydrates ($n$ = 7), hydrolyzed starch ($n$ = 1), mayonnaise ($n$ = 1) and maize ($n$ = 1). Protein fortificants included whey protein ($n$ = 15 articles), protein concentrates/isolates ($n$ = 5; Protifar, Hyperprotidine, L-Carnitine…), soy ($n$ = 3), pea ($n$ = 2), meat ($n$ = 2), collagen ($n$ = 1), casein ($n$ = 1), and gelatine ($n$ = 1). Energy and protein fortificants included milk powder ($n$ = 10), cheese ($n$ = 7), milk ($n$ = 5), eggs ($n$ = 3) and almonds ($n$ = 3). Finally, Figures 2, 3 illustrate the wide variability regarding the additional load of energy and

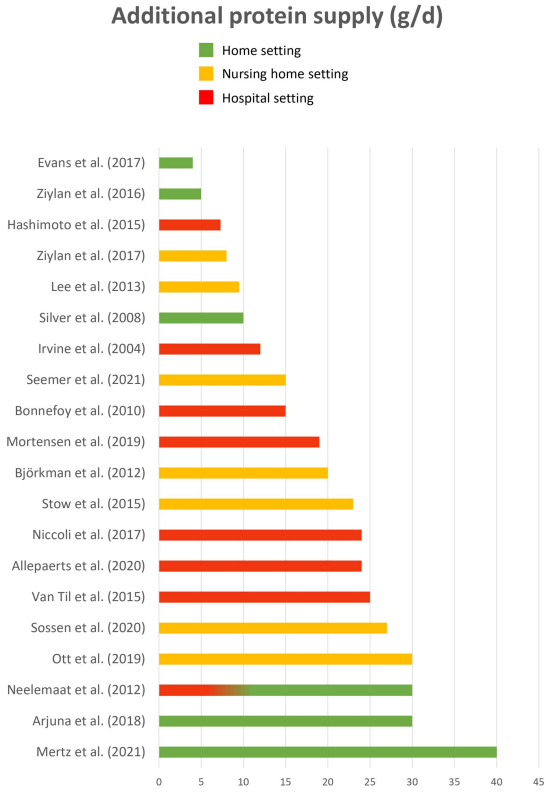


FIGURE 2
Additional protein load (g/d).

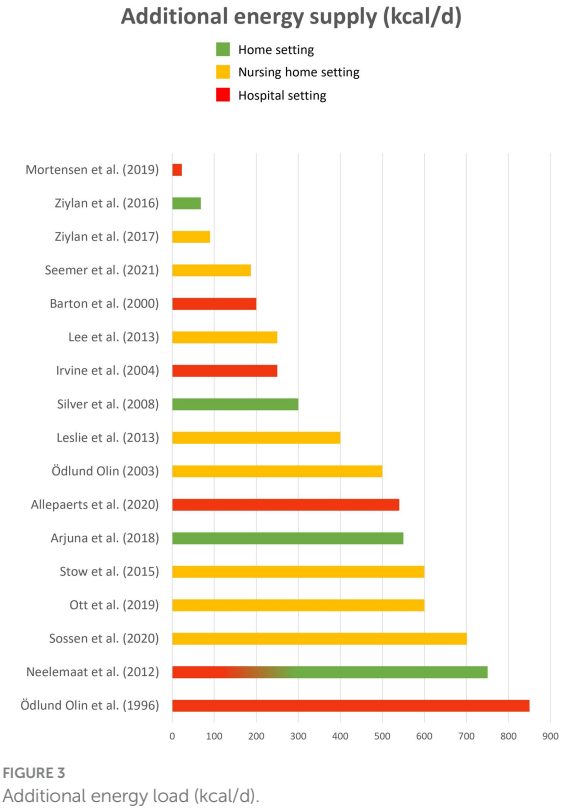


FIGURE 3
Additional energy load (kcal/d).

protein provided by fortified food across the studies. This additional load varies from 23 to 850 kcal / day for energy (M = 403; SE = 62) and from 4 to 40 g / day for protein (M = 19; SE = 2).

## 3.4. Assessment of DIY fortified foods acceptability

Thirteen studies have assessed consumer acceptability for DIY fortified foods (Table 3). All these studies conducted the acceptability evaluation with older people except for one (71), who asked nursing home staff to provide feedback on product acceptance based on residents' observation. Six articles (33, 34, 43, 44, 52, 59) used liking scales to assess product acceptance while the others only collected qualitative data through interviews, focus groups or an acceptability survey. However, most of the articles do not provide enough information about the methodology used to assess acceptability and/or about the results. In most of the articles ($n = 10/13$), acceptability was only a secondary outcome while nutrition was the first one. In these studies, acceptability tests were usually conducted with the same sample as the one recruited for nutritional assessment (the whole sample in 6 articles; a smaller sub-sample in 2 articles). Three articles (33–35) were dedicated to assessing acceptability of DIY fortified foods versus regular foods.

Seven articles provided results on comparison between DIY fortified and regular foods. Among them, 4 articles (37, 43, 44, 59, 75) reported no significant difference in acceptability when comparing fortified and regular foods while 2 articles (33, 35) reported that fortified foods were less appreciated than regular food. Only one article reported that some fortified foods were more appreciated than regular food, but it depended on the nature of the fortificant added to the food (34). In fact, tomato sauce fortified with cream or with a mix of whey protein and maltodextrin were more liked than regular tomato sauce, but tomato sauce fortified with butter was less liked than regular tomato sauce. Wendin et al. (35) also showed some difference between foods fortified with different fortificants: the regular muffin was more liked than the muffin fortified with almond flour, which was more liked than the whey muffin, itself more liked than the soy muffin.

## 3.5. Assessment of the nutritional impact of DIY food-based fortification

Forty studies assessed the impact of diet enrichment including DIY food-based fortification on nutritional outcomes (food and/or nutrient intakes, nutritional status or body weight) compared to a standard diet (Table 4). Among these studies, 3 combined DIY food-based and diet-based fortification (i.e., modifying the diet by adding nutritionally rich foods), 6 combined food-based fortification and fortified foods marketed by the Food Industry, 1 combined food-based fortification and Oral Nutritional Supplements (ONS), and 2 combined food-based fortification, diet-based fortification and ONS, while 27 studies assessed the impact of DIY food-based fortification alone. Nutritional intake was mainly measured by using dietary record. Nutritional status was mainly assessed by measuring body weight or BMI (20 studies), by using the Mini-Nutritional Assessment Questionnaire [MNA, 8 studies – (39, 48, 49, 52, 57, 72, 73, 77)] or by measuring muscle mass [4 studies – (39, 46, 49, 58)]. A few studies

TABLE 3 DIY fortified food acceptability assessment.

| Author(s) (year), Country | Panel | Products | Tests/outcomes | Main results |
|---|---|---|---|---|
| Norton et al. (2020) (33), UK | Home ($n = 32$)<br>75 y<br>56% of women | FF vs. SF products:<br>Cupcakes | Liking scale<br>Free comment | FF significantly reduced overall liking compared to SF. Generally positive comments relating to flavor of both FF and SF. FF resulted in a greater number of negative comments related to texture compared to SF. |
| | Home ($n = 42$)<br>74 y<br>55% of women | FF vs. SF products:<br>Cakes and biscuits | Liking scale<br>Free comment<br>Preference test | FF significantly reduced overall liking compared to SF. Generally positive feedbacks for SF while negative feedbacks were generated for FF related to both flavor and texture. |
| Tsikritzi et al. (2015) (34), UK | Home ($n = 67$)<br>71 y | FF vs. SF products:<br>Tomato sauce and gravy | Liking scale | Tomato sauce: 2 FF were significantly more liked than SF, while 1 FF was not different from SF.<br>Gravy: FF and SF not different. |
| Wendin et al. (2017) (35), Sweden | Home ($n = 7$)<br>60–69 y<br>71% of women | FF vs. SF products:<br>Muffin | Focus group | SF significantly more liked and accepted than the FF versions. |
| Arjuna et al. (2018) (48), Australia | Home with HDM ($n = 29$)<br>83 y<br>55% of women | FF and SF products | Acceptability survey | FF and SF not compared.<br>For both FF and SF, 50% of participant were (very) satisfied, 16% were unsure and 33% dissatisfied. |
| Beelen et al. (2017a) (45), Netherlands | Hospital and nursing home ($n = 22$)<br>83 y<br>59% of women | FF and SF products:<br>Bread, soup, fruit juice, mashed potatoes | Free comment | Results not provided. |
| Castellanos et al. (2009) (59), USA | Nursing home ($n = 21$ subjects different from the main study) | FF vs. SF products:<br>Oatmeal, soup, start dish | Hedonic test | FF and SF not different.<br>(data not shown) |
| Munk et al. (2013) (66), Denmark | Hospital ($n = 11$ subjects different from the main study) | FF menu | Focus group<br>Tasting session | Results not provided. |
| Nykänen et al. (2019) (52), Finland | Home with home care ($n = 85$)<br>83 y<br>72% of women | FF products:<br>Snack | Liking scale | Participants reported acceptability with the product's taste.<br>(data not shown) |
| Ott et al. (2019) (71), Germany | Nursing staff from the nursing home | FF menu | Nursing staff's feedback based on residents' observation | Enhanced appetite and pleasure with eating were described for 5 residents, whereas 1 did not like the food. |
| Silver et al. (2008) (37), USA | Older foodservice staff and registered dietitian from the study | FF vs. SF products | Tasting session | Results not provided. |
| Stelten et al. (2015) (75), Netherlands | Hospital ($n = 47$)<br>80 y<br>55% of women | FF vs. SF products:<br>bread and drinking yoghurt | Acceptability survey | For both FF and SF, majority of participants were neutral/positive (77% for bread, 87% for drinking yoghurt) about the taste of the products with no differences between FF and SF. |
| Ziylan et al. (2016) (43), Netherlands | Home ($n = 120$)<br>71 y<br>54% of women | FF vs. SF products:<br>beef and chicken meal | Liking scale | No differences between FF and SF products.<br>Overall liking varied between 5.4 to 6.0. |
| Ziylan et al. (2017) (44), Netherlands | Nursing home ($n = 42$)<br>74 y<br>67% of women | FF vs. SF products:<br>meals and bread | Liking scale<br>Acceptability | No differences about overall evaluation of products. Both FF and SF meals were score 7.7. |

y, year old; FF, fortified foods; SF, standard foods.

used other indicators such as the Subjective Global Assessment (74) or albumin and pre-albmin (40, 47, 52, 58, 72).

When all the studies are considered, results highlight that provided protein-fortified foods led to a significant increase in protein intake (26 studies over 29) and that provided energy-fortified led to a significant increase in energy intake (15 studies over 20). Only a few studies showed a significant impact of DIY fortification on nutritional status compared to regular food offer: 3 out 8 observed a significant

TABLE 4 Comparison between DIY fortified diet and standard diet on nutritional outcomes.

| Author(s) (year), Country | Population | Design | Intervention | Control | Fortification type | Additional load of the intervention | Food volume equivalence | Main nutritional outcomes | Main results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Evolution in control group[a] | Evolution in intervention group[a] | Intervention *vs* control group[b] |
| Arjuna et al. (2018) (48),Australia | Home with HDM (*n* = 29)<br>83 y<br>55% of women | Between-subject parallel Longitudinal (3 m) | Fortified HDM lunch + dietary counseling | Standard HDM lunch + dietary counseling | Protein & Energy | + 550 kcal/d<br>+ 30 g proteins/d | IG = CG | Protein intake<br>Energy intake<br>MNA<br>BMI | 0<br>0<br>0<br>0 | +<br>+<br>+<br>0 | Not specified<br>Not specified<br>Not specified<br>Not specified |
| Barton et al. (2000) (55),UK | Hospital (*n* = 35)<br>77 y<br>63% of women | Within-subject cross-over Cross-sectional | Reduced size fortified diet | Standard diet | Energy | + 200 kcal/d<br>- 5 g proteins/d<br>- 20% portion size/meal | IG < CG | Energy intake | NA | NA | + |
| Beelen et al. (2017a) (45),Netherlands | Hospital and nursing home (*n* = 22)<br>83 y<br>59% of women | Within-subject pre-post Longitudinal (10 d) | Fortified diet and substitution + Fortified foods/snacks | Standard diet | Protein | Not specified | IG > CG | Protein intake | NA | + | NA |
| Beelen et al. (2017b) (56),Netherlands | Hospital (*n* = 147)<br>79 y<br>55% of women | Between-subject Cross-sectional | Fortified diet + Fortified snacks | Standard diet | Protein | Not specified | IG > CG | Protein intake | NA | NA | + |
| Beelen et al. (2018) (57),Netherlands | Home (*n* = 75)<br>77 y<br>56% of women | Between-subject RCT Longitudinal (3 m) | Fortified foods + Fortified extra options | Standard diet | Protein | Not specified | IG > CG | Protein intake<br>MNA<br>BW | Not specified<br>+<br>+ | Not specified<br>+<br>0 | +<br>Not specified<br>Not specified |
| Beerman et al. (2016) (42),Denmark | Hospital (*n* = 62)<br>69 y<br>Not specified | Between-subject Cross-sectional | Fortified breakfast | Standard breakfast | Protein | Maximum intake: 20 g proteins/ breakfast | Not specified | Protein intake | NA | NA | + |
| Björkman et al. (2012) (39),Finland | Nursing home (*n* = 99)<br>84 y<br>76% of women | Between-subject RCT Longitudinal (6 m) | Fortified juice during the main meals | Standard juice during the main meals | Protein | + 20 g proteins/d | IG = CG | MNA<br>BW<br>Muscle mass | 0<br>-<br>0 | 0<br>+<br>0 | 0<br>+<br>0 |

*(Continued)*





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TABLE 4 (Continued)

| Author(s) (year), Country | Population | Design | Intervention | Control | Fortification type | Additional load of the intervention | Food volume equivalence | Main nutritional outcomes | Main results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Evolution in control group[a] | Evolution in intervention group[a] | Intervention *vs* control group[b] |
| **Bonnefoy et al. (2010)** (58),**France** | **Hospital (*n* = 26) 81 y 58% of women** | **Between-subject RCT Longitudinal (2 w)** | **Fortified lunch and dinner** | **Standard diet** | **Protein** | **+ 11–18 g proteins/d (of which 47.5% BCAAs)** | **IG = CG** | **Protein intake Muscle mass Albumin Pre-albumin** | **0 0 0 0** | **0 0 0 0** | **0 0 0 0** |
| Castellanos et al. (2009) (59), USA | Nursing home (*n* = 26) 87 y 70% of women | Within-subject cross-over Cross-sectional | IG1: Fortified lunch only IG2: Fortified breakfast and lunch | Standard diet | Protein & Energy | + 4.75 kcal/g food + 0.09 g protein/g food | IG = CG | Protein intake Energy intake | NA | NA | + (IG1) + (IG2) + (IG1) + (IG2) |
| **Evans et al. (2017)** (46),**Canada** | **Home (*n* = 41) 60 y 64% of women** | **Between-subject RCT Longitudinal (2 m)** | **IG1: L-carnitine fortified orange juice IG2: L-carnitine combination fortified orange juice** | **Placebo orange juice** | **Protein** | **+ 1.5–6.5 g proteins/d** | **IG = CG** | **Muscle mass** | **0** | **0 (IG1) + (IG2)** | **0 (IG1) + (IG2)** |
| Gall et al. (1998) (60), UK | Hospital (*n* = 143) 67 y 66% of women | Between-subject Cross-sectional | Fortified lunch and dinner +2 standard snacks | Standard diet | Protein & Energy | + 966 kcal/d + 22.2 g proteins/d | IG > CG | Protein intake Energy intake | NA | NA | 0 + |
| **Hashimoto et al. (2015)** (61),**Japan** | **Hospital (*n* = 28) 74 y 57% of women** | **Between-subject parallel Longitudinal (1 m)** | **IG1: Fortified lunch with soy protein IG2: Fortified lunch with casein protein** | **Standard diet** | **Protein** | **+ 7.1–7.5 g proteins/d** | **IG = CG** | **BW** | **0** | **0 (IG1) 0 (IG2)** | **0 (IG1) 0 (IG2)** |
| **Irvine et al. (2004)** (36),**France** | **Hospital (*n* = 12) 84 y 33% of women** | **Within-subject cross-over Cross-sectional** | **IG1: Standard breakfast + fortified low-protein drink IG2: Standard breakfast + fortified high-protein drink** | **Standard breakfast** | **Protein & Energy** | **+ 250 kcal/d + 3.5–20 g proteins/d** | **IG > CG** | **Protein intake Energy intake** | **NA** | **NA** | **0 (IG1) + (IG2) 0 (IG1) 0 (IG2)** |
| Iuliano et al. (2013) (62), Australia | Nursing home (*n* = 130) 88 y 78% of women | Between-subject RCT Longitudinal (1 m) | Substitution, fortification and additional food items | Standard diet | Protein & Energy | Not specified | IG > CG | Protein intake Energy intake | 0 0 | + + | Not specified Not specified |

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TABLE 4 (Continued)

| Author(s) (year), Country | Population | Design | Intervention | Control | Fortification type | Additional load of the intervention | Food volume equivalence | Main nutritional outcomes | Main results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Evolution in control group[a] | Evolution in intervention group[a] | Intervention *vs* control group[b] |
| **Lee et al. (2013) (40),Taiwan** | **Nursing home (*n* = 83) 80 y 58% of women** | **Between-subject RCT Longitudinal (6 m)** | **Fortified warm drink snack** | **Warm soup snack** | **Protein** | **+ 250 kcal/d + 9.5 g proteins/d** | **IG = CG** | **BW Albumin** | - **0** | **0** + | + + |
| Leslie et al. (2013) (63), UK | Nursing home (*n* = 31) 91 y 88% of women | Between-subject RCT Longitudinal (3 m) | Fortified diet + standard snack | Standard diet | Energy | + 400 kcal/d | IG > CG | Energy intake BW | 0 0 | 0 + | 0 0 |
| **Lorefält et al. (2005) (64),Sweden** | **Hospital (*n* = 10) 82 y 60% of women** | **Within-subject Cross-sectional** | **Reduced size fortified lunch and dinner + 2 standard snacks** | **Standard diet + 2 standard snacks** | **Protein & Energy** | **+ 0 kcal/d + 0 g proteins/d – 50% portion size** | **IG < CG** | **Protein intake Energy intake** | **NA** | + + | **NA** |
| **Mertz et al. (2021) (65),Denmark** | **Home (*n* = 184) 70 y 46% of women** | **Within-subject pre-post Longitudinal (12 m)** | **IG1: Fortified whey protein drink IG2: Fortified collagen protein drink** | **Standard diet** | **Protein** | **+ 40 g protein/d** | **IG = CG** | **Protein intake BW** | **NA** | **+ (IG1) + (IG2) 0 (IG1) 0 (IG2)** | **NA** |
| **Mortensen et al. (2019) (51),Denmark** | **Hospital (*n* = 92) 69 y 56% of women** | **Between-subject Cross-sectional** | **Fortified snacks** | **Standard snacks** | **Protein** | **+ 18–27 kcal/d + 15–23 g proteins/d** | **IG = CG** | **Protein intake** | **NA** | **NA** | + |
| **Munk et al. (2013) (66),Denmark** | **Hospital (*n* = 79) 73 y 75% of women** | **Between-subject Cross-sectional** | **Standard diet + fortified small dishes** | **Standard diet** | **Energy** | **Not specified** | **IG > CG** | **Energy intake** | **NA** | **NA** | **0** |
| **Munk et al. (2014) (41),Denmark** | **Hospital (*n* = 78) 75 y 58% of women** | **Between-subject RCT Longitudinal (15 d)*** | **Standard diet + Fortified small meals** | **Standard diet** | **Protein & Energy** | **+ 0.6–4.7 kcal/g + 6.1–11.5 g proteins/serving** | **IG > CG** | **Protein intake Energy intake BW** | **NA NA 0** | **NA NA 0** | + **0** **0** |

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TABLE 4 (Continued)

| Author(s) (year), Country | Population | Design | Intervention | Control | Fortification type | Additional load of the intervention | Food volume equivalence | Main nutritional outcomes | Main results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Evolution in control group[a] | Evolution in intervention group[a] | Intervention *vs* control group[b] |
| Neelemaat et al. (2012) (67), Netherlands | Hospital + Home ($n = 150$)<br>75 y<br>55% of women | Between-subject RCT<br>Longitudinal (3 m) | Individual nutritional care (fortified diet (only during hospital stay), ONS, telephone counseling, vitamin D3) | Standard nutritional care | Protein & Energy | Hospital phase: + 750 kcal/d; + 30 g proteins/d<br>Home phase: + 600 kcal/d; + 24 g proteins/d | IG > CG | Protein intake<br>Energy intake<br>BW | Not specified<br>Not specified<br>Not specified | Not specified<br>Not specified<br>Not specified | +<br>+<br>+ |
| **Niccoli et al. (2017) (47),Canada** | **Hospital ($n = 47$)<br>81 y<br>68% of women** | **Between-subject RCT<br>Longitudinal (2026 d)*** | **Fortified diet** | **Standard diet** | **Protein** | **+ 24 g proteins/d** | **IG = CG** | **Protein intake<br>Albumin<br>Pre-albumin** | **NA<br>0<br>0** | **NA<br>0<br>0** | **+<br>0<br>0** |
| Nykänen et al. (2019) (52), Finland | Home with home care ($n = 85$)<br>83 y<br>72% of women | Between-subject RCT<br>Longitudinal (3 m) | Standard diet + Fortified snacks | Standard diet | Energy | + 272–282 kcal/d<br>+ 14.3–14.9 g proteins/d | IG > CG | MNA<br>BMI<br>Albumin<br>Pre-albumin | 0<br>0<br>-<br>- | +<br>0<br>0<br>0 | +<br>0<br>+<br>0 |
| **Ödlund Olin (2003) (69),Sweden** | **Nursing home ($n = 35$)<br>82 y<br>52% of women** | **Between-subject parallel<br>Longitudinal (17 w)** | **Fortified diet** | **Standard diet** | **Energy** | **+ 500 kcal/d** | **IG = CG** | **Energy intake<br>BW** | **0<br>0** | **+<br>0** | **+<br>0** |
| **Ödlund Olin et al. (1996) (70),Sweden** | **Hospital ($n = 36$)<br>82 y<br>67% of women** | **Within-subject cross-over<br>Longitudinal (6 w)** | **Fortified lunch and dinner + fortified snacks** | **Standard diet + regular snacks** | **Energy** | **+ 850 kcal/d** | **IG = CG** | **Energy intake<br>BW** | **Not specified<br>0** | **Not specified<br>+** | **+<br>+** |
| **Ott et al. (2019) (71),Germany** | **Nursing home ($n = 16$)<br>87 y<br>88% of women** | **Within-subject pre-post<br>Longitudinal (6 w)** | **Fortified textured-modified diet + 1 fortified snack + extra fortified choice** | **Standard texture-modified diet + 3 standard snacks** | **Protein & Energy** | **+ 600 kcal/d<br>+ 30 g proteins/d** | **IG = CG** | **Protein intake<br>Energy intake<br>BW** | **0<br>0<br>0** | **0<br>0<br>0** | **+<br>+<br>+** |

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TABLE 4 (Continued)

| Author(s) (year), Country | Population | Design | Intervention | Control | Fortification type | Additional load of the intervention | Food volume equivalence | Main nutritional outcomes | Main results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Evolution in control group[a] | Evolution in intervention group[a] | Intervention *vs* control group[b] |
| **Park et al. (2018)** (49),**Korea** | **Home (*n* = 99)**<br>**77 y**<br>**65% of women** | **Between-subject RCT Longitudinal (3 m)** | **IG1: fortified tea to reach 1.2 g proteins/kg/d**<br>**IG2: fortified tea to reach 1.5 g proteins/kg/d** | **Placebo tea to reach 0.8 g proteins/kg/d (in tea)** | **Protein** | **+ 0.4–0.7 g proteins/kg/d** | **IG = CG** | **Protein intake**<br>**MNA**<br>**Muscle mass** | **Not specified**<br>**Not specified**<br>**Not specified** | **Not specified**<br>**Not specified**<br>**Not specified** | **+ (IG1) + (IG2)**<br>**0 (IG1) 0 (IG2)**<br>**0 (IG1) + (IG2)** |
| Polonen et al. (2017) (72), Finland | Home with home care (*n* = 227)<br>84 y<br>71% of women | Between-subject parallel Longitudinal (6 m) | Individual nutritional care (dietary counseling for increasing protein and energy intake, ONS when needed, vitamin D) | Standard nutritional care | Protein & Energy | Not specified | IG > CG | MNA<br>BMI<br>Albumin | 0<br>0<br>0 | +<br>0<br>+ | +<br>0<br>+ |
| Seemer et al. (2021) (54), Germany | Nursing home (*n* = 50)<br>84 y<br>74% of women | Within-subject pre-post Longitudinal (6 w) | Individualized nutritional intervention (reshaped texture-modified meals and 3 enriched supplements) | Usual nutritional care | Protein | + 125–470 kcal/d<br>+ 1,042 g protein/d | IG > CG | Protein intake<br>BW | NA | +<br>0 | NA |
| **Silver et al. (2008)** (37),**USA** | **Home with HDM (*n* = 45)**<br>**84 y**<br>**69% of women** | **Within-subject cross-over Cross-sectional** | **Fortified HDM lunch** | **Standard HDM lunch** | **Protein & Energy** | **+ 300 kcal/d**<br>**+ 10 g proteins/serving** | **IG = CG** | **Protein intake**<br>**Energy intake** | **NA** | **NA** | **+**<br>**+** |
| **Smoliner et al. (2008)** (73),**Germany** | **Nursing home (*n* = 52)**<br>**83 y**<br>**73% of women** | **Between-subject RCT Longitudinal (3 m)** | **Fortified soup and sauce + 2 fortified snacks** | **Standard diet** | **Protein & Energy** | **Not specified** | **IG > CG** | **Protein intake**<br>**Energy intake**<br>**MNA**<br>**BW** | **NA**<br>**NA**<br>**+**<br>**+** | **NA**<br>**NA**<br>**+**<br>**+** | **+**<br>**0**<br>**0**<br>**0** |
| **Sossen et al. (2020)** (74),**Australia** | **Nursing home (*n* = 122)**<br>**88 y**<br>**76% of women** | **Within-subject pre-post Longitudinal (6 m)** | **Fortified diet** | **Standard diet** | **Protein & Energy** | **+ 701 kcal/d**<br>**+ 27 g proteins/d** | **IG = CG** | **SGA**<br>**BW** | **NA** | **0**<br>**0** | **NA** |

*(Continued)*





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TABLE 4 (Continued)

| Author(s) (year), Country | Population | Design | Intervention | Control | Fortification type | Additional load of the intervention | Food volume equivalence | Main nutritional outcomes | Main results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Evolution in control group[a] | Evolution in intervention group[a] | Intervention *vs* control group[b] |
| Starke et al. (2011) (38), Switzerland | Hospital ($n = 132$) 73 y Not specified | Between-subject RCT Longitudinal (16 d)* | Individual nutritional care (detailed nutritional assessment, individual food supply, fortified meals, ONS, in between-meals snacks) | Standard nutritional care (ONS, Nutritional therapy) | Protein & Energy | Not specified | IG > CG | Protein intake<br>Energy intake<br>BW | NA<br>NA<br>- | NA<br>NA<br>0 | +<br>+<br>+ |
| Stelten et al. (2015) (75), Netherlands | Hospital ($n = 47$) 80 y 55% of women | Between-subject Cross-sectional | Fortified bread and drinking yoghurt | Standard diet | Protein | + 16 g proteins/serving (*ad libitum*) | IG = CG | Protein intake | NA | NA | + |
| **Stow et al. (2015)** (76),**UK** | **Nursing home ($n = 67$) Not specified 82% of women** | **Between-subject RCT Longitudinal (6 m)** | **Standard diet + Fortified meals** | **Standard diet** | **Protein & Energy** | **+ 600 kcal/d + 20–25 g proteins/d** | **IG > CG** | **Protein intake<br>Energy intake<br>BW** | **Not specified<br>Not specified<br>Not specified** | **Not specified<br>Not specified<br>Not specified** | **0 (M3) 0 (M6)<br>+ (M3) + (M6)<br>+ (M3) 0 (M6)** |
| Van Til et al. (2015) (77), Netherlands | Hospital ($n = 34$) 78 y 68% of women | Between-subject RCT Longitudinal (3 w) | Fortified bread and drinking yoghurt | Standard diet | Protein | + 17 kcal/serving + 8 g proteins/serving | IG = CG | Protein intake<br>MNA<br>BW | NA<br>0<br>0 | NA<br>0<br>0 | +<br>0<br>0 |
| Young et al. (2018) (50), Australia | Hospital ($n = 320$) 81 y 53% of women | Between-subject Cross-sectional | Fortified diet + Standard snacks + ONS | Standard diet + Standard snacks + ONS | Protein & Energy | Maximum intake: 2030 kcal/d 77 g proteins/d | IG = CG | Protein intake<br>Energy intake | NA | NA | +<br>+ |
| **Ziylan et al. (2016)** (43),**Netherlands** | **Home ($n = 120$) 71 y 54% of women** | **Within-subject cross-over Cross-sectional** | **Fortified beef meal and chicken meal** | **Standard beef meal and chicken meal** | **Protein & Energy** | **+ 45–90 kcal/d + 5 g proteins/d** | **IG = CG** | **Protein intake<br>Energy intake** | **NA** | **NA** | **+<br>+** |
| Ziylan et al. (2017) (44), Netherlands | Nursing home ($n = 42$) 74 y 67% of women | Between-subject RCT Longitudinal (2 w) | Fortified bread and meals | Standard bread and meals | Protein | + 90 kcal/d + 8 g proteins/d | IG = CG | Protein intake | Not specified | Not specified | + |

y, year old; d, days; m, months; w, weeks; RCT, randomized controlled trial; HDM, home-delivery meal; FF, fortified group; SF, standard group; BMI, body mass index; BW, body weight; MNA, Mini Nutritional Assessment; SGA, Subjective Global Assessment; NA, not applicable; +, significant increase; −, significant decrease; 0, no significant differences. Articles with outcomes labeled "Not specified" did not show statistical value of p test for outcomes concerned. **Bold:** study that assess the impact of DIY fortification alone. *Mean length of stay from admission to discharge. [a]Comparison with baseline and follow-up; [b]Comparison between control group and fortified group (in this column "+" means that results are significantly higher for fortified group compared to control group).





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impact on MNA score, 7 out 20 observed a significant impact on body weight or BMI and 2 out 4 observed a significant impact on muscle mass. None observed a negative impact.

When only the studies which assessed the impact of DIY fortification alone are considered (in bold in the Table 4), results still highlight that provided protein-fortified foods led to a significant increase in protein intake (16 studies over 18) and that provided energy-fortified led to a significant increase in energy intake (9 studies over 13). Only a few studies showed a significant impact of DIY fortification on nutritional status compared to regular food offer: 1 out 5 observed a significant impact on MNA score, 4 out 13 observed a significant impact on body weight or BMI and 1 out 3 observed a significant impact on muscle mass.

## 3.6. Comparison of DIY food-based fortification with other alternatives

Seven studies evaluated two DIY food-based fortification strategies with either different energy/protein loads (36, 49, 59), different fortificants (46, 61, 65) or different portion sizes (43). Four studies compared DIY food-based fortification with another alternative such as ONS (76), (74), adding high-energy and/or high-protein food items to the menu (55), or increased staff assistance to older people during mealtime (50) (Table 5). However, very few studies have produced statistics to compare the different options. Not surprisingly, higher energy/protein loads are associated with higher energy/protein intake (36, 49). However, there was no significant difference between the 1.2 and the 1.5 g of protein / kg of body weight / day in the evolution of nutritional status and muscle mass over the 12-week intervention (49). In Ziylan et al. (43), the reduced-size enriched chicken meal led to a significantly higher energy intake than the normal-size meal. However, the difference in intake was rather small and no impact of portion size was observed for the enriched beef meals. In Evans et al. (46), a combination of three amino acids significantly improved muscle mass over 2 months while no change was observed when a single amino acid was used to fortify the orange juice. Stow et al. (76) observed no difference between food-based fortification and ONS while Sossen et al. (74) observed a slight advantage for DIY food-based fortification compared to ONS. Energy and protein intakes were higher with DIY fortification than with ONS, and body weight was stable with DIY fortification whereas it decreased with ONS during the 6 months of follow-up. Finally, providing DIY fortified food led to higher energy and protein intake when compared with improving staff assistance to older people during mealtime (50).

TABLE 5 Comparison between DIY fortification and other alternatives.

| Author(s) (year), Country | Population | Design | Fortified group (FG) | Alternative group (AG) | Fortification type | Food volume equivalence | Main nutritional outcomes | Main results |
|---|---|---|---|---|---|---|---|---|
| Barton et al. (2000) (55), UK | Hospital ($n = 35$) 77 y 63% of women | Within-subject cross-over Cross-sectional | Fortified breakfast | Breakfast with additional energy and protein foods | Energy | Not specified | Nutritional intake | FG vs. AG not compared. |
| Castellanos et al. (2009) (59), USA | Nursing home ($n = 26$) 87 y 70% of women | Within-subject cross-over Cross-sectional | Fortified lunch only | Fortified breakfast and lunch | Protein & Energy | FG = AG | Nutritional intake | FG vs. AG not compared. |
| Evans et al. (2017) (46), Canada | Home ($n = 41$) 60 y 64% of women | Between-subject RCT Longitudinal (2 m) | Fortified orange juice with carnitine | Fortified orange juice with carnitine, creatine and leucine | Protein | FG = AG | Muscle mass | FG vs. AG not compared. FG did not change while AG significantly increased over time. |
| Hashimoto et al. (2015) (61), Japan | Hospital ($n = 28$) 74 y 57% of women | Between-subject parallel Longitudinal (1 m) | Fortified lunch with soy | Fortified lunch with casein | Protein | FG = AG | BW | FG vs. AG not compared. FG and AG did not change over time. |
| Irvine et al. (2004) (36), France | Hospital ($n = 12$) 84 y 33% of women | Within-subject cross-over Cross-sectional | Fortified low-protein drink | Fortified high-protein drink | Protein & Energy | FG = AG | Nutritional intake | FG < AG |

*(Continued)*

TABLE 5 (Continued)

| Author(s) (year), Country | Population | Design | Fortified group (FG) | Alternative group (AG) | Fortification type | Food volume equivalence | Main nutritional outcomes | Main results |
|---|---|---|---|---|---|---|---|---|
| Mertz et al. (2021) (65), Denmark | Home ($n = 184$)<br>70 y<br>46% of women | Between-subject RCT<br>Longitudinal (12 m) | Fortified whey protein drink | Fortified collagen protein drink | Protein | FG = AG | Nutritional intake<br>Body weight | FG vs. AG not compared. FG and AG significantly increased over time.<br>FG vs. AG not compared. FG and AG did not change over time. |
| Park et al. (2018) (49), Korea | Home ($n = 99$)<br>77 y<br>65% of women | Between-subject RCT<br>Longitudinal (3 m) | Fortified tea with 1.2 g proteins/kg/d | Fortified tea with 1.5 g proteins/kg/d | Protein | FG = AG | Nutritional intake<br>Nutritional status<br>Muscle mass | FG < AG.<br>No significant difference between FG and AG.<br>No significant difference between FG and AG. |
| Sossen et al. (2020) (74), Australia | Nursing home ($n = 122$)<br>88 y<br>76% of women | Between-subject parallel<br>Longitudinal (6 m) | Fortified meals | ONS | Protein & Energy | Not specified | Nutrition intake<br>Nutritional status<br>BW | FG > AG<br>FG vs. AG not compared. FG and AG did not change over time.<br>FG vs. AG not compared. FG did not change and AG significantly decreased over time. |
| Stow et al. (2015) (76), UK | Nursing home ($n = 67$)<br>Not specified<br>82% of women | Between-subject RCT<br>Longitudinal (6 m) | Fortified meals | ONS | Protein & Energy | Not specified | Nutritional intake<br>BW | No significant difference between FG and AG.<br>No significant difference between FG and AG. |
| Young et al. (2018) (50), Australia | Hospital ($n = 320$)<br>81 y<br>53% of women | Between-subject<br>Cross-sectional | Fortified meals | Assistance during meals | Protein & Energy | Not specified | Nutritional intake | FG > AG |
| Ziylan et al. (2016) (43), Netherlands | Home ($n = 120$)<br>71 y<br>54% of women | Within-subject cross-over<br>Cross-sectional | Normal size enriched meal | Reduced size enriched meal | Protein & Energy | FG > AG | Nutritional intake | Beef meal: No significant difference between FG and AG.<br>Chicken meal: AG > FG |

y, year old; RCT, randomized controlled trial; m, months; FG, fortified group; AG, alternative group; NS, non-significant; ONS, oral nutritional supplement; BW, body weight; BMI, body mass index; RDA, recommended daily allowance.

# 4. Discussion

## 4.1. Originality/value of the present review

A survey of the literature allowed the identification of five systematic literature reviews close to the topic of the present review (21–24, 30). Firstly, the systematic review of Trabal and Farran-Codina (23) investigated whether, compared to a standard diet, DIY food-based fortification with regular ingredients and/or powdered modules could improve energy and protein intake in older adults in hospital settings, long-care facilities or home settings. This review included 9 articles. The authors concluded that DIY fortification is a valid intervention for improving energy intake in older adults yet there was insufficient evidence for protein intake, nutritional status and body weight. Secondly, Morilla-Herrera et al. (21) targeted all studies related to DIY food-based fortification with macronutrients to prevent the risk of malnutrition in older patients receiving hospital services for acute or chronic disease, in older people living in nursing homes and in older people with home-care. This review encompassed 7 articles, and the meta-analysis highlighted that DIY food-based

fortification yields positive results in the total amount of ingested calories and protein. Thirdly, Douglas et al. (22) aimed to evaluate the effect of DIY fortification with regular food ingredients (excluding protein powders) on energy and protein intake compared to standard diet among adults aged 60 and more in acute-care hospitals, long-term care settings or living at home. Ten articles were included. This review suggested that DIY fortification was effective in increasing energy and protein intake among older individuals. Fourthly, the systematic review by Mills et al. (24) explored the evidence for the use of energy and/or protein dense meals (DIY food-based fortification) or additional snacks (diet-based fortification) to increase the dietary energy and protein intake of adults older than 60 in hospital or rehabilitation facilities. Ten articles were identified. Authors reported that when compared with usual nutritional care, DIY fortification could be an effective, well-tolerated and cost-effective intervention to improve dietary intake among hospitalized patients. Finally, Sossen et al. (30) investigated the effect of food-based and diet-based fortification on energy and protein intake compared to any/no nutritional strategy in residents living in nursing homes. Sixteen articles were included. The results of the meta-analysis showed that fortified menus may significantly increase energy and protein intakes compared with standard menus.

The present review retrieved 44 articles that tested DIY food-based fortification in people over the age of 65. This review differs from previous reviews in the following respects. Firstly, we focused the review on DIY food-based fortification, i.e., the addition of regular food ingredients or macronutrient extracts into conventional food matrices to increase energy and protein content in the final dishes. Douglas et al. (22) considered only culinary ingredients. Mills et al. and Sossen et al. (24, 30) considered both food-based fortification and diet-based fortification via the addition of supplementary conventional foods like snacks to participants' diets. Second, we considered all living settings, i.e., at home, with or without assistance, institutions and hospitals [Morilla-Herrera et al. (21) only considered dependent older people]. Thirdly, we considered not only nutritional outcomes but also acceptability outcomes. In addition, we used a wide range of keywords to account for the lack of consensual terminology regarding the concept of DIY food-based fortification (Supplementary material). This allowed us to identify a much larger number of articles than in previous reviews.

## 4.2. Description of DIY fortified recipes

A wide variety of DIY fortified recipes were extracted from this review, including liquid (35% of the recipes), semi-solid (17%) and solid food matrices (48%). However, the quality evaluation of the articles highlighted the lack of information provided by the authors on the description of fortified recipes. Only 8 articles provided sufficient information for a third party to reproduce the same fortified recipes as used in the articles. In order to identify efficient DIY fortified solutions, it is essential that in future articles provide a detailed description of the fortified recipes, including the nature of food matrices and fortificants, final energy and protein concentration, additional nutrient load provided by the fortified food compared to the standard food, consumption time, and portion size. From the information collected, energy fortification is mainly achieved through the use of fats and dairy products (cream, butter, oil) while protein fortification is mainly achieved through protein extracts. Such products are usually in powder form ('protein powders') and proved to have varied applications and uses within food processing as well as high nutritional and functional value (68). The present review showed that the protein products used in fortified recipes were mainly derived from animal sources (85% of the recipes), especially from milk (67% of the recipes), and to a lesser extent from plant sources (15% of the recipes). Animal-derived proteins are more readily digestible and effective in muscle protein synthesis than plant derived proteins (78).

## 4.3. Evaluation of DIY food-based fortification solutions

Results suggest that food-based fortification is an effective strategy to improve energy and/or protein intake. This trend is observed whether all the studies – including the ones that combined DIY fortification with other strategies (i.e., providing ONS, additional food items, fortified foods from Food Industry) or whether only the studies which assessed the impact of DIY fortification alone are considered. In other words, DIY fortification seems to be an effective strategy to improve nutritional intake, whether used alone or combined with other enrichment strategies. However, no strong evidence is observed regarding the impact of DIY fortification to improve the nutritional status (e.g., MNA score, body weight, muscle mass).

It should be noted that providing fortified food was not necessarily enough to get participants to meet the recommended nutritional allowance (50, 55, 60, 75). For instance, in Stelten et al. (75), 64% of the fortified group did not reach the threshold of 1.2 g protein/kg of body weight/day. This raises the question of the need for new fortification solutions with higher levels of energy and protein content. In addition, consuming fortified foods throughout the various meals of the day may be more efficient than consuming fortified foods only once per day. For instance, Castellanos et al. (59) reported higher energy intake when both breakfast and lunch were fortified than when only lunch was fortified, but they did not carry out statistical analysis to compare these two conditions.

Besides the relatively large number of studies that have tested the impact of DIY food-based fortification on nutritional outcomes, very few studies have looked at the acceptability of DIY fortified food. Only 10 of the 41 nutrition-related articles reported an evaluation of the acceptability of DIY fortified foods and only 3 of the 44 articles included in this review were completely devoted to the assessment of acceptability of DIY fortified food. Unsurprisingly, the quality of the acceptability studies is much better in the articles focused only on this outcome than in the articles that conducted an acceptability study alongside a nutritional study. In the latter, the sample size is often insufficient, the methods are often qualitative and the results are often imprecise and incomplete. In addition, the people who assess the acceptability of fortified food are sometimes different from the end-users [e.g., the fortified foods are tasted by the staff (37)]. Overall, the results tend to show that DIY fortified foods are equally or less appreciated than standard foods – never more. However, before drawing any final conclusions, there is a need to carry out further acceptability studies with a higher quality, taking into account the good practices and the norms of sensory evaluation (79, 80). Indeed, fortified foods should not only be good from a nutritional point of view, but also "good to eat" to ensure that they are actually consumed by the target population. Furthermore, it would be worthwhile to optimize the sensory quality of fortified foods by recruiting older

adults in tasting panels. Fortification improvement based on older people's feedback led to increased food intake in nursing homes (81, 84).

### 4.4. Limitations and strengths of the present SLR

The strength of this paper is its reliable literature search, with a complete overview of nutritional and acceptability issues for fortified food targeting older people. Given the lack of a consensual definition of the concept of food-based fortification, we have used a broad set of keywords to retrieve articles of interest. The limitations of the present literature review are the following: the literature search strategy did not include trial registries, nor grey literature, and it was restricted to English papers. There are two discrepancies between the present method and the one published before the review was carried out. In the published method, we considered including papers published in both English and French (the authors' native language), but papers in French were ultimately excluded in order to avoid a language bias in the literature search. In addition, in the published method, we considered including papers related to micronutrients fortification, but ultimately focused the scope of the present review on macronutrient fortification, otherwise the scope of the review would have been too broad. Finally, a limitation lies in the fact that it was not always easy to determine whether the products used in the nutritional interventions were a DIY fortified food, a fortified food marketed by the Food Industry or an ONS. For instance, we excluded the studies where enrichment consisted of providing participants with a sachet of nutrient constituents to be dissolved in water [for instance (82, 83)]. Indeed, dissolving a sachet of powder in water is more like taking a drug than having a drink. Conversely, all the interventions consisting of adding a nutrient-dense ingredient to a food matrix were included, even when the fortificant was very specific [for example, branched chain amino acids powder (58), L-carnitine (46)]. However, the question arises as to the accessibility of this type of fortificant to the end-user in real life.

## 5. Conclusion

The present systematic literature review highlighted that, compared to a standard diet, DIY food-based fortification – i.e., incorporating ingredients of nutritional interest into commonly consumed foods – is a valuable strategy for increasing energy and protein intake in older people. However, no strong evidence was observed regarding the impact of DIY fortification to improve the nutritional status (i.e., MNA score, body weight, muscle mass). In addition, further research is needed to better assess the acceptability of this strategy among end-users. Given the limitations of the studies included in this systematic review, we put forward four recommendations for future research. First, we emphasize the need to develop a consistent definition of DIY food-based fortification that clearly distinguishes this strategy from other enrichment strategies such as the consumption of ONS or fortified food from food industry. Second, it would be useful for studies to better describe the recipes used for DIY fortification. This information would result in a better understanding of the factors that maximize the impact of food-based fortification on nutritional outcomes. Third, it would be relevant to systematically assess the acceptability of DIY fortified foods in addition to the nutritional outcomes. This should be done by implementing consumer tests that respect the good practices and the recommendations defined in sensory evaluation for such tests (sample size, methods…). To achieve this, it is essential to encourage more pluri-disciplinary research projects involving experts in nutrition, sensory evaluation and food technology. Fourth, we encourage researchers to further compare the impact of food-based fortification with other enrichment strategies, and in particular ONS, in order to better decipher the impact of each of these strategies in tackling undernutrition in the older people. Finally, future research should also study how to promote DIY food fortification among the older people, their caregivers, as well as among catering and health professionals. Indeed, despite this strategy has proved effective in sustaining caloric and protein intake in older people, it remains largely unknown and underused. Several dissemination strategies could be considered. A first one could be the development and the diffusion of DIY fortified recipes booklets. Such booklets should indicate the amount of protein provided by each portion. These booklets would also need to be co-created with end-users, to ensure the feasibility and acceptability of the recipes in the field, considering various settings (home cooking, home-delivery meals, nursing home, hospital). A second dissemination strategy could be the organization of therapeutic workshops at hospital discharge or in day hospital, bringing together dieticians, chefs and older people to promote DIY food fortification. However, from a more global perspective, public policies are needed to raise awareness of the nutritional needs of the older people. These policies must combine information and tools to maintain adequate energy and protein intakes, in order to prevent undernutrition in the older population.

## Data availability statement

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

## Author contributions

AG: methodology, investigation, formal analysis, and writing – original draft. MP: methodology, investigation, formal analysis, and writing – review and editing. VW-D: conceptualization and writing – review and editing. CS-R: conceptualization, methodology, formal analysis, writing – original draft, and funding acquisition. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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The remaining 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.2023.1232502/full#supplementary-material

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# Nutritional status of hospitalized elderly patients in Ethiopia: a cross-sectional study of an important yet neglected problem in clinical practice

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**Background:** Malnutrition is a common geriatric syndrome affecting approximately half of the older population with a more pronounced occurrence rate in those hospitalized. It affects the physiology, and results in poor humanistic and clinical outcomes. In Africa, particularly in Ethiopia, albeit multiple studies are available on malnutrition in non-hospitalized older population, similar studies in inpatient settings are scarce. Therefore, this study was conducted with the intention to quantify the prevalence of malnutrition in older patients on inpatient admission and determine its associated factors.

**Methods:** A total of 157 older inpatients aged 60 years and above were included in the present study. The data collection format was developed after an in-depth review of relevant literatures. The full Mini-Nutritional Assessment (MNA) tool was employed to assess the nutritional status on admission. Data completeness was checked thoroughly. Descriptive statistics and logistic regression analysis were conducted using STATA 15.0. The area under the receiver operating characteristic curve (ROC), Hosmer–Lemeshow test, and classification table were computed to evaluate the final model goodness-of-fit.

**Results:** Of the total study subjects, 81% were malnourished (MNA score <17) and 17% were at risk for malnutrition (MNA score of 17.5–23.5). However, upon review of the patients' medical charts, malnutrition diagnosis was recorded in only two patients. Rural residence (AOR = 2.823, 95%CI: 1.088, 7.324), self-reported financial dependence for expenses (AOR = 4.733, 95%CI: 1.011, 22.162), and partial dependence in functional autonomy on admission (AOR = 3.689, 95%CI: 1.190, 11.433) significantly increased the risk of malnutrition. The area under the ROC curve (0.754) and the Hosmer–Lemeshow test ($p$ = 0.7564) indicated that the final model reasonably fits the data. The model`s sensitivity is 96.85%.

**Conclusion:** In the present study, an alarmingly high prevalence of malnutrition was identified older inpatients. The problem went undiagnosed in a similar percentage of patients. Several available literatures indicate the presence of an association between nutritional status and patient outcomes, thus strict nutritional screening at inpatient admission and intervention are recommended with special emphasis for those from rural areas, with financial dependence, and with functional impairment on admission.

KEYWORDS
aged, inpatients, nutrition assessment, risk factors, Jimma

## Introduction

The global population dynamics show that the proportion of the older population is growing over time (1). Older populations are defined as those aged 65 years and above in developed countries, whereas for developing countries, such as Ethiopia, international organizations define older as a person aged 60 years and above (2). The proportion of individuals in this age group is projected to grow by two-fold, from 1 billion in 2020 to 2.1 billion in 2050. The projection also shows that in 2050, approximately 80% of older people will be residing in low- and middle-income countries (3). Ethiopia is also experiencing a demographic transition consistent with the global trend (4). This is presumed to affect almost all aspects of the global society, including the healthcare system (5).

Older people are usually fragile and vulnerable to malnutrition (6), which denotes failure to meet one's energy or protein requirements of high biological value (7). It is estimated that approximately half of the elderly population is affected by malnutrition (8), with a higher rate in hospitalized patients (9, 10). In this age group, low education, older age, anorexia of aging, multimorbidity, cognitive decline, polypharmacy, age-related functional decline, frailty, hospitalization, financial constraints, and empty nest syndrome are among the contributing factors to malnutrition (9, 11, 12). Furthermore, previously available studies mentioned factors such as sex (13, 14), age (13–15), rural residency (11), no formal education (11, 13, 14), low economic status (14, 15), functional impairment (11, 16, 17), smoking (18), having depression (11, 13–15), hospitalization history, alcohol consumption (14), and occupations (15) as malnutrition associated factors.

The occurrence of malnutrition results in deranged physiology and poor clinical outcomes. It affects the quality of life, increases the incidence of infection, causes sarcopenia, results in poor hospital outcomes, and increases the risk of life-threatening complications and mortality (9, 13, 15, 19, 20). As a result, malnutrition screen-and-treat policies are recommended in the hospital setting (21). However, malnutrition and nutritional aspects of some common clinical conditions of older age are often neglected in clinical practice (22). There are various nutritional assessment tools for screening malnutrition among hospitalized patients, but none of them are considered gold standard (23). The Mini-Nutritional Assessment (MNA) tool, a valid nutrition screening and assessment tool for elderly patients (24), has been employed in several nutritional assessment studies (25–27).

The prevalence of malnutrition among hospitalized older patients prominently varies across the available studies. In Europe, malnutrition has been reported in up to 80% of geriatric hospital patients (9), and at risk of malnutrition in nearly half of the elderly population (28). Studies from Australia recorded malnutrition and at risk for malnutrition in up to 88% of hospitalized elderly patients, respectively (25, 29). In one study from Brazil, moderate and severe malnutrition was recorded in more than half (55%) of the elderly patients (28), while in Asia, malnutrition prevalence was as high as 45% (26, 30–35) and at risk for malnutrition up to 67.1% (26, 30, 33–35) were reported.

In Africa, malnutrition among older people is a major challenge to the health care system and requires special pressing consideration. Almost all the available studies on the nutritional status of elderly people in the continent are from community settings (36–39). A review of observational studies from the community and pocket studies from the hospital settings in Africa revealed malnutrition prevalence of up to 56% in the hospitalized older population using the MNA tool (38). In other review studies involving mostly community-based and a few facility-based outpatient studies from Africa, malnutrition prevalence of 17% ranging from 1.8 to 39.47% was reported in the elderly population. The studies incorporated in the review assessed nutritional status using either body mass index (BMI) or MNA (36). In addition, a scoping review of community- and few facility-based, outpatient studies from sub-Saharan Africa indicated malnutrition prevalence between 6 and 54% in older people. The investigators of the studies included in the review employed BMI, the MNA tool, and Mid-Upper Arm Circumference (MUAC), alone or in combination, to assess nutritional status (37). On the other hand, a multi-country, multi-center prospective cohort study was conducted in selected hospitals from South Africa, Ghana, and Kenya. In the study, using Nutritional Risk Screening-2002®, 75.1% of patients screened at admission to the hospitals were at risk of malnutrition (40).

In previously available studies involving older patients, female sex, a low education level (41), older age (42, 43), unmarried (43, 44), polypharmacy, dysphagia, depression, low functional capacity, eating-related problems, lowered cognitive function (45), diabetes (26), alcohol abuse, and socio-economic status were described as independent risk factors of malnutrition (46–48).

In Ethiopia, a review of community-based studies that assessed undernutrition in the elderly population using BMI recorded a 20.53% pooled prevalence of undernutrition among the older population (39). Hitherto, studies on the prevalence of malnutrition among elderly inpatients in Africa, particularly in Ethiopia, are limited. Therefore, this study was conducted with the primary intention of determining the prevalence of malnutrition in older patients on admission to medical wards and determining its associated factors.

## Materials and methods

### Study design and participants

This cross-sectional study was conducted in the period from 6 September 2021 to 26 December 2022 in the medical wards of Jimma Medical Center (JMC), which is a Jimma University-affiliated institution in Jimma town, 352 km south-west of Addis Ababa. It is the only teaching and referral medical center in the southwestern part of the country with a bed capacity of 800, and provides services for a catchment population of about 15 million people. The center has over 1,000 health professionals, and 16 service departments, including

emergency, ambulatory, internal medicine, pediatrics, adult and pediatric oncology, surgery, dentistry, physiotherapy, radiology, gynecology and obstetrics, sexual and reproductive health, and pharmacy (49, 50). In the present study, 157 consented older adult patients aged 60 years and above who were admitted to the medical wards (general unit, cardiac unit, stroke unit, and pulmonary unit) of JMC over the study period were considered. Participants with aphasia problems ($n = 2$) and re-admissions ($n = 12$) were excluded from the study.

## Sample size estimation and sampling procedure

Single population proportion formula was employed for calculating the sample size assuming a confidence level of 95%, a margin of error of 0.05, and a critical value (Z) of 1.96. For the purpose of this study, the prevalence of malnutrition in older people ($P = 21.2\%$) was taken from a previous study in Ethiopia (14). In the year 2019–2020, approximately 398 older adult patients aged 60 years and above were admitted to the medical wards of JMC and this number was considered as a source population. The final minimum sample size was $n = 157$ after correction. Thus, 157 eligible older adult patients were consecutively assessed over the study period.

## Data collection tool and procedure

The data collection tool comprised both, standard tools and tools designed after an in-depth review and extraction from relevant literatures. It was designed to capture relevant socio-demographic, behavioral, functional, clinical, nutritional, and related information of the participants. The tool was translated to two locally predominant languages (Afan Oromo and Amharic) and back translated into English to check the consistency. Two data collectors (Bachelor's degree nurses) were trained on the data collection tool and procedure. Prior to the actual data collection period, a pre-test was conducted. The data collection procedure throughout the study period was carried out under close supervision of the investigators. Patient charts, laboratory results, patient/caregiver interviews, and practitioners in charge were the sources of data for the present study. All data were collected from eligible patients within 48 h of admission to the ward. Each patient's diagnosis was reviewed from their medical chart to check on how many of these patients were diagnosed with malnutrition over their hospital stay.

## Study variables

The independent variables were socio-demographic and related variables [age, sex, residence, marital status, educational level, patient's current working status, occupation, and self-reported financial dependence (not able to cover their personal expense)]; behavioral, functional, and related information [alcohol drinking, cigarette smoking, and khat chewing history; recent traditional medicine use history, cohabitation, and activities of daily living (ADL)]; clinical and related information (presence of past medical history, hospitalization in the previous 1-year, psychological condition on admission). Katz Index of independence was employed to assess ADL, which indicates the functional health status of older patients on admission (51). The tool assesses performance in six daily living functions (eating, dressing, bathing, transferring, continence, and toileting), each of which is assigned a score of 1 or 0. Accordingly, patients are categorized as independent (full function), partially dependent (moderate impairment), or dependent (severe functional impairment) if they scored 6, 3–5, and 2 or less points, respectively. The shortened self-report form of the Geriatric Depression Scale (GDS) which comprised 15 items, was used to objectively assess the psychological condition of older patients on admission (52). Each question in GDS has two alternative responses, either yes or no, and the patients are categorized as having no psychological problem (0–4), mild depression/dementia (5–9), or severe depression/dementia (10–15). The outcome of this study is the nutritional status of older patients on admission to medical wards based on the full MNA tool score.

## Nutritional assessment

The nutritional assessment on admission was carried out using the full MNA tool. The MNA tool (24, 53) is recommended as a screening tool for malnutrition in older inpatients. The tool has been evaluated in the older population in Ethiopia (54). It is widely employed in studies and has good reliability and validity. It has 18 questions that can be categorized into four parts: anthropometric, overall assessment, diet assessment, and subjective assessment. The summative score is 30 points: 24–30 points indicate good nutrition; 17.0–23.5 points indicate risk of malnutrition; and less than 17.0 points indicate malnutrition. MNA has 96% sensitivity and 98% specificity (55). In assessing nutritional status on admission, body mass index (BMI) was calculated using the standard formula: BMI = weight in kg/(height in m)$^2$. The weight of the study participants was measured using beam balance. For taking the weight of the participant, each of them was requested to take off their shoes and heavy clothes, including jackets, jerseys, and belts; the balance was calibrated; and the figure was approximated to the nearest 0.01 kg. For measuring height, a seca vertical height scale was used. Patients were asked to take off their shoes and stand upright in the middle of the board. Thereafter, height was measured to the nearest 0.01 cm by making the participant's back of the head, the shoulder blades, the buttocks, and the heels to touch the measuring board. Upon encountering patients who cannot erect upright because of their illness, their height was estimated from demi-span (56). In line with a standard recommendation, the length from the sternal notch to the finger roots (demi-span) was measured by a flexible validated plastic tape with the patient sitting upright or recumbent depending on the patient's abilities. Then, height was estimated as follows: for female individuals: Height in cm = (1.35 × demi-span in cm) + 60.1; for male individuals: Height in cm = (1.40 × demi-span in cm) + 57.8.

## Data management and statistical analysis

Data were checked for completeness and accuracy during the data collection period, entry, and before the analysis. Epi data version 4.2.0.0 and STATA V.15.0 were employed for data entry and analysis, respectively. Categorical variables were described in frequency and percentage. Upon performing the Shapiro-Wilk test, the distribution

of continuous variables was non-normal, thus presented in the median and interquartile range (IQR). For the binary logistic regression model, nutritional status was dichotomized into 0 = no malnutrition (normal and at risk of malnutrition) and 1 = malnutrition. Candidate variables for regression analysis were selected based on the existing literatures, and all variables with a $p < 0.25$ in simple logistic regression were incorporated into multiple logistic regression analysis. Collinearity was checked using the variance inflation factor (VIF); all factors included in the multiple logistic regression analysis had a VIF of <10 (maximum 1.48). The interaction was evaluated using statistical models by including product terms for two independent variables presumed to have interactions in the model. The goodness-of-fit of the final model was evaluated by computing the area under the receiver operating characteristic curve (ROC), Hosmer–Lemeshow test, and classification table. In all the analyses, a two-tailed $p < 0.05$ was used to declare statistical significance.

## Results

The median age of the participants was 65 years, and most of them were men (82.2%). Of the total study subjects, farmers accounted for 24.2%, and self-reported financial independence for healthcare expenditure was captured in over three-fourths (78.3%). The socio-demographic and behavioral information of the study subjects are shown in Table 1.

### Clinical and related information of the study participants

On assessing the activities of daily living using the Katz score, 78% of the participants had impairment in their functional autonomy at admission. Past medical history was captured in 65.6% of the participants, and each of these patients had three known diseases on average. A little above one-third (33.8%) of the participants had a previous hospitalization history. The functional, clinical, and related information of the study subjects is presented in Table 2.

### Nutritional status of the study participants

On the MNA tool-based nutritional status assessment at admission, 81% of the study participants had a score less than 17 and were categorized as malnourished. However, upon a thorough review of patients` medical charts over the hospital stay, malnutrition diagnosis was recorded in only two. The prevalence of elderly inpatients' nutritional category is depicted in Figure 1.

The full MNA tool questions with data captured from the study subjects are presented in Table 3.

### Factors associated with the nutritional status of elderly patients

Six variables achieved a $p < 0.25$ in the simple logistic regression analysis; only residence ($p = 0.017$) and financial dependence ($p = 0.041$) were significantly associated with nutritional status. Subsequently, multiple logistic regression analysis was performed by incorporating the main variables achieving a $p < 0.25$ and some pertinent interaction terms (financial dependence#residence, financial dependence#sex, and functional autonomy#sex). However, none of the interaction terms were statistically significant, thus removed from the model and the analysis was rerun without the interaction terms. In the final model, significantly higher odds of malnutrition were observed in older patients from rural areas (AOR = 2.823, 95%CI: 1.088, 7.324, 0.033), with financial dependence (AOR = 4.733, 95%CI: 1.011, 22.162, 0.048), and with partial dependence in functional autonomy on inpatient admission (AOR = 3.689, 95%CI: 1.190, 11.433, 0.024). The model achieved an area under the ROC curve of 0.754 and an insignificant Hosmer–Lemeshow test $p$-value (0.756) indicating a good fit. On classification table analysis, the model correctly classified 82.20% of the participants achieving a sensitivity of 96.85%. The regression analysis is shown in Table 4.

## Discussion

This single-center prospective cross-sectional study is a pioneer in quantifying the prevalence of malnutrition and determining associated factors in older patients on admission to medical wards in Ethiopia. Patients were assessed for nutritional status within 48 h of admission to medical wards using the full MNA tool. Accordingly, almost all admitted elderly patients (98%) were either malnourished (81%) or at risk of malnutrition (17%). However, clinicians recorded malnutrition diagnosis in only two patients' medical charts, which indicates that malnutrition diagnosis is neglected in almost all patients.

In the previous studies from Ethiopia, the pooled prevalence of undernutrition among the older population was 20.53% (39); however, the included studies were entirely community based. In Egypt, a similar study involving 194 older patients admitted with cancer reported malnutrition in 33% of the participants (57). In the study from Egypt (57), the study participants were a cohort of patients with cancer, which along with other dissimilarities in the study participants' characteristics might have contributed to a lower prevalence of malnutrition as compared to our result. In Europe, malnutrition has been reported in as high as 80% of older patients (9), which is consistent with our findings. Other similar studies from Europe (27, 28), Australia (25, 29), Brazil (28), and Asia (26, 30–35) reported malnutrition far lower than our findings. This could be attributed to potential differences in the study participants' characteristics. The observed, alarmingly high prevalence of malnourished patients in our study requires immediate intervention. In fact, the elderly often become dependent on others for their food and nutrition (58), in the context of poor social support status seen in Ethiopia (59), huge vulnerability to malnutrition is expected. The policy direction for old age and food insecurity seen in Ethiopia due to underlying multifactorial causes might also contribute to the observed malnutrition prevalence in older inpatients (60). Evidence also shows that medical comorbidity, physical impairments (9, 10), and hospitalization (9, 11) affect nutritional status in elderly people. In the present study, a higher proportion of elderly patients had a past medical history (65.6%) and physical impairment (59.2%). However, in this study, the presence of past medical history was not significantly associated with malnutrition.

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TABLE 1 Socio-demographic and behavioral information of the study subjects.

| Variables | n (%) |
|---|---|
| Sex | |
| Male | 129 (82.2) |
| Female | 28 (17.8) |
| Age, Median (IQ) | 65 (60–70)* |
| Young old (60–74) | 121 (77.8) |
| Middle old (75–84) | 30 (18.5) |
| Older old (≥85) | 6 (3.7) |
| Residence | |
| Urban | 32 (20.4) |
| Rural | 125 (79.6) |
| Marital status | |
| Never married (single) | 1 (0.6) |
| Married | 129 (82.2) |
| Divorced | 8 (5.1) |
| Widowed | 19 (12.1) |
| Educational status | |
| No formal education | 148 (94.3) |
| Primary education (grade 1–8) | 6 (3.8) |
| Collage and above | 3 (1.9) |
| Occupation | |
| No job | 65 (41.4) |
| Farmer | 38 (24.2) |
| Housewife | 23 (14.7) |
| Retired | 20 (12.7) |
| Merchant | 6 (3.8) |
| Daily laborer | 4 (2.6) |
| Public employee | 1 (0.6) |
| Currently working | |
| Yes | 49 (31.2) |
| No | 108 (68.8) |
| Self-reported financial dependence | |
| Dependent | 34 (21.7) |
| Independent | 123 (78.3) |
| Alcohol consumption history | |
| Yes | 45 (28.7) |
| No | 112 (71.3) |
| Cigarette smoking history | |
| Yes | 38 (24.2) |
| No | 119 (75.8) |
| Khat chewing history | |
| Yes | 113 (72) |
| No | 44 (28) |
| Cohabitation | |
| With spouse and children | 80 (51) |
| With spouse | 41 (26.1) |
| With children | 29 (18.5) |
| Alone | 7 (4.5) |

*Median (IQR), IQR, interquartile range.

TABLE 2 Functional, clinical, and related information of the study subjects.

| Variables | n (%) |
|---|---|
| Katz score, median (IQR) | 3 (0–6)* |
| Functional autonomy | |
| Dependent (2 or less) | 64 (40.8) |
| Partially dependent (3–5) | 49 (31.2) |
| Fully independent (6) | 44 (28) |
| Past medical history | |
| Yes | 103 (65.6) |
| No | 54 (34.4) |
| Number of diseases diagnosed on admission, median (IQR) | 3 (3–4)* |
| Top five previously diagnosed diseases | |
| Heart failure | 25 (15.9) |
| Hypertension | 49 (31.2) |
| Type 2 diabetes mellitus | 13 (8.3) |
| Bronchial asthma | 12 (7.6) |
| Ischemic heart disease | 8 (5.1) |
| Previous hospitalization history | |
| Yes | 53 (33.8) |
| No | 104 (66.2) |
| Surgical procedure history | |
| Yes | 8 (5.1) |
| No | 149 (94.9) |

*Median (IQR), IQR, interquartile range.

In this study, significantly higher odds of malnutrition were observed in older patients who were from rural areas. This finding is in line with other study findings from Ethiopia (18, 61). The possible difference in socio-economic status and dietary habits may have increased rural residents' risk for malnutrition. Also, several studies involving elderly people reported the existence of a significant association between functional autonomy and malnutrition (62, 63). A similar finding has also been observed in our study where the risk of malnutrition is high among patients who do have partial impairment in performing activities of daily living on admission in contrast to those who do not. Older patients with partial dependence on functional autonomy on admission had over 3.6-fold increased risk for malnutrition as compared to those who are fully independent. This is due to the fact that these patients lack functional autonomy to care after oneself and to prepare and eat foods requiring the attention of others (64). This fact is corroborated by our study finding in which

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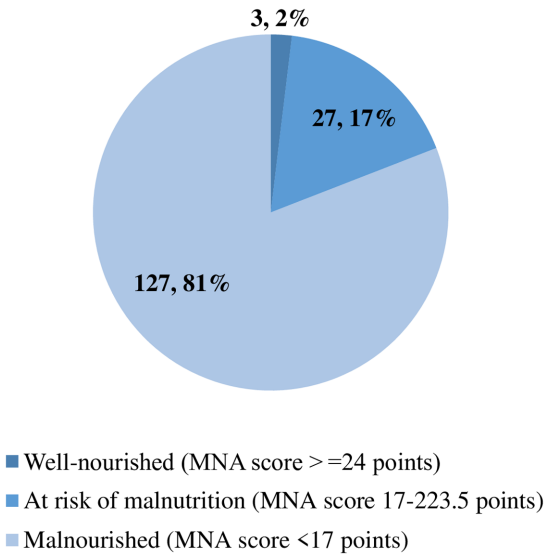


FIGURE 1
The proportion of hospitalized elderly patients according to their nutritional category.

most of the participants (86.6%) believed their food intake was decreased either moderately or severely.

Food and nutrition insecurity due to lower economic status also increases the risk for malnutrition (48), which is also observed in our study where older patients who were financially dependent for their expenses had a 4.73-fold increased risk for malnutrition as compared to their counterparts. This finding is consistent with other similar studies (15, 48). On the other hand, previously existing studies described female sex, low education level (41), older age (42, 43), unmarried (43, 44), polypharmacy, dysphagia, neuropsychological problem (45), alcohol abuse, and tobacco use as independent risk factors of malnutrition. The relatively longer life expectancies than men and the higher likelihood to encounter adverse economic and social circumstances in old age are assumed to increase the risk of malnutrition in women. As people get older, age-related alterations, such as physical frailty, loss of taste and poor appetite, the feeling of worthlessness, and a sense of neglect, can impact eating habits with adverse consequences on nutritional status (65). Beyond their impact on nutritional status, educational level, marital status, and sex, they were also found to affect discharge outcomes (66). In the present study, as seen in Table 4, the crude odds ratio shows an increased risk of malnutrition in the female sex, in patients with no formal education, older age, marital status of single, and alcohol abuse, however, none of them achieved a statistically significant association with malnutrition. This could be due to the small sample size employed in our study. Regarding polypharmacy (prescription drugs taken by the patients) and neuropsychological problems, these variables are already components of the full MNA tool used for outcome measurement (see Table 3), thus rationally excluded from considering them as independent variables in the logistic regression analysis in the present study.

TABLE 3 Full MNA tool questions with data captured from the study subjects.

| Variables | n (%) |
|---|---|
| Has food intake declined over the past 3 months | |
| Severe decrease in food intake | 61 (38.8) |
| Moderate decrease in food intake | 75 (47.8) |
| No decrease in food intake | 21 (13.4) |
| Weight loss during the last 3 months | |
| Weight loss greater than 3 kg | 23 (14.6) |
| Dose not know | 99 (63.1) |
| Weight loss between 1 and 3 kg | 19 (12.1) |
| No weight loss | 16 (10.2) |
| Mobility | |
| Bed or chair bound | 79 (50.3) |
| Able to get out of bed/chair but does not go out | 66 (42.0) |
| Goes out | 12 (7.7) |
| Has suffered psychological or acute disease in the past 3 months | |
| Yes | 19 (12.1) |
| No | 138 (87.9) |
| Neuropsychological problem | |
| Severe dementia or depression | 32 (20.4) |
| Mild dementia | 92 (58.6) |
| No psychological problem | 33 (21.0) |
| Body mass Index (BMI) | |
| BMI less than 19 | 57 (36.3) |
| BMI 19 to less than 21 | 67 (42.7) |
| BMI 21 to less than 23 | 19 (12.1) |
| BMI 23 or greater | 14 (8.9) |
| Lives independently (not in a nursing home or hospital) | |
| Yes | 4 (2.6) |
| No | 153 (97.4) |
| Takes more than 3 prescription drugs per day | |
| Yes | 143 (91.1) |
| No | 14 (8.9) |
| Pressure sores or skin ulcers | |
| Yes | 21 (13.4) |
| No | 136 (86.6) |
| How many full meals does the client eat daily? | |
| 1 meal | 11 (7.0) |
| 2 meal | 82 (52.2) |
| 3 meal | 64 (40.8) |
| Meat, fish, or poultry every day | |
| If 0 or 1 yes | 69 (44) |
| If 2 yes | 77 (49.0) |
| If 3 yes | 11 (7) |

*(Continued)*

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TABLE 3 (Continued)

| Variables | n (%) |
|---|---|
| Consume two or more servings of fruit or vegetables per day | |
| No | 119 (75.8) |
| Yes | 38 (24.2) |
| How much fluid (water, juice, coffee, tea, milk…) is consumed per day? | |
| Less than 3 cups | 53 (33.8) |
| 3–5 cups | 95 (60.5) |
| More than 5 cups | 9 (5.7) |
| Mode of feeding | |
| Unable to eat without assistance | 54 (34.4) |
| Self-fed with some difficulty | 54 (34.4) |
| Self-fed without any problem | 49 (31.2) |
| Self-view of nutritional status | |
| View self as being malnourished | 41 (26.1) |
| Is uncertain of nutritional status | 89 (56.7) |
| View self as having no nutritional problem | 27 (17.2) |
| In comparison with other people of the same age, how does the client consider his /her health status | |
| Not as good | 5 (3.2) |
| Dose not know | 132 (84.1) |
| As good | 15 (9.5) |
| Better | 5 (3.2) |
| Mid–arm circumference (MAC) in cc | |
| MAC less than 21 | 93 (59.2) |
| MAC 21–22 | 31 (19.8) |
| MAC greater than 22 | 33 (21.0) |
| Calf circumference (CC) in cm | |
| CC less than 31 | 132 (84.1) |
| CC 31 or greater | 25 (15.9) |

From the results of the present study and the potential complications of undernutrition in elderly patients, the investigators recommend the installation of a system for the prevention, early detection, and management of malnutrition in elderly patients. First, for the prevention of malnutrition and its complications, Ethiopia: Food-Based Dietary Guidelines (67) encourage elderly people to take adequate fluid and diversified diets, such as meat, poultry products, fruits, and vegetables to prevent malnutrition. However, practically, given that the elderly are one of the poorest and most marginalized sections of the population in Ethiopia (68, 69), the authors have reservation on the possibility for successful implementation of governmental and non-governmental stakeholders. Second, the authors of the present study recommend early screening of elderly patients for nutritional status and managing those affected by malnutrition with oral nutritional supplementation, such as plumpy nut, and diet enhancement in the hospital settings according to the

TABLE 4 Logistic regression analysis to identify factors associated with the nutritional status of elderly patients on hospital admission.

| Variables | COR (95%CI) | *P*-value | AOR (95%CI) | *P*-value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 1 | | | |
| Female | 2.206 (0.619, 7.858) | 0.222 | 1.347(0.343, 5.295) | 0.670 |
| Age | | | | |
| 60–74 | 1 | | | |
| ≥75 | 1.615 (0.569, 4.577) | 0.368 | | |
| Residence | | | | |
| Urban | 1 | | | |
| Rural | 2.922 (1.215, 7.030) | 0.017 | 2.823 (1.088, 7.324) | 0.033 |
| Marital status | | | | |
| Single/divorced/ widowed | 1.515 (0.483, 4.748) | 0.476 | | |
| Married | 1 | | | |
| Educational status | | | | |
| No formal education | 1 | | | |
| Formal education | 2.241 (0.527, 9.527) | 0.275 | | |
| Financial dependence | | | | |
| Independent | 1 | | | |
| Dependent | 4.716(1.063, 20.913) | 0.041 | 4.733 (1.011, 22.162) | 0.048 |
| Alcohol consumption history | | | | |
| Yes | 1.1306(0.462, 2.767) | 0.788 | | |
| No | 1 | | | |
| Cigarette smoking history | | | | |
| Yes | 0.690 (0.285, 1.671) | 0.412 | | |
| No | 1 | | | |
| Khat chewing history | | | | |
| Yes | 1.368 (0.581, 3.215) | 0.473 | | |
| No | 1 | | | |
| Traditional medicine use | | | | |
| Yes | 1.005 (0.312, 3.237) | 0.994 | | |
| No | 1 | | | |
| Autonomy for ADL | | 0.056 | | |
| Fully independent | 1 | | | |

*(Continued)*

TABLE 4 (Continued)

| Variables | COR (95%CI) | *P*-value | AOR (95%CI) | *P*-value |
|---|---|---|---|---|
| Partially dependent | 3.344 (1.154, 9.691) | 0.026 | 3.689 (1.190, 11.433) | 0.024 |
| Dependent | 2.52 (0.998, 6.362) | 0.050 | 2.461 (0.914, 6.623) | 0.075 |
| Past medical history | | | | |
| Yes | 0.943 (0.406, 2.190) | 0.892 | | |
| No | | | | |
| Previous hospitalization history | | | | |
| Yes | 1.237 (0.522, 2.929) | 0.629 | | |
| No | 1 | | | |
| Surgical procedure history | | | | |
| Yes | 0.694 (0.133, 3.623) | 0.665 | | |
| No | 1 | | | |
| Number of diseases diagnosed on admission | 1.150 (0.882, 1.498) | 0.301 | | |
| Bronchial asthma | | | | |
| Yes | 0.437 (0.122, 1.561) | 0.202 | 0.476 (0.118, 1.921) | 0.297 |
| No | 1 | | | |
| Heart failure | | | | |
| Yes | 1.886 (0.525, 6.770) | 0.331 | | |
| No | 1 | | | |
| Hypertension | | | | |
| Yes | 0.617 (0.270, 1.407) | 0.251 | | |
| No | 1 | | | |
| Ischemic heart disease | | | | |
| Yes | 0.694 (0.133, 3.622) | 0.665 | | |
| No | 1 | | | |
| Type 2 diabetes mellitus | | | | |
| Yes | 0.336 (0.101, 1.113) | 0.074 | 0.374 (0.096, 1.261) | 0.108 |
| No | 1 | | | |

ADL, activity of daily living; AOR, adjusted odd ratio; COR, crude odds ratio.

national and relevant international guidelines, such as European Society for Clinical Nutrition and Metabolism (70). In doing so, special consideration for older patients with functional impairment on admission might be helpful. Finally, we also recommend a multicenter, large sample size study to increase the power of generalizability of the findings in the present study.

In this study, the collection of relevant data objectively from the older patients using standardized techniques and the exploratory nature of the study for the setting, as well as for Ethiopia, could be mentioned as merits. However, the study has some limitations. The single-center consideration and the small sample size employed may affect the accuracy and generalizability of the findings. Also, the causal association cannot be assessed due to the intrinsic nature of the cross-sectional design. Some pertinent variables, such as a number of family size, the presence of eating-related problems, and biochemical parameters for nutritional assessments were not addressed in the present study. We could not also rule out the possibility of response bias where some respondents may not actually answer some questions truthfully, which may distort study results.

In conclusion, using the full MNA tool, an alarmingly high prevalence of malnutrition and at risk of malnutrition was identified. Nevertheless, the problem went undiagnosed in a similar proportion of the patients. Owing to the existence of multiple evidences on the adverse clinical and humanistic consequences of malnutrition, the authors recommend designing immediate strategies for routine screening at admission and nutritional intervention with special emphasis on older patients from rural areas, with financial constraints, and with functional impairment on admission. Further large sample size study, incorporating pertinent variables missed in the present study and possibly assessing the clinical consequences of malnutrition in older patients in the local context is recommended.

## 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 study involving humans was approved by the Institutional Review Board (IRB) of Jimma University. The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

BT, MY, and DB substantially contributed to the data acquisition and results explanation and drafted the manuscript. BT performed the data analysis. TB contributed to the explanation of the results and revised the manuscript. 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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# Measurement of body composition in postpartum South African women living with and without HIV infection

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**Background:** While several methodologies are available to measure adiposity, few have been validated in sub-Saharan African (SSA) and none in postpartum African women living with HIV (WLHIV). We compared bioelectrical impendence analysis (BIA) and air displacement plethysmography (ADP) against dual *x*-ray absorptiometry (DXA) in South African women and examined differences by HIV and body mass index (BMI) status.

**Methods:** Lin's concordance correlation coefficient (CCC) test was used to examine fat mass (FM), fat free mass (FFM), and total body fat percent (%BF) difference between BIA vs. DXA, and ADP vs. DXA in women living with HIV ($n$ = 57) and without HIV ($n$ = 25). The Bland Altman test was used to assess mean differences and the direction of bias.

**Results:** The median age was 31 years (IQR, 26–35) and months postpartum were 11 (IQR, 7–16), 44% of the women had obesity. Lin's CCC for BIA and ADP vs. DXA were both 0.80 for %BF and 0.97 for FM, and 0.86 and 0.80 for FFM, respectively. Mean differences (DXA-BIA and ADP estimates) were $0.22 \pm 4.54\%$ ($p$ = 0.54) and $3.35 \pm 3.27\%$ ($p < 0.01$) for %BF, $-0.82 \pm 3.56$ kg ($p$ = 0.06) and $1.43 \pm 2.68$ kg ($p$ = 0.01) for FM, $-1.38 \pm 3.61$ kg (p = 0.01) and $-3.34 \pm 2.37$ kg ($p < 0.01$) for FFM, respectively. BIA overestimated %BF in WLHIV and underestimated it in women with obesity.

**Conclusion:** Body composition measurements using BIA and ADP correlated well with DXA, thereby providing alternative, safe tools for measuring postpartum FM and FFM in SSA women, including WLHIV.

KEYWORDS

**body composition, women with HIV, postpartum, dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), air displacement plethysmography (ADP)**

# Introduction

Pregnancy and the postpartum period (after childbirth) are recognised as a future window for metabolic health, including long-term obesity and subsequent risk for non-communicable diseases (NCDs) (1). However, data for postpartum body composition amongst Sub-Saharan Africa (SSA) women of African origin, including women living with HIV (WLHIV) are lacking. SSA has the highest rates of HIV worldwide, with women of reproductive age being predominately affected (2). Historically, weight loss was a common symptom in people living with HIV. However, with the recent policy shift to immediate treatment upon HIV diagnosis, there are increasing concerns about high levels of obesity and NCDs in people living with HIV (3). Indeed, in a recent study of Black South African WLHIV compared to those without HIV, it was found that irrespective of HIV status, women gained rather than lost weight at 12 months postpartum (4). However, it has been shown that body composition may differ by HIV status, with altered body fat partitioning (5, 6), as well as the long-term consequences to gaining differential fat mass (FM) or fat free mass (FFM), implicated in long-term metabolic health outcomes (7).

While dual-energy X-ray absorptiometry (DXA) is currently the gold standard for the analyses of FM and FFM, exposure to radiation and the requirement for a radiographer create significant limitations in low-income settings. Alternatively, bioelectrical impedance (BIA) and air displacement plethysmography (ADP) are safe and rapid methodologies that have been validated against DXA in other settings (8, 9). As with DXA, both BIA and ADP provide detailed body composition data including FM and FFM, which are more closely associated with health outcomes than anthropometry and body mass index (BMI) (10, 11). Increased FM is a risk factor for adverse maternal health outcomes, including diabetes and cardiovascular disease (CVD) (12). In contrast, FFM is a metabolically active tissue that is associated with reduced risk of metabolic disorders, including reduced mortality (7, 13). Accordingly, differentiating between FM and FFM using a safe and simple method in low-resourced communities can assist with risk stratification to help direct limited intervention resources to high-risk groups. Therefore, the goal of this study was to compare BIA and ADP against DXA in South African women within the postpartum period and examine differences by HIV and BMI status.

# Methods

## Study participants

A convenience sample of 82 South African women (aged ≥18 years) who were followed through in a larger study ($n = 250$) study of cardiometabolic health complications, were recruited between May 2021 and June 2022 and evaluated between 6 and 25 months postpartum. Women resided in Gugulethu, a low-income urban informal township, which is part of the greater Cape Town metropole, and home to almost 300,000 people of predominantly black African ethnic group (98.8%) (14). WLHIV were on ART for at least 1 year; and were either using efavirenz- (tenofovir 300 mg + emtricitabine 200 mg/lamivudine 300 mg + efavirenz 600 mg) or dolutegravir-based ART (tenofovir 300 mg + emtricitabine 200 mg/lamivudine 300 mg + dolutegravir 50 mg) provided as a fixed-dose combination pill taken once daily. Anthropometry and body composition assessment using the three methods (BIA, ADP, and DXA) were conducted on the same day in fasted (10 h) participants. All study procedures were reviewed and approved by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (HREC 653/2020), and all participants signed a written informed consent explained in their local isiXhosa language prior to participation.

## Anthropometry

Weight (kg) and height (cm) measurements were examined in light clothing and no shoes using a calibrated scale (Charder, Taichung City, Taiwan) accurate to within 0.2 kg and a stadiometer (Seca, Birmingham, United Kingdom) accurate to within 0.1 cm. BMI was then calculated as weight divided by height squared; and categorised based on World Health Organisation criteria as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9) and obese (≥30) in kg/m$^2$ (15).

## Body composition

Three methods of whole-body composition were used to measure total body FM and FFM reported in absolute measures (kg). Total body FM is also presented relative to total body mass and reported as a percentage (%BF).

## Dual-energy X-ray absorptiometry

The participants were scanned using a low intensity *x*-ray beam by the study radiologist, while lying in a supine position wearing a laboratory gown with no jewellery. DXA scans (Hologic Discovery-W [S/N 71201], Bedford, MA, United States) were analysed using APEX software version 12.7.3.7 (16). *In vivo* precision was previously determined in our laboratory for FFM (0.7%) and FM (1.67%) by measuring 30 individuals twice on the same day with repositioning (17). The DXA unit was calibrated daily using a spine phantom, and participants received approximately 8.3 micro-Sieverts of radiation, considerably less than a transcontinental flight (60 micro-Sieverts).

## Bioelectrical impedance

A single-frequency (50 kHz) impedance analyser (model BIA 101Q; RJL Systems, Clinton Township, MI, United States) was used to obtain measures of resistance and reactance. Following this, the measured whole-body electrical resistance, reactance, height, weight and sex were entered into a BIA-specific equation, previously validated in Black South African women (18), and used to estimate measures of FM and FFM. The BIA unit was calibrated weekly using a test resistor.

## Air displacement plethysmography

Participants wore tight-fitting clothing and a cap, and were tested for body and lung volumes using the BodPod system (Cosmed, Rome, Italy). Body weight and volume assessments were conducted and corrected for thoracic gas volume (TGV) using predicted values. The ORTIZ equation for African descent population was used to calculate FM and FFM based on density and volume (19). The BodPod System is calibrated daily using a two-point calibration procedure.

## Statistical analysis

All statistical analyses were performed using STATA version 14 (Statacorp, Texas, United States) and figures were generated using R (R Foundation, Vienna, Austria). An alpha $p$ value of 0.05 was used to denote statistical significance. Participant characteristics were summarised and presented as median (25–75th percentile) for continuous and $n$ (%) for categorical variables. Characteristics stratified by HIV status were compared using Wilcoxon rank-sum test for continuous variables, significance was set at $p < 0.05$. Lin's concordance correlation coefficient (CCC) method (95% CI) was used to test the difference between BIA and ADP against DXA for the assessment of %BF, FM, and FFM. This method assesses both precision and accuracy to determine how far the observed data deviate from the line of perfect concordance (20, 21). The range is −1 to 1, with 1 being the perfect agreement between two measures. Next, we applied the Bland Altman test to examine the differences between the measures and to understand the direction of the bias (22) in the overall sample as well as in sub-groups stratified by HIV, BMI and months postpartum. To calculate the mean differences for BIA and ADP against DXA, BIA and ADP measurements were subtracted from those obtained using the DXA scan. Heteroscedasticity was tested to examine a linear relationship between the mean difference and %BF, FM and FFM.

# Results

## Participant characteristics

Of the 82 participants, 78 (95%) had both BIA and DXA, while 53 (65%) had both ADP and DXA assessments. The median age was 31 years (IQR, 26–35) and time postpartum was 11 months (IQR, 7–16), few (18%) women were primigravid and 70% were living with HIV (Supplementary Figure 1). Overall, the median weight was 75.9 kg (IQR, 66.2–90.8) and BMI was 28.9 kg/m$^2$ (IQR, 25.1–34.9). Women with HIV were lighter (72.5 kg [IQR, 63.3–87.3] vs. 88.8 kg [IQR, 73.8–96.1], $p = 0.03$) and had lower BMI (28.3 kg/m$^2$ [IQR 23.4–32.8] vs. 32.8 kg/m$^2$ [IQR 27.6–36.7], $p = 0.03$) compared to women without HIV. 44% women had obesity, 52% of which were women without HIV, and 40% were WLHIV ($p = 0.22$).

## DXA body composition

Using DXA, overall body composition was 46.2% (IQR 42.9–50.7) for %BF, 33.9 kg (IQR 27.1–44.4) for FM and 39.8 kg (IQR 35.3–43.4) for FFM (Supplementary Figure 1). Compared to women without HIV, WLHIV had significantly lower FM (31.9 vs. 40.9 kg, $p = 0.02$) and FFM (39.3 vs. 41.7 kg, $p = 0.01$), which was driven by their overall lower body weights.

## BIA vs. DXA

Lin's CCC for BIA vs. DXA was 0.80 (95% CI 0.71–0.87) for %BF, 0.97 (95% CI 0.95–0.98) for FM and 0.86 (95% CI 0.79–0.91) for FFM (Figures 1A–C). The mean differences (DXA minus BIA) were 0.22 ± 4.54% ($p = 0.54$) for %BF, −0.82 ± 3.56 kg ($p = 0.06$) for FM and − 1.38 ± 3.61 kg ($p = 0.01$) for FFM (Figures 1D–F). Overall, while differences were considered small and not clinically meaningful, %BF measurements using BIA were consistently lower than %BF measured using DXA, but that both FFM and FM BIA measurements were higher compared to DXA. Notably, the mean difference decreased with increasing %BF ($r^2 = 0.06$, $p = 0.03$), although this was not the case for FM and FFM. The direction of bias for %BF (indicated by positive or negative sign of the mean difference) was different in HIV and BMI sub-groups (Figure 2A, light blue lines and Supplementary Figure 2). %BF derived using BIA was higher for WLHIV (mean difference − 0.07 ± 4.66%) but lower for women without HIV (mean difference 0.85 ± 4.28%). This result is likely driven by BMI differences between the two groups (28.3 vs. 32.8 kg/m$^2$, $p = 0.03$; Supplementary Figure 1). Similarly, %BF using BIA was on average higher for women with normal BMI (mean difference − 1.05 ± 3.66%) but lower for women with overweight (mean difference 1.31 ± 6.10%) and obesity (mean difference 0.15 ± 3.67%) (Figure 2A, light blue lines and Supplementary Figure 2). A difference in the direction of bias was also observed in BMI sub-groups for FM measurements. Using BIA, FM was higher for women with normal BMI (mean difference − 1.32 ± 2.16 kg) and obesity (mean difference − 1.18 ± 3.49 kg) but lower for women with overweight (mean difference 0.13 ± 4.42 kg) (Figure 2B, light blue lines and Supplementary Figure 2). Postpartum months (≤12 vs. >12 months) did not affect the direction of the bias for all BIA vs. DXA measurements.

## ADP vs. DXA

Lin's CCC was 0.80 (95% CI 0.70–0.87) for %BF, 0.97 (95% CI 0.95–0.98) for FM and 0.80 (95% CI 0.71–0.87) for FFM (Figures 3A–C). The mean difference (DXA minus ADP) was 3.35 ± 3.27% ($p < 0.01$) for %BF, 1.43 ± 2.68 kg ($p = 0.01$) for FM and − 3.34 ± 2.37 kg ($p < 0.01$) for FFM (Figures 3D–F). This shows that %BF and FM measurements completed using ADP were lower than those completed using DXA, but that FFM ADP measurements were higher compared to DXA measurements. The mean difference decreased with increasing %BF ($r^2 = 0.22$, $p < 0.01$) and FM ($r^2 = 0.19$, $p = 0.01$) but not FFM. The direction of this bias (represented by the positive or negative sign of the mean difference) for ADP did not differ between sub-groups of HIV, BMI or postpartum months (Figures 2A–C, dark blue lines).

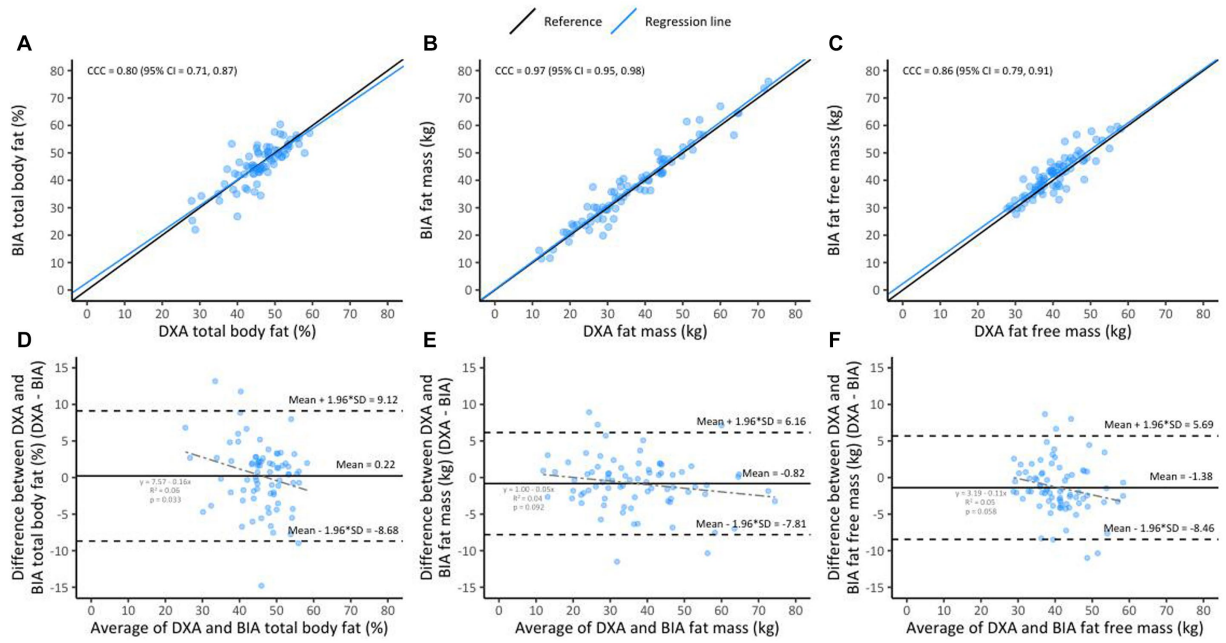


FIGURE 1
Lin's concordance between BIA and DXA in the overall sample ($n = 78$, **A–C**); the black line indicates perfect concordance while the blue line indicates the observed relationship between BIA and DXA for %BF **(A)**, FM **(B)**, and FFM **(C)**. Bland Altman limit of agreement between BIA and DXA **(D–F)**; the solid line indicates the mean difference between BIA and DXA for %BF **(D)**, FM **(E)**, and FFM **(F)**. The area inside the dotted lines indicate 95% limits of agreement (HIV+ [$n = 54$] and HIV– [$n = 24$]).

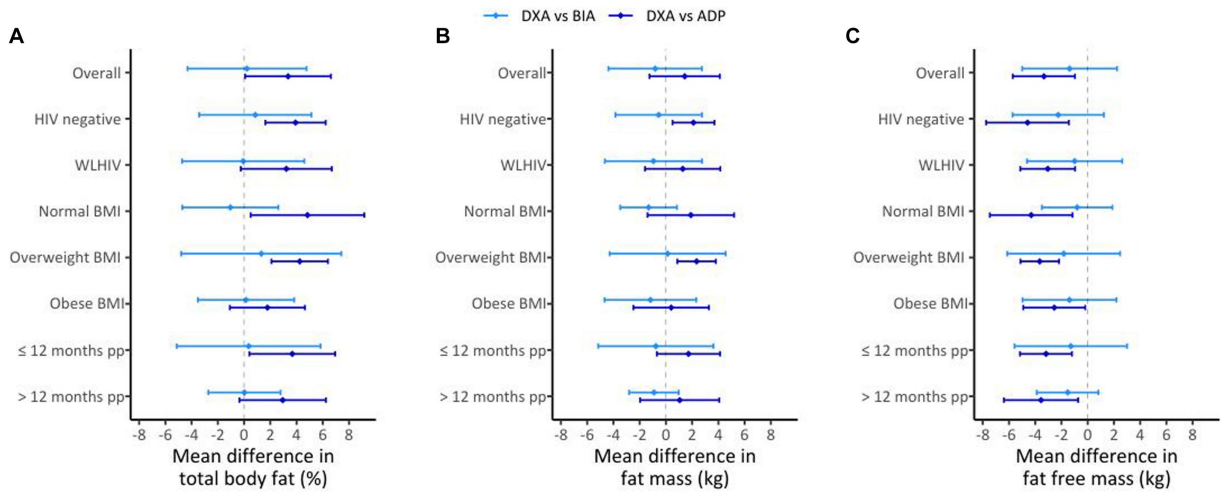


FIGURE 2
Mean differences for DXA vs. BIA (light blue lines) and DXA vs. ADP (dark blue lines) in the overall sample ($n = 82$, **A–C**) and by HIV, BMI, and postpartum (pp) duration; for %BF **(A)**, FM **(B)**, and FFM **(C)**. The diamond represents the estimate of the mean difference for the comparisons and the bars represent the mean difference +/– the estimated SD of the mean difference.

## Discussion

To our knowledge, this is the first study to examine body composition measurements comparing BIA and ADP against the gold-standard DXA in postpartum WLHIV and women without HIV in SSA. Using Lin's CCC, we found that the agreement for both BIA and ADP with the gold standard test was overall high, but with some variation depending on HIV and BMI status but not postpartum months.

Bioelectrical impendence analysis is a portable, quick and inexpensive measure of body composition based on the electrical resistance principle. We found that BIA assessments were highly correlated with DXA, especially for FM ($r = 0.97$). FM is associated with increased risk of adverse metabolic health including a lifetime risk of CVDs (23). However, changes in FM may not always be reflected through postpartum weight, hence, body composition assessment is a superior measure. This was shown in a study by Cho

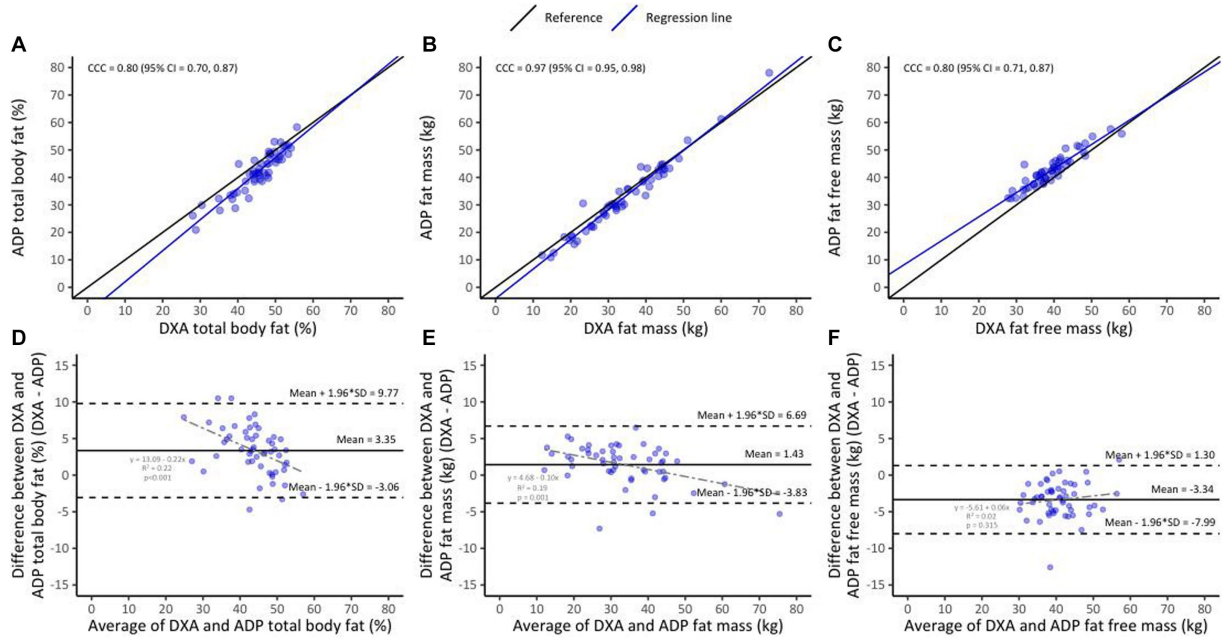


FIGURE 3
Lin's concordance between ADP and DXA in the overall sample ($n = 53$, **A–C**); the black line indicates perfect concordance while the purple line indicates the observed relationship between ADP and DXA for %BF **(A)**, FM **(B)**, and FFM **(C)**. Bland Altman limit of agreement between BIA and DXA **(D–F)**; the solid line indicates the mean difference between ADP and DXA for %BF **(D)**, FM **(E)**, and FFM **(F)**. The area inside the dotted lines indicate 95% limits of agreement (HIV+ [$n = 43$] and HIV– [$n = 10$]).

and Junamala, who found that FM was increased in postpartum women despite lack of changes in weight (24, 25). The mean differences between BIA and DXA were between 1 and 3% for %BF, FM and FFM. While there are no established criteria for acceptable differences, this difference is considerably low. Therefore, these results suggest that BIA is a good measure of adiposity in this population. Indeed, BIA body composition estimation equations used in this study were validated against doubly labelled water method in populations of African origin, including South African women (18). However, we noted that in the overall sample, BIA underestimated %BF, albeit by a mean of 0.22%. When stratified by HIV and BMI status, BIA overestimated %BF amongst WLHIV and underestimated it amongst women with overweight and obesity. This observation of HIV group differences is likely driven by BMI differences, and both the HIV and BMI comparisons are in agreement as they indicate that the mean difference decreases with increasing %BF. There was no bias observed in the FFM in kg.

Air displacement plethysmography is a rapid, non-invasive but relatively costly new technology for assessment of body composition (26). Like BIA, we found that ADP assessments were highly correlated with DXA, especially for FM ($r = 0.97$). The mean differences between ADP and DXA assessments ranged between 4 and 8% for %BF, FM and FFM. The women included in the development of the ORTIZ equation used to estimate body composition amongst African descent populations were African Americans (27), with no representation of SSA women. As a result, we speculate that this may have contributed to the observed larger percentage error of ADP and that the development of an equation using SSA women might improve measurement precision. ADP underestimated %BF and FM, and overestimated FFM. However, with increasing adiposity, the mean difference decreased. Overestimation of FFM and underestimation of the fat content by ADP compared to DXA was also reported in other studies (28, 29). Obesity above 40 kg/m$^2$ has been shown to invert the ADP bias direction resulting in underestimation of FFM and overestimation of fat content (28). This would be an important consideration for our population as there is a high prevalence of overweight and obesity (64%) in South African women (30).

Our study is not without limitations. Firstly, we note that in our study there was variation in the timing of the postpartum visit attendance, which may have led to increased variability in the adiposity observed. This variability was however, mitigated by completing all the body composition assessments on the same day, allowing participants to act as their own controls. Secondly, we had fewer women enrolled without HIV. On the other hand, our study exploring body composition during the postpartum period, using the gold standard technique is a significant strength. In conclusion, we show that body composition assessment's using both BIA and ADP correlated well with DXA, offering alternative tools for measuring postpartum body composition. Implementation of such tools for routine monitoring of FM and FFM would be an important step towards achieving WHO sustainable development goal 3 target of one third reduction in premature mortality from NCDs by 2030.

## 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 Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town. 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

HM: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft. LM: Conceptualization, Methodology, Supervision, Writing – review & editing, Investigation. HG: Formal Analysis, Writing – review & editing. DM: Data curation, Project administration, Writing – review & editing. AM: Data curation, Writing – review & editing. JG: Conceptualization, Resources, Writing – review & editing, Supervision. AB: Conceptualization, Writing – review & editing. LD: Conceptualization, Investigation, Methodology, Supervision, 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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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1280425/full#supplementary-material

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# Agreement between parent-report and EMR height, weight, and BMI among rural children

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**Introduction:** Remote anthropometric surveillance has emerged as a strategy to accommodate lapses in growth monitoring for pediatricians during coronavirus disease 2019 (COVID-19). The purpose of this investigation was to validate parent-reported anthropometry and inform acceptable remote measurement practices among rural, preschool-aged children.

**Methods:** Parent-reported height, weight, body mass index (BMI), BMI z-score, and BMI percentile for their child were collected through surveys with the assessment of their source of home measure. Objective measures were collected by clinic staff at the child's well-child visit (WCV). Agreement was assessed using correlations, alongside an exploration of the time gap (TG) between parent-report and WCV to moderate agreement. Using parent- and objectively reported BMI z-scores, weight classification agreement was evaluated. Correction equations were applied to parent-reported anthropometrics.

**Results:** A total of 55 subjects were included in this study. Significant differences were observed between parent- and objectively reported weight in the overall group (−0.24 kg; $p = 0.05$), as well as height (−1.8 cm; $p = 0.01$) and BMI (0.4 kg/m$^2$; $p = 0.02$) in the ≤7d TG + Direct group. Parental reporting of child anthropometry ≤7d from their WCV with direct measurements yielded the strongest correlations [$r = 0.99$ (weight), $r = 0.95$ (height), $r = 0.82$ (BMI), $r = 0.71$ (BMIz), and $r = 0.68$ (BMI percentile)] and greatest classification agreement among all metrics [91.67% (weight), 54.17% (height), 83.33% (BMI), 91.67% (BMIz), and 33.33% (BMI percentile)]. Corrections did not remarkably improve correlations.

**Discussion:** Remote pediatric anthropometry is a valid supplement for clinical assessment, conditional on direct measurement within 7 days. In rural populations where socioenvironmental barriers exist to care and surveillance, we highlight the utility of telemedicine for providers and researchers.

KEYWORDS

**remote anthropometry, parent-report anthropometry, child weight classification, child growth monitoring, pediatric telemedicine, BMI corrections, obesity detection, healthcare during COVID-19**

# 1 Introduction

Childhood obesity poses an imminent threat to the wellbeing of children worldwide (1, 2). Obesity is associated with non-communicable diseases such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), musculoskeletal disorders, cancer, and increased mortality risk (2).

The coronavirus disease 2019 (COVID-19) pandemic has placed increased strain on children at risk or already classified as overweight or obese. The prevalence of childhood obesity has increased rapidly from 19.3 to 22.4% amid the pandemic (3). Children's ability to achieve adequate physical activity has been hampered and supplanted with increased time spent engaged in sedentary behavior (4). The metabolic storm generated from the upheaval of physical activity exacerbates the progression of the disease state and worsens obesity-related sequelae (5).

A constellation of factors influences the presence of childhood obesity; however, the living environment and geography may predispose children to a greater likelihood of developing overweight or obesity. Specifically, children in rural areas face higher odds of developing obesity than those in urban areas (6–8). An array of socioenvironmental factors is associated with obesogenic disparities observed in rural children, some of which function as barriers to clinical care (8, 9). Rural patients face long clinic commutes, and those from low-income households may have unreliable transportation. The American Academy of Pediatrics (AAP) identifies telemedicine as an essential strategy to reduce such barriers (10). While utilization has increased during the pandemic, broadband technology access presents a novel barrier for rural patients (11–13).

Telemedicine offers convenience but presents challenges for physical exams, as indicated in monitoring child growth. The use of age- and sex-specific body mass index (BMI) as an acceptable metric for classifying childhood overweight or obesity by providers was established by the US Preventative Services Task Force (USPSTF) in 2005 (14). The gold standard for anthropometric surveillance data is objectively measured height and weight, used to calculate BMI and related BMI indices (15). BMI indices are plotted on age- and sex-specific growth charts generated from population samples, establishing reference norms and allowing providers to determine where a child falls along the reference continuum (15). While variable for children in normal weight ranges due to variance in lean mass, BMI is associated with acceptable sensitivity as an indicator of adverse weight in children with an excess of adiposity (16).

Parent-proxy anthropometric reporting is an emerging strategy to supplement well-child visit (WCV) delays and demonstrate pediatric telemedicine utility. However, there are challenges in obtaining these metrics annually (15). WCV delays during the pandemic resulted in an aggravation of the existing concerns regarding annual anthropometric surveillance (17). To combat these concerns, a shift toward self- or parent-proxy-reported height and weight has been initiated to supplement clinical monitoring (15, 18–28). Measurement continuity is crucial when seeking to collect valid proxy-report measures. Smart scales or other technologically advanced tools may be optimal, but socioeconomically disadvantaged populations (i.e., rural) rarely have sufficient access to technology allowing them to utilize these instruments (23). Studies using widely available measurement tools display utility, though they may be subject to the risk of reporting bias (23). Further, home measurements are more acceptable when solely using direct measurements (19). Bias mitigation strategies should include consideration of the time gap (TG) between parent-proxy reported and WCV anthropometrics (23, 29–31). Parental underreporting of child weight and/or overreporting of child height are common in studies assessing the relationship between self-report and objective measures (18, 21, 22, 26). These inaccuracies are pronounced to a greater degree in children with pre-existing overweight or obesity (22, 32). Chronic misreporting can lead to chronic misrepresentation of BMI accuracy and the identification of overweight and obesity.

Correction equations for parent-reported height and weight have been assessed for their ability to ameliorate parental reporting bias (29–31, 33–39). These equations are derived from individual datasets, rendering them unique to sociodemographic characteristics from their reference sample (29, 35, 37–39). As pediatric healthcare delivery in rural settings faces residual scheduling challenges and loss of follow-up amid a transition to telemedicine, validation of parent-reported height and weight in underrepresented age groups is pivotal (17, 40, 41). To date, there is limited evidence utilizing correction equations in preschool-aged children. Hence, the objectives of the present investigation are: (1) determining correlations between parent-reported and objective clinical measures (weight, height, BMI, BMI z-score, and BMI percentile); (2) assessing the impact of the TG between parent and clinical report on these relationships; (3) discerning whether the source of the home measure impacts the relationships (e.g., measured vs. estimated values); and (4) evaluating the utility of corrections and their ability to improve correlations between parent-reported and objective clinical measures.

# 2 Methods

## 2.1 Study context—secondary analysis using data from the ENCIRCLE study

The patient-cliNic-Community Integration to prevent obesity in Rural preschool ChiLdrEn (ENCIRCLE) study is a pragmatic, cluster randomized controlled trial (RCT) that was conducted across Geisinger primary care clinics in central and northeast Pennsylvania (42). This study was designed to compare the effectiveness of clinic, patient-clinic, or patient-clinic-community interventions to attenuate the prevalence of obesity among preschool-aged children exposed to obesogenic environments (42). Many of these clinic locations are rural and serve an array of socioeconomic backgrounds within their respective communities.

Primary care providers (PCPs) from family medicine ($n = 51$) or pediatric ($n = 54$) clinics were randomized to one of the three potential intervention arms: standard WCV, patient-reported outcome (PRO) enhanced WCV, or PRO enhanced WCV plus Food Care. The WCV arm consisted of routine care aligned with clinical practice guidelines, including BMI screening and provider-led counseling (43). The PRO WCV and PRO WCV plus Food Care arms both integrate the parent-reported Family Nutrition and Physical Activity (FNPA) risk assessment tool into the WCV (44, 45). Food Care enhancements to the intervention involved patient referrals to community health professionals responsible for providing evidence-based obesity

prevention in conjunction with telehealth guidance on economical dietary planning (46). The ENCIRCLE study was incidentally launched in March 2020, in concordance with the COVID-19 pandemic. Telehealth has emerged as a critical component in maintaining continuous healthcare delivery amid efforts to mitigate transmission during the pandemic. The ENCIRCLE study was approved by Geisinger's Institutional Review Board and is presently registered with ClinicalTrials.gov (NCT04406441).

## 2.2 Study participants

This study incorporates a subset of the ENCIRCLE study population that has both clinical and parent-reported height and weight metrics ($n = 55$) for children.

## 2.3 Data collection

### 2.3.1 Parent-proxy reported anthropometrics

Data collection from consenting parents included self-reported children's age, biological sex, race/ethnicity, children's height and weight, relationship to the child, educational level, annual household income indices, and employment status. Respondents indicated whether weight and height were estimated or measured directly at home. Values were reported to the nearest inch/cm and pound/kilogram. A screenshot of these questions is included (Supplementary Figure S1) as the parent would view them. No details about home equipment were collected.

### 2.3.2 Objectively assessed anthropometrics

Children's height and weight were recorded using standardized procedures during WCVs by trained clinic staff. Height was measured to the nearest 0.1 cm using a stadiometer (SECA 264), and weight was measured to the nearest 0.1 kg using a calibrated digital scale (Health-o-meter 599KL).

### 2.3.3 Calculation of BMI, BMI z-score, and BMI percentile

Parent-proxy and objectively measured BMI were calculated from parent-reported and objectively measured height and weight, respectively. Children's BMI z-score and BMI percentile for age and sex were calculated from the Centers for Disease Control (CDC) programs designed for children from 2 to 19 years of age.

### 2.3.4 Weight classifications

Sex-specific BMI-for-age percentiles were calculated in the EHR system to identify children by weight status: normal weight (> 5th and < 85th), overweight (≥ 85th and < 95th), obese (≥ 95th and < 99th), and severely obese (≥ 99th).

### 2.3.5 Population sociodemographic characteristics

Demographic characteristics of the ENCIRCLE study population were recorded into the REDCap database during the eligibility screening process and inclusion/exclusion survey criteria from consenting parents. Additional characteristics were collected during a study team follow-up call.

### 2.3.6 Correction methods

Correction equations were derived using an univariate analysis to determine subject characteristics to be applied to the correction model. Adjusted $R^2$ statistics assess the fit of the model. The model in the present investigation was extrapolated from parents reporting their child's height and weight ≤ 7 days prior to the WCV ($n = 37$) to accommodate the influence of the TG between parent-proxy and objective measurements. Indirect corrections for parent-proxy reported BMI, i.e., applying correction equations to parent-proxy reported height and weight to subsequently calculate a corrected BMI, were employed. Correction models were uniquely generated for our given dataset due to the lack of established correction models for preschool-aged children and consideration of previous literature that has advised against the application of correction equations to multiple datasets (34, 47, 48). Correction modeling procedures were carried out in SAS (SAS Institute, Cary, NC, USA).

## 2.4 Statistical analyses

To mitigate potential reporting bias in parent-proxy measurements, only anthropometrics that were reported prior to the child's WCV were included in analyses. Sociodemographic factors were included to characterize the study population. Differences between parent-proxy and objective clinic measurements were reported to describe the distribution of height, weight, BMI, BMI z-score, and BMI percentile. The calculation of age- and sex-specific BMI z-scores and percentiles was performed using SAS procedures provided by the CDC. A stratification based on the TG was performed to identify differences between parent-proxy and objective anthropometrics. TG differences were applied to compare measurements that occurred ≤7 days before the WCV against measurements that occurred >7 days before the WCV. REDCap surveys were given to participating parents, representing each parent–child dyad. Parents were asked whether their reported measurements (height or weight) were directly measured or estimated. To differentiate subjects whose heights and weights were directly measured, TG groups (≤7 days and > 7 days) were subject to additional stratification based on survey responses.

Independent samples *t*-tests were employed to assess between-group differences for child demographic characteristics. Paired samples *t*-tests assess differences between parent-proxy and objectively reported measures (height, weight, BMI, BMI z-score, and BMI percentile). The significance level was set at a value of $p$ of ≤0.05. Pearson's correlation coefficient (R) acts as the ratio of covariance between variables and was calculated to assess the relationship between parent-proxy and objective measures. Scatter plots comparing parent-proxy and objective measures were generated to display correlations and the data distribution.

Bland–Altman plots were used to assess agreement between parent-proxy and objective measurements for height, weight, BMI, BMI z-score, and BMI percentile (47).

Sensitivity (true positive) and specificity (true negative) analyses were employed in the present analysis to discern weight classification error and agreement based on parent-proxy BMI z-score. In the present study, sensitivity identified the proportion of children who are objectively classified as obese and concurrently classified as obese by parent-proxy reports. Specificity identified the proportion of children

who are objectively classified as non-obese and concurrently classified as non-obese by parent-proxy reports. Cutoff values for BMI z-score weight categories are described as normal (−2 SD > BMI > 1 SD), overweight (1 SD > BMI > 2 SD), and obese (BMI > 2 SD) in accordance with previous literature (48). Positive predictive value (PPV), negative predictive value (NPV), and accuracy were also calculated in the present analysis (48).

Cohen's Kappa quantified the agreement of weight categorization (normal weight, overweight, or obese) between parent-proxy and objective measurements using calculated BMI z-scores. Cohen's Kappa is interpreted by a range of scores from 0.0 to 1.0; <0 indicating a 'less than chance' agreement, 0.01–0.20 indicating a 'slight' agreement, 0.21–0.40 indicating 'fair' agreement, 0.41–0.60 indicating 'moderate' agreement, 0.61–0.80 indicating 'substantial' agreement, and 0.81–0.99 indicating 'almost perfect' agreement (49). The intraclass correlation coefficient (ICC) assessed the outcome variation between parent-proxy and objective measures (50). ICC is interpreted along a spectrum from 0.0 to 1.0, where values <0.5 are indicative of 'poor reliability,' values between 0.5 and 0.75 are indicative of 'moderate' reliability, values between 0.75 and 0.9 are indicative of 'good' reliability, and values >0.9 indicate 'excellent' reliability (51). Histograms were created, displaying the frequency of agreement between parent-proxy and objective measures.

## 3 Results

A total of 55 parent–child dyads represent the overall study population. Most children in this study were female (53%). The mean age at the time of parental reporting was 46.4 months, and 46.9 months at their WCV. The average TG between parent-report and WCV was 16.9 days. Demographic characteristics for all stratification groups are described in Table 1. Certain parental demographic data (i.e., parent gender, ethnicity, race, education, or employment) were calculated based on a smaller reference sample due to the presence of occasional missing survey report data.

Regardless of the TG, parents tend to report their child's height (74.5%) and weight (85.5%) as "1" (direct) most of the time. Parents reporting their child's measurements >7 days before their WCV utilize direct measurements more for height (83.3%) and weight (94.4%) than those reporting ≤7 d (70.3, 81.1%, respectively).

Table 2 describes means, differences, and agreement analyses (ICC, Pearson's R) for parent- and objectively reported anthropometrics for the overall study population, and individual stratification groups. A significant difference between parent-reported weight and objectively measured weight was detected across the overall sample ($p = 0.05$). Significant differences were detected for height ($p = 0.01$) and BMI ($p = 0.02$) in the ≤7d TG + Direct group.

Weight classification agreement measured using Cohen's Kappa for BMI z-score within the overall population yielded a Kappa coefficient of 0.22, indicating fair agreement.

Sensitivity, specificity, PPV, NPV, and accuracy are calculated using parent-proxy reported BMI z-score for weight classification, derived from parent-reported height and weight (Table 3). Sensitivity in normal weight subjects decreased as stratification level increased across the three groups (66, 60, 53%), and specificity increased similarly across the three groups (55, 83, 86%). Overweight specificity decreased across the three groups (67, 60, and 55%), and sensitivity increased (38, 71, and 100%). Sensitivity and specificity did not notably change among obese subjects.

Table 4 describes the classification accuracy of parent-reported anthropometrics for all stratification groups. Unanimously, the ≤7d TG + Direct group displayed the greatest level of classification agreement (weight, 91.67%; height, 54.17%; BMI, 83.33%; BMI z-score, 91.67%; and BMI percentile, 33.33%). Conversely, the >7d TG + Direct group displayed the lowest rates of classification agreement for height (26.67%) and weight (60%), while the >7d TG group displayed the lowest rates of classification agreement for all three BMI indices (BMI, 38.89%; BMI z-score, 55.56%; BMI percentile, 22.22%). An agreement gradient emerged across classification groups, ranking highest to lowest agreement from ≤7d TG + Direct, ≤7d TG, Overall, >7d TG + Direct, and > 7d TG.

The limits of agreement (LOA) are representative of the mean difference ± 1.96 standard deviations and are calculated and displayed within each respective Bland–Altman plot (Supplementary Figures S2A–E). These include LOA for weight (1.48, −1.95), height (8.65, −10.31), BMI (3.2, −2.95), BMI z-score (2.19, −2.08), and BMI percentile (55.39, −57.87).

Correction models were applied to parent-reported height and weight, as subsequently described.

- $Corrected\ Weight = 0.489 + (0.984 * Weight_{Self})$
- $Corrected\ Height = 38.952 + (0.462 * Height_{Self}) + (0.350 * months)$

Correlations (Pearson's R) were calculated to assess the agreement between corrected parent- and objectively reported height, weight, and indirectly calculated BMI. In the ≤7d TG + Direct group ($n = 37$), the weight correlation remained unchanged (0.99), decreased for height (0.95 to 0.94), and decreased for indirect BMI (0.82 to 0.72). In the >7d TG + Direct group ($n = 15$), weight correlation remained unchanged (0.93), height remained unchanged (0.89), and indirect BMI improved (0.53 to 0.63).

## 4 Discussion

Amid strong agreement between parent- and objectively reported height and weight within the overall population, BMI metrics (BMI, BMI z-score, and BMI percentile) were poorly correlated. Thus, we sought to explore stratification methods and corrections to strengthen this agreement. We observed the marked influence of the TG, noting that measurements recorded and reported within 7 days displayed higher indications of agreement when compared to those greater than 7 days from the child's WCV. These improvements were augmented by controlling for the source of the home measure (i.e., including only direct measures). However, our application of corrections to parent-reported height, weight, and BMI did not accentuate agreement. Our findings support the utility of remote anthropometry under the conditions of reporting within 7 days and confirming that the child's at-home measurement was direct.

Objective assessments performed by trained clinical staff are considered the gold standard of anthropometric assessment (15, 52–55). As telemedicine becomes a staple of clinical practice in the wake of COVID-19, the validation of remote anthropometry in children has garnered increased attention (15, 18–28). Previous research has leveraged pre-recorded at-home video instruction (23), live at-home

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TABLE 1 Demographic characteristics of the study population.

| Participant (Child) Characteristics* | Overall (*n* = 55) | ≤7d TG (*n* = 37) | >7d TG (*n* = 18) | ≤7d TG + Direct (*n* = 24) | >7d TG + Direct (*n* = 15) |
|---|---|---|---|---|---|
| Child age (mo)† | | | | | |
| Age at report | 46.4 (11.0) | 47.0 (11.4) | 45.1 (10.0) | 47.4 (10.8) | 45.8 (10.4) |
| Age at WCV | 46.9 (11.0) | 47.4 (11.4) | 46.6 (10.0) | 47.4 (10.8) | 47.2 (10.5) |
| Time gap (d)[a]† | 16.9 (25.3) | 2.7 (2.0) | 45.3 (26.4) | 2.3 (2.1) | 42.3 (26.3) |
| Child sex† | **n = 55** | **n = 37** | **n = 18** | **n = 24** | **n = 15** |
| Male | 26 (47) | 16 (43) | 10 (56) | 11 (46) | 8 (53) |
| Female | 29 (53) | 21 (57) | 8 (44) | 13 (54) | 7 (47) |
| Parent characteristics‡ | | | | | |
| Sex‡ | **n = 53** | **n = 35** | **n = 18** | **n = 23** | **n = 15** |
| Male | 1 (2) | 1 (3) | 0 (0) | 1 (4) | 0 (0) |
| Female | 52 (98) | 34 (97) | 18 (100) | 22 (96) | 15 (100) |
| Ethnicity‡ | **n = 54** | **n = 36** | **n = 18** | **n = 23** | **n = 15** |
| Hispanic | 2 (4) | 1 (3) | 1 (6) | 0 (0) | 1 (7) |
| Non-Hispanic | 52 (96) | 35 (97) | 17 (94) | 23 (100) | 14 (93) |
| Race‡ | **n = 54** | **n = 36** | **n = 18** | **n = 23** | **n = 15** |
| Caucasian | 52 (96) | 35 (97) | 17 (94) | 22 (96) | 14 (93) |
| African American | 1 (2) | 0 (0) | 1 (6) | 0 (0) | 1 (7) |
| Mixed race | 1 (2) | 1 (3) | 0 (0) | 1 (4) | 0 (0) |
| Education‡ | **n = 54** | **n = 36** | **n = 18** | **n = 23** | **n = 15** |
| HS/GED | 21 (39) | 12 (33) | 9 (50) | 8 (35) | 8 (53) |
| College degree | 15 (28) | 10 (28) | 5 (28) | 6 (26) | 3 (20) |
| Graduate degree | 14 (26) | 10 (28) | 4 (22) | 7 (30) | 4 (27) |
| Other[b] | 4 (7) | 4 (11) | 0 (0) | 2 (9) | 0 (0) |
| Employment‡ | **n = 45** | **n = 30** | **n = 15** | **n = 20** | **n = 13** |
| Full-time | 19 (42) | 14 (47) | 5 (33) | 7 (35) | 3 (23) |
| Part-time | 14 (31) | 9 (30) | 5 (33) | 8 (40) | 5 (38) |
| Unemployed | 8 (18) | 5 (17) | 3 (20) | 3 (15) | 3 (23) |
| Other[c] | 4 (9) | 2 (7) | 2 (13) | 2 (10) | 2 (15) |

*Independent sample *T*-test was utilized to compare differences in child characteristics within each stratification group; no significant differences were detected.
†Values are presented as Mean ± Standard Deviation (SD).
[a]Time gap refers to the number of days (d) between the time of parent-reporting and well-child visit (WCV) assessment.
‡Sum of parent characteristic variables differs due to missing data.
‡Values are presented as n (n%).
[b]Other educational backgrounds reported include trade school, some college, or a doctorate.
[c]Other employment situations were unspecified.

video conference (37), and smart-scale technology (56, 57) when collecting height and weight remotely. In the present study, we neither provided home equipment nor collected specific information regarding tools that parents used to measure their children on their own accord. Regardless, we found that direct measurements indicated by survey responses positively impacted the agreement between parental and clinical raters. Skinner et al. underscore the importance of clarifying the source of the home measure, finding that younger children were more likely to be misclassified into an incorrect weight classification following parental guessing (19). Our findings are further supported by a recent investigation by Forseth et al. where negligible differences were found between the use of at-home, study-provided, or objectively measured (school-based stadiometer) height and weight among rural children (23). While measurement instructions may provide a feasible strategy to mitigate reporting bias, broadly accessible tools for home-based measurements are acceptable.

Our study is among the few to identify the TG between reported measures and objective assessments as a critical component of moderating agreement (29, 58). Cheng et al. provide a framework for examining the TG as it relates to reporting accuracy and stratifying their patient population into those reporting within 7 and 30 days, respectively. In line with our findings, this group found that reporting within 7 days of objective measurement was associated with a lesser difference between reported and objective assessments. We found that controlling for TGs within 7 days improved agreement for the overall sample. The magnitude of agreement was amplified when additional

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TABLE 2 Means, differences, and agreement between parent-proxy reported measures and objective measures from clinic visits.

| | Parent-report[a] | Objective report[a] | Mean difference[b†] | Agreement | |
|---|---|---|---|---|---|
| | | | | ICC[c] | Pearson's R[d] |
| Overall group ($n = 55$) | | | | | |
| Weight (kg) | 17.1 (3.4) | 17.4 (3.5) | −0.2 (0.9)[‡] | 0.97 | 0.97 |
| Height (cm) | 101.3 (11.4) | 102.2 (9.5) | −0.8 (4.8) | 0.89 | 0.91 |
| BMI (kg/m$^2$) | 16.7 (1.8) | 16.5 (1.6) | 0.1 (1.6) | 0.57 | 0.57 |
| BMI z-score | 0.6 (1.2) | 0.6 (1.1) | 0.1 (1.1) | 0.55 | 0.55 |
| BMI % | 65.6 (30.5) | 66.9 (27.0) | −1.2 (28.9) | 0.50 | 0.50 |
| ≤7d TG group ($n = 37$) | | | | | |
| Weight (kg) | 17.5 (3.6) | 17.7 (3.6) | −0.2 (0.6) | 0.98 | 0.98 |
| Height (cm) | 101.6 (12.5) | 102.7 (9.6) | −1.1 (4.7) | 0.91 | 0.94 |
| BMI (kg/m$^2$) | 16.9 (1.8) | 16.7 (1.6) | 0.3 (1.5) | 0.61 | 0.62 |
| BMI z-score | 0.8 (1.2) | 0.7 (1.0) | 0.2 (1.0) | 0.58 | 0.59 |
| BMI % | 70.5 (29.8) | 68.4 (26.1) | 2.1 (26.9) | 0.53 | 0.53 |
| >7d TG group ($n = 18$) | | | | | |
| Weight (kg) | 16.5 (3.2) | 16.8 (3.5) | −0.3 (1.2) | 0.93 | 0.94 |
| Height (cm) | 100.7 (9.1) | 101.0 (9.4) | −0.3 (5.0) | 0.86 | 0.85 |
| BMI (kg/m$^2$) | 16.2 (1.7) | 16.3 (1.5) | −0.2 (1.7) | 0.44 | 0.43 |
| BMI z-score | 0.2 (1.2) | 0.4 (1.3) | −0.2 (1.2) | 0.48 | 0.47 |
| BMI % | 55.6 (30.4) | 63.7 (29.1) | −8.2 (31.5) | 0.44 | 0.44 |
| ≤7d TG + Direct group ($n = 24$) | | | | | |
| Weight (kg) | 17.2 (3.0) | 17.4 (2.9) | −0.2 (0.4) | 0.99 | 0.99 |
| Height (cm) | 101.2 (9.6) | 103.0 (8.6) | −1.8 (2.9)[‡] | 0.93 | 0.95 |
| BMI (kg/m$^2$) | 16.8 (1.5) | 16.4 (1.4) | 0.4 (0.9)[‡] | 0.79 | 0.82 |
| BMI z-score | 0.8 (0.9) | 0.5 (1.0) | 0.3 (0.7) | 0.67 | 0.71 |
| BMI % | 72.2 (25.7) | 64.8 (26.6) | 7.3 (20.8) | 0.69 | 0.68 |
| >7d TG + Direct group ($n = 15$) | | | | | |
| Weight (kg) | 16.4 (3.4) | 16.6 (3.6) | −0.2 (1.3) | 0.93 | 0.93 |
| Height (cm) | 99.2 (7.9) | 100.3 (9.9) | −1.1 (4.5) | 0.87 | 0.89 |
| BMI (kg/m$^2$) | 16.5 (1.6) | 16.3 (1.6) | 0.2 (1.6) | 0.54 | 0.53 |
| BMI z-score | 0.5 (1.1) | 0.3 (1.4) | 0.1 (1.0) | 0.66 | 0.67 |
| BMI % | 62.6 (27.2) | 62.4 (31.2) | 0.1 (24.4) | 0.67 | 0.66 |

[†]Paired samples *T*-test; [‡]significant difference (Overall; Weight [$p = 0.05$], ≤7d TG + Direct; Height [$p = 0.01$], ≤7d TG + Direct; BMI [$p = 0.02$]).
[a]Values shown as mean ± standard deviation (SD).
[b]Mean difference calculated by subtracting the mean of the objectively reported values from the mean of the self-reported values ($Mean_{Self}$-$Mean_{Obj}$).
[c]Intraclass correlation coefficient (ICC); <0.50 indicates poor reliability, 0.50–0.75 indicates moderate reliability, 0.75–0.90 indicates good reliability, and >0.90 indicates excellent reliability.
[d]Pearson's correlation coefficient (Pearson's R); values are interpreted on a continuum between −1 (perfect negative correlation), 0 (no correlation) and +1 (perfect positive correlation).

control for the source of the home measure was included. Our validation provides clinicians and researchers with an opportunity to enhance the accuracy of their use of remote anthropometry in telemedicine.

Accurate weight classification is critical for gauging the breadth of childhood overweight and obesity. The WHO recommends using BMI z-scores in research for the sake of continuity (59). Using a clinically measured BMI z-score as an anchor, we found parental reporting accuracy to gradually improve when controlling for the TG within 7 days, followed by a compounded increase in accuracy when controlling for the source of the home measure. Several reviews have identified a high prevalence of parental weight misclassification for their children (60–64). A review by Sherry et al. found parental reporting of BMI to be 55–76% sensitive for identification, and the prevalence of overweight decreased by −0.4 to −17.7% when calculated BMI was derived from parental reports, indicating chronic underreporting (65). These findings align with ours, where overweight sensitivity was low for the overall parent-reported sample (38%), indicating poor ability to correctly classify children as overweight. Only when additional control was integrated for the TG within 7 days, a direct source of home measure, did sensitivity improve (38, 71, and 100%, respectively). While limited, the literature suggests that the rationale for parental reporting bias is potentially due to factors such as digit preference,

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TABLE 3 Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of parent-reports for predicting weight classification with parent-reported BMI z-score.

| | Parent-report overall (*n* = 55) | | | Parent-report ≤ 7d TG (*n* = 37) | | | Parent-report ≤ 7d TG + Direct (*n* = 24) | | |
|---|---|---|---|---|---|---|---|---|---|
| | NM (n%) | OW (n%) | OB (n%) | NM (n%) | OW (n%) | OB (n%) | NM (n%) | OW (n%) | OB (n%) |
| Sensitivity[a] | 66 | 38 | 60 | 60 | 71 | 50 | 53 | 100 | 50 |
| Specificity[b] | 55 | 67 | 98 | 83 | 60 | 97 | 86 | 55 | 100 |
| PPV[c] | 72 | 26 | 75 | 88 | 29 | 67 | 90 | 31 | 100 |
| NPV[d] | 48 | 78 | 96 | 50 | 90 | 94 | 43 | 100 | 96 |
| Accuracy[e] | 62 | 60 | 95 | 68 | 62 | 92 | 63 | 63 | 96 |

NM, normal weight; OW, overweight; OB, obese.
[a]Sensitivity = True Positives / (True Positives + False Negatives).
[b]Specificity = True Negatives / (True Negatives + False Positives).
[c]Positive Predictive Value = True Positives / (True Positives + False Positives).
[d]Negative Predictive Value = True Negatives / (True Negatives + False Negatives).
[e]Accuracy = (True Positives + True Negatives) / Total "n."

TABLE 4 Accuracy of parent-proxy reported anthropometric data for weight, height, BMI, BMI z-score, and BMI percentile.

| Accuracy of parent-report data | | | | | |
|---|---|---|---|---|---|
| Classification[†] | Overall (*n* = 55) | ≤7d TG (*n* = 37) | >7d TG (*n* = 18) | ≤7d TG + Direct (*n* = 24) | >7d TG + Direct (*n* = 15) |
| Weight (kg)[a] | n% | | | | |
| Accurate | 67.27 | 81.08 | 66.67 | 91.67 | 60.00 |
| Underestimation | 27.27 | 16.22 | 16.67 | 8.33 | 20.00 |
| Overestimation | 5.45 | 2.70 | 16.67 | 0.00 | 20.00 |
| Height (cm)[b] | n% | | | | |
| Accurate | 36.36 | 40.54 | 27.78 | 54.17 | 26.67 |
| Underestimation | 43.64 | 43.24 | 44.44 | 41.67 | 53.33 |
| Overestimation | 20.00 | 16.22 | 27.78 | 4.17 | 20.00 |
| Body mass index (BMI)[c] | n% | | | | |
| Accurate | 58.18 | 67.57 | 38.89 | 83.33 | 53.33 |
| Underestimation | 18.18 | 10.81 | 33.33 | 16.67 | 33.33 |
| Overestimation | 23.64 | 21.62 | 27.78 | 0.00 | 13.33 |
| BMI z-score[d] | n% | | | | |
| Accurate | 72.73 | 83.78 | 55.56 | 91.67 | 73.33 |
| Underestimation | 10.91 | 5.41 | 22.22 | 8.33 | 13.33 |
| Overestimation | 16.36 | 10.81 | 22.22 | 0.00 | 13.33 |
| BMI percentile[e] | n% | | | | |
| Accurate | 27.27 | 29.73 | 22.22 | 33.33 | 26.67 |
| Underestimation | 32.73 | 27.03 | 44.44 | 20.83 | 33.33 |
| Overestimation | 40.00 | 43.24 | 33.33 | 45.83 | 40.00 |

[†]All accuracy, underestimations, and overestimations reference the comparison of parent-reported measurements to well-child visit (WCV) measurements as the standard.
[a]Accurate within ± 1 kg, underestimation by > 1 kg, overestimation by > 1 kg.
[b]Accurate within ± 2 cm, underestimation by > 2 cm, overestimation by > 2 cm.
[c]Accurate within ± 1 BMI pt, underestimation by > 1 BMI pt, overestimation by > 1 BMI pt.
[d]Accurate within ± 1 SD, underestimation by > 1 SD, overestimation by > 1 SD.
[e]Accurate within ± 5%, underestimation by > 5%, overestimation by > 5%.

inconsistent assessment timepoint, rounding error, and social desirability bias that may create misconceptions about their children's weight (32, 66–68). Further elucidation of socioenvironmental and interpersonal influences on parental weight misclassification is warranted.

Under- or overreporting of child height and weight typically yields poor agreement between BMI calculated from parental reporting and BMI calculated from objective measures (26, 29). Underestimations of BMI have been reported to the degree of 0.5 kg/m$^2$ (26, 37) and 0.6 kg/m$^2$, respectively (69). Shields et al. have identified BMI

overreporting as well, by a margin of 0.7 kg/m$^2$ based on parental reports (34). Our study finds BMI to be overestimated by 0.13 kg/m$^2$, despite underreporting of height and weight within the overall sample. Correction modeling provides an opportunity to combat misreporting and improve agreement between parent- and objectively reported height, weight, and BMI (29–31, 33–39). In one study utilizing correction modeling, agreement quantified by ICC improved from 0.33 to 0.64 for the classification of overweight or obese status after indirect corrections were applied for reporting within 7 days (29). Ghosh-Dastidar et al. show increased sensitivity for obesity regardless of sex and smaller RMSE values using indirect corrections, while noting heterogeneity of model applicability due to gender and outcome (37). We sought to control out-of-context equation applications by generating our own equations for our population. We align our use of 'indirect' BMI corrections with research that has shown favorable outcomes using this modeling technique (29, 37). However, no improvements in agreement parameters were found in our study. We speculate that the heightened levels of agreement we were able to achieve when controlling for the TG and source of home measure negated the capacity for corrections to further improve these relationships.

We provide validation for the concordance between parent-reported and objectively measured data, although the present study is not without limitations. Our omission of collecting information about home equipment used to measure children's height and weight stymies the evaluation of factors that may contribute to parental reporting bias. Additionally, our predominantly low-income, rural population may be inordinately impacted by a lack of internet access, hindering their capacity to engage with telehealth (70, 71). Additional limitations include the sample size and geographical constraints that restrict the generalizability of these findings to populations with comparable demographic characteristics. Overall, the present study serves to inform emergent literature regarding the use of parent-reported anthropometrics during the pandemic. These outcomes will advise clinicians, healthcare administrators, policymakers, and researchers who seek to leverage remote anthropometry as a supplement for clinical measures.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data from the present study are available from the corresponding author upon request. Requests to access these datasets should be directed to LB-D, ldbaileydavis@geisinger.edu.

## Ethics statement

The studies involving humans were approved by the Declaration of Helsinki, and ethical approval was obtained from the Institutional Review Board of Geisinger (#2020–0207, Version 1.19, 9/7/2022). Informed consent and parental permission were obtained from all participants. 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

BP: Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. GW: Data curation, Formal analysis, Software, Supervision, Writing – review & editing. LB-D: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, 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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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1279931/full#supplementary-material

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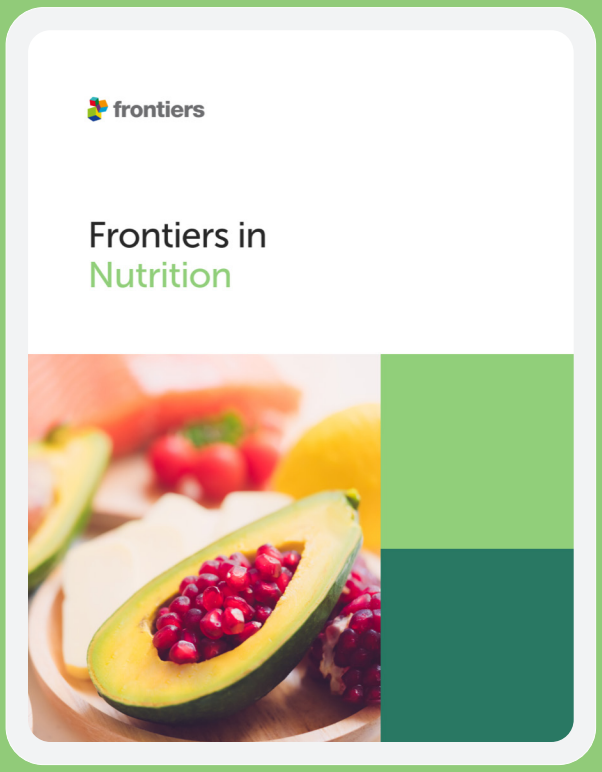


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