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# Nutritional management of childhood obesity and related diseases

**Edited by**
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# Nutritional management of childhood obesity and related diseases

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# Editorial: Nutritional management of childhood obesity and related diseases

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**childhood obesity, nutritional interventions, dietary pattens, risk factor, metabolic diseases**

Editorial on the Research Topic
Nutritional management of childhood obesity and related diseases

Childhood obesity constitutes one of the most challenging public health problems of our century due to its epidemic proportions and the related significant morbidity and mortality, increasing also public healthcare costs (1). Alarmingly enough, children with obesity demonstrate a fold-fold higher risk of remaining obese in adulthood (2). Notably, childhood obesity is a major risk factor for many chronic pathological conditions (3). A common risk factor associated with childhood obesity concerns the type of nutrition that the children adopt in their daily life (4). Several nutritional interventions have been proposed with the aim at reducing the prevalence of childhood obesity (5). In this aspect, novel research efforts should be performed, aiming to evaluate potential nutritional interventions, including either specific dietary pattern or foodstuffs ingredients, which may prevent or even co-treat childhood obesity and related diseases.

In view of the above considerations, a population-based study showed that the incidence of hyperuricemia was high in children and adolescents with obesity aged 6–17 years. In addition, this study emphasized that the combination of triponderal mass index and waist-to-height ratio could be applied as a potential early predictor of hyperuricemia risk in children and adolescents with obesity, and especially in girls (Niu et al.). In a cross-section MRI study, adolescents with metabolically healthy obesity showed lower hepatic fat, improved liver markers, and healthier dietary patterns compared to metabolically unhealthy obese peers. This evidence highlights the potential impact of prenatal and lifestyle factors in differentiating metabolic health profiles in adolescents affected by obesity (Moran-Lev et al.). Another cross-sectional study from NHANES 2011–2016 was designed to evaluate the association between the composite dietary antioxidant index (CDAI) and the prevalence of overweight or obesity among children and adolescents aged 6–19 years in the United States. This survey developed a modified CDAI, comprising of vitamins A, C, E, carotenoids, and zinc, and identified a consistent negative association between modified CDAI and overweight/obesity risk, regardless of energy adjustment method. This evidence suggests that a diet rich in antioxidants may exert a protective role in preventing obesity in adolescents aged 12–19 years (Chen and Shi).

A comprehensive national cross-sectional study in preschool children in Jordan was designed to assess feeding practices of infants and young children, determining the frequency of consuming micronutrient-rich foods, evaluating causes of anemia, assessing the health status of specific subgroups, and comparing findings to the previous 2010 national study (Barham et al.). In the previous 2010 national study, high rates of iron and vitamin D deficiencies among preschool children, with about 20% experiencing vitamin A deficiencies were recorded. The 2019 national study highlights ongoing nutritional challenges among Jordanian preschoolers. Although severe anemia was rare, 11% were anemic, and 22.4% had iron deficiency, including 5% with iron deficiency anemia. Vitamin D deficiency affected 22.9%, impacting growth and immunity. While stunting and wasting improved, childhood overweight and obesity rates remained steady. Anemia decreased, but iron deficiency rose by 7%. Despite reduced vitamin A deficiency, stable iron deficiency anemia rates indicate ongoing concerns. Overall, this study supported evidence that undernutrition is uncommon, but vitamin D and iron deficiencies, along with childhood obesity, need sustained attention and targeted interventions to improve children's health in Jordan (Barham et al.). A retrospective study analyzed clinical data from 159 school-aged children to investigate the potential association between vitamin D deficiency and childhood obesity rates, and its impact on serum calcium, alkaline phosphatase, and bone age in children. This study showed that the 25-hydroxyvitamin D3 [25(OH)D3] deficiency cohort exhibited significantly higher body mass index (BMI), total cholesterol (TC), triglycerides (TG), and alkaline phosphatase (ALP) levels, with lower Calcium (Ca) levels and delayed bone age compared to the normal group. These findings supported evidence that $25(OH)D_3$ deficiency is strongly associated with obesity in school-aged children and may negatively affect normal skeletal development. This study also suggests that regular monitoring of $25(OH)D_3$ levels in school-aged children is essential for ensuring proper growth and development, especially in those at risk for obesity (Xu et al.).

Another study explored the potential associations of micronutrients and lipids with prediabetes, glycemic parameters, and glycemic indices among 1,520 adolescent girls aged 16–18 years of the DERVAN cohort study from rural India. This study found a substantial deficiency of micronutrients and an absence of dyslipidemia. Moreover, this study highlights the need for lipid and micronutrient-based interventions in adolescence to improve glycemic outcomes, supporting that maintaining adequate storage of not only micronutrients but also lipids in adolescent girls is likely to reduce diabetes risk in adulthood (Patil et al.). A cross-sectional study was designed to assess the synergistic impact of Mediterranean diet, lifestyle and technology on glycemic control in 112 children with type 1 diabetes (T1D) from Gran Canaria (median age 12 years). This study showed that Mediterranean diet compliance, insulin delivery methods, age, and number of years with T1D could be important factors to consider in the management of T1D in children (Nóvoa-Medina et al.).

A multicenter cross-sectional nutritional and health surveillance study of a nationally representative sample of urban populations from eight Latin American countries aimed to explore the potential associations between the energy imbalance gap (EIG) and sociodemographic and anthropometric variables. A total of 680 adolescents aged 15–18 were included in this study, while the estimation of energy intake was based on two non-consecutive 24-h dietary recalls. This study supported evidence that sex and BMI were associated with EIG in adolescents from Latin America (Hernandez et al.). An institutional-based cross-sectional study design was conducted among 366 mothers with children aged 6–23 months in Ethiopia. This survey was designed to explore complementary food hygiene practices and their associated factors. It was found that the prevalence of complementary food hygiene practices was poor. This survey supported evidence that healthcare professionals should promote starting breastfeeding at the age of 6 months. In addition, media companies ought to make an effort to create a positive social and cultural environment that encourages complementary feeding practices for young children (Addis et al.). A cross-sectional study aimed to assess Online food delivery applications (OFDA) usage trends among adolescent users in the United Arab Emirates (UAE), focusing on their perceptions of healthy food options and food safety ($n = 532$). Most participants used OFDAs weekly (65.4%), favoring fast food (85.7%). Factors like appearance and price drove food choices (65.0%), while taste and cost hindered healthy food orders. Younger and frequent users had lower scores for perceiving healthy food, while seeking healthy options was associated with higher scores. Females and those seeking healthy food showed higher food safety scores. The study suggests tailored interventions to promote healthier choices and improve food safety perceptions among adolescents using OFDAs in the UAE (Saleh et al.).

Conclusively, the currently available research reinforces the urgent demand for the development and implementation of well-organized public strategies and policies that could inform the future parent about the beneficial effects of diverse nutritional interventions at the early stages of their children life in combination with other lifestyle factors, e.g., physical activity, mental health, metabolic disturbances, against childhood overweight, and obesity. Most of the currently available studies have a cross-sectional design, which cannot support causality effects. In this aspect, the performance of longitudinal studies is highly recommended.

## Author contributions

CG: Writing – original draft, Writing – review & editing, Conceptualization, Project administration, Visualization. SP: Writing – original draft, Conceptualization, Supervision, Visualization.

## Conflict of interest

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

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# Impact of a Mediterranean diet, physical activity, body composition, and insulin delivery methods on metabolic control in children with type 1 diabetes

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**Aims:** To evaluate the synergistic impact of diet, lifestyle and technology on glycemic control in children with type 1 diabetes (T1D).

**Methods:** This cross-sectional study included 112 randomly selected patients with T1D from Gran Canaria (median age 12 years; 51.8% female). The study collected data on height, weight, body composition (bioimpedance), age, disease duration, and method of insulin delivery. Physical activity was evaluated using the Krece questionnaire and an accelerometer (GENEActiv). Adherence to the Mediterranean diet was assessed using the KIDMED Quick Nutrition Test. Glycemic control was evaluated using HbA1c and the percentage of time in range. SPSS version 21 and RStudio were used for statistical analysis of the data. Stepwise linear regression analysis (backwards) was used to identify factors independently associated with metabolic control.

**Results:** Insulin pump use, age and adherence to the Mediterranean diet were found to be significantly and independently associated with better glycemic control, whereas years with T1D was associated with worse HbA1c values. No relationship was found between body composition and physical activity measured by accelerometry or questionnaire.

**Conclusion:** Adherence to the Mediterranean diet, insulin delivery methods, age, and number of years with T1D are important factors to consider in the management of T1D in children.

KEYWORDS

type 1 diabetes, children, HbA1c, nonpharmacological, diet, physical activity, body composition

# 1 Introduction

Since the introduction of insulin therapy in 1922 (1), the life of people with diabetes has greatly improved. After the results of the Diabetes Control and Complications Trial (DCCT) were published (2, 3), demonstrating the impact of intensive therapy on the development of vascular complications, more stringent metabolic control has become the standard of care for type 1 diabetes (T1D) patients. Recommended control targets have been decreasing over the years, with current advances such as continuous glucose monitoring and integrated insulin pumps helping to diminish the risk of hypoglycemia (4). International guidelines currently recommend an HbA1c level less than 7% or more than 70% of the time in range (interstitial glucose concentration between 70 and 180 mg/dL) as the goal of treatment for pediatric patients with T1D (4, 5), whereas national guidelines such as the National Institute for Health and Care Excellence (NICE) from the United Kingdom recommend even lower targets (6.5%) (6).

Alongside insulin therapy, nutrition and physical activity are important pillars of T1D management. These factors favor overall health in youth with T1D and are, therefore, routinely included in the guidelines of the American Diabetes Association (ADA) (4) and the International Society for Pediatric and Adolescent Medicine (ISPAD) (5). High rates of concurrent overweight and obesity are reported in youth with T1D, and some studies show up to 9% more body fat in these individuals than in children without T1D (7). Additionally, excessive body fat has been shown to increase the risk of cardiovascular disease in children and adults (8) and to have a negative impact on glycemic management (9).

It is increasingly recognized that strategies that emphasize activity and a healthy diet are needed, as studies have shown that children who are more active (10) and who adhere to the Mediterranean diet, which focuses on vegetables, fruits, whole grains, beans, nuts, and legumes with some lean proteins from fish and poultry and good fats from sources such as extra virgin olive oil (11), present better metabolic control.

Given the high incidence of T1D in the Canary Islands (12, 13), we wanted to evaluate the influence of nonpharmacological factors such as adherence to the Mediterranean diet, body composition, physical activity, and mode of insulin delivery on HbA1c in our patients with T1D.

# 2 Methods

## 2.1 Design and population

This was an observational, cross-sectional study. Inclusion criteria: patients under 16 years of age living in Gran Canaria diagnosed with T1D according to ADA criteria (4), disease duration of more than 1 year, who were being followed by the Pediatric Endocrinology Unit of the Insular-Materno Infantil University Hospital (CHUIMI). All patients (and their parents) consented to participate in the study. The exclusion criteria included other types of diabetes, a diagnosis of T1D in the 12 months prior to the beginning of the study and a lack of consent to participate in the study.

## 2.2 Data collection

Patients from our unit were randomized (a randomized list including 280 eligible patients who met the inclusion criteria was created) before being invited to participate in the study, and those who accepted the study were scheduled for an appointment at the Pediatric Endocrinology Unit of CHUIMI. Only the first 200 patients were called due to time restrictions in order to perform the study. One phone call was attempted for each patient. At the scheduled appointment, patients' height, weight, and body composition were measured and recorded. Patients were weighed and measured without shoes and with light clothing. Overweight was defined as a weight-for-height greater than 1 standard deviation above the median, and obesity was defined as a weight-for-height greater than 2 standard deviations above the median, as established in the World Health Organization (WHO) Child Growth Standards for Children >5 years of age (14). Body composition was measured using bioelectrical impedance analysis. A portable DC 360-S bioelectrical impedance analyzer (TANITA, Tokyo, Japan) was used to determine weight and estimate the percentages of fat and muscle for each child. Other recorded variables were age, disease duration, and method of insulin delivery.

## 2.3 Questionnaires

We used the Krece Plus short physical activity questionnaire to evaluate the amount of time dedicated to sedentary activities (score 1–5) and the amount of time dedicated to extracurricular physical activity (score 0–4) the patients or their parents thought they engaged in. The patients´ level of activity was classified as good, fair, or poor based on the resulting scores (0–3: bad; 4–6: fair; ≥ 7: good). We used the KIDMED Quick Nutrition Test to evaluate adherence to the Mediterranean diet. Both the Krece plus and KIDMED (15) questionnaires were obtained from the enKid study (16) and have been extensively used in Spain (11), Italy (17), Portugal (18), and other Mediterranean countries (19). The KIMED is a 16-item questionnaire that evaluates the adoption of healthy nutritional Mediterranean habits and scores +1 or −1 depending on the answers (possible results ranging from −4 to 12). Interpretation of the final scores determined the presence of low, medium or optimal adherence to the Mediterranean diet (≤ 3: low-quality diet; 4–7: needs to be improved to adjust to the Mediterranean model; ≥ 8: optimal Mediterranean diet). Both questionnaires were answered by the children, when

possible, with varying support from the parents depending on the children's age.

## 2.4 Accelerometry data

We used the GENEActiv accelerometer (Activinsights Ltd., Kimbolton, United Kingdom) to evaluate the actual physical activity performed by our patients. The participants were instructed to wear the accelerometer on their dominant wrist for 5 consecutive days and nights. The data were recorded with an activity sample frequency of 100 Hz. The data were segmented into several time intervals labeled as six different classes (sedentary, light, moderate and intense physical activity, sleep and nonwear) using RStudio [RStudio Team (2022). RStudio: Integrated Development Environment for R (version 2022.07.2 + 576) (computer software). Boston, MA: RStudio, PBC] software and the data processing codes provided by the manufacturer. In this study, only data relating to moderate or intense physical activity were considered.

## 2.5 Metabolic control, insulin treatment, and technology adoption

The data on HbA1c levels, time in range (70–180 mg/dL; TIR), time above target, time below target, and coefficient of variation were extracted from the participants' medical records. The average value from the last two visits was used. Good metabolic control was defined as an HbA1c level less than 7% (53 mmol/mol) or a percentage of time in the glucose range of 70–180 mg/dL above 70%. For all our patients receiving multiple doses of insulin (MDI), either a Dexcom G6 real-time continuous glucose monitor (CGM) or a Freestyle Libre 2 intermittently scanned CGM was used. Continuous subcutaneous insulin infusion (CSII) was performed via the hybrid closed loop system Medtronic 780G paired with Guardian 4 CGM and Smart Guard Technology or Tandem (t:slim X2) paired with Dexcom G6 CGM and Control-IQ Technology (all patients on CSII used hybrid closed loop systems).

## 2.6 Statistical analysis

SPSS version 21 (IBM SPSS Statistics for Windows, Armonk, NY, United States) and RStudio [RStudio Team (2022) were used. RStudio: Integrated Development Environment for R (version 2022.07.2 + 576; computer software). Boston, MA: RStudio, PBC] were used for statistical analysis of the data. For descriptive statistics, the mean and standard deviation were determined for normally distributed quantitative variables, while the median and interquartile range were calculated for nonnormally distributed variables. The Kolmogorov–Smirnov test was used to verify the normality of the distribution. Qualitative variables are described as frequencies. The hypothesis test was used to compare proportions and verify the difference between proportions, and Student's *t* test was used to analyze the differences between the means of two samples. The Mann–Whitney U test was used for nonparametric variables. Correlation analysis was performed to assess the relationships between the KIDMED questionnaire score and HbA1c and TIR scores, between the enKid questionnaire score and the accelerometry score and between BMI and body fat percentage. Stepwise linear regression analysis (backwards) was used to identify factors independently associated with metabolic control (both HbA1c and TIR). A stepwise linear regression analysis was also used to evaluate which items included in the KIDMED questionnaire had an impact on HbA1c. $p < 0.05$ was considered to indicate statistical significance.

# 3 Results

A total of 200 randomly selected T1D patients were initially contacted to participate in the study, and a total of 112 agreed to participate (56%). Accelerometry data were successfully recorded and processed for only 94 children. The recruitment process is summarized in Figure 1.

Table 1 describes the characteristics of the participants included in the study. There was a slight majority of MDI users compared to CSII users. The data showed significantly better HbA1c levels in patients treated with insulin pumps than in those receiving MDI [6.6% (49 mmol/mol) vs. 7.1% (54 mmol/mol); *p* value = 0.008].

In the study population, 76.7% of our patients had a normal weight, whereas 13.4 and 9.5% were overweight and obese, respectively (Figure 2).

To compare the results with those from Dominguez et al. (11), we performed a correlation analysis between HbA1c and the KIDMED score and obtained a negative correlation ($R = -0.23$; $p = 0.016$). A positive correlation was obtained between the TIR and KIDMED scores ($R = 0.23$; $p = 0.014$).

Correlation analysis revealed a moderate correlation between the enKid score and the average daily moderate-intense activity hours measured by accelerometry [$R = 0.38$; $p = 0.000$ ($N = 91$)]. Additionally, BMI and body fat percentage were strongly correlated [$R = 0.7$;

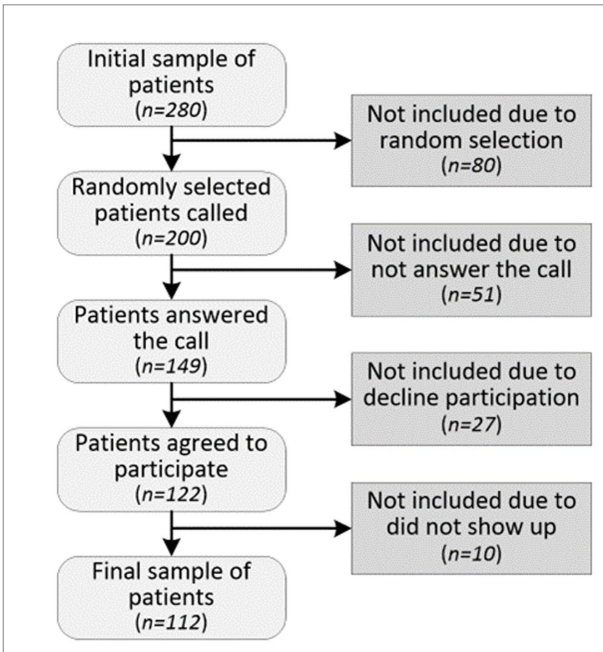


FIGURE 1
Recruitment process.

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TABLE 1 Characteristics of the participants included in the study.

| | *N*/% | Descriptive variables |
|---|---|---|
| Sex (% Female) | 58/51.8 | |
| Insulin delivery systems (%hybrid closed loop) | 49/45 | |
| Average HbA1c [mean (CSII/MDI)] | 111 | 6.93 (0.9) (6.6/7.1) |
| HbA1c < 7% (53 mmol/mol) (%) | 67 | 60 |
| HbA1c ≥ 7% & < 7.5% (≥ 53 & <58 mmol/mol) (%) | 18 | 16.2 |
| HbA1c > 7.5% (≥ 58 mmol/mol) (%) | 26 | 23.4 |
| Age (years. Median) | 112 | 12 (5) |
| Time from onset (years. Median) | 112 | 4 (4) |
| BMI (kg/m$^2$/Zscore. Median) | 112 | 19.7 (5.3)/ 0.19 (1.3) |
| Body fat percentage (mean) | 111 | 22.65 (8.8) |
| Average daily screen time in hours (median) | 111 | 2 (2) |
| Average enKid score (median) | 112 | 5 (2) |
| Average KIDMED score (median) | 112 | 8 (2) |
| Time in range (median) | 110 | 73.5 (27.5) |
| Time in hypoglycemia (median) | 108 | 3.3 (3.6) |
| Time in hyperglycemia (median) | 103 | 25.25 (28.4) |
| Variation coefficient (median) | 106 | 35.09 (6.8) |
| Average daily sleep hours (median) | 92 | 6.45 (1.3) |
| Average daily moderate-intense activity hours (median) | 91 | 3.3 (1.6) |

Descriptive variables: mean (SD) or median (interquartile range); BMI, Body mass index.

$p = 0.000$ ($n = 111$)]. Table 2 summarizes the results of the correlation analyses.

Backward stepwise linear regression analysis revealed that the variables significantly associated with HbA1c were the average score on the KIDMED questionnaire, insulin delivery method, years with T1D and age (Table 3, Model 1; other variables included in the analysis were BMI, body fat percentage, enKid score, sex, daily moderate-intense activity hours, and daily sleep hours). The model predicted 20% of the change in HbA1c. Body composition and activity measured by accelerometry or questionnaires were not significantly associated with HbA1c according to multivariate analyses.

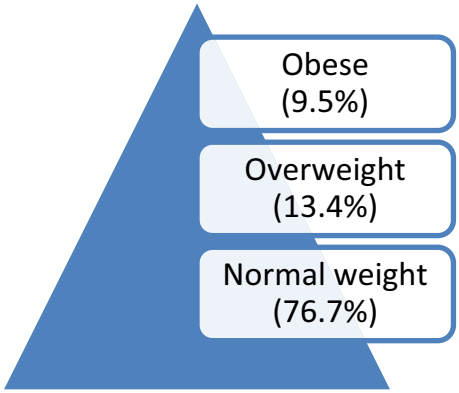


FIGURE 2
Weight distribution among patients with T1D.

Additionally, stepwise linear regression analysis showed that when analyzed independently, the only item included in the KIDMED questionnaire associated with HbA1c was not having eaten breakfast (beta = 0.32; $p = 0.001$).

A similar analysis was performed to determine the factors influencing the percentage of patients with a glucose concentration ranging from 70 to 180 mg/dL according to the sensor data. Insulin delivery method and diabetes duration were the only significantly associated variables, and the resulting model explained 27% of the variability in time in range ($p = 0.007$; Table 3, Model 2).

## 4 Discussion

This report evaluated the associations of body composition and nonpharmacological interventions (physical activity, insulin delivery methods, and adherence to a Mediterranean diet) with metabolic control. We showed a favorable association between self-reported nutritional habits, age, and the use of insulin pumps as well as a negative impact of the number of years with T1D on HbA1c levels.

The population studied included 45% of hybrid closed-loop pump users. With an average HbA1c of 6.9% (52 mmol/mol), our values are lower than those reported in Spanish (20) (7.3%) and international registries such as German-Austrian (DPV) and the American T1D exchange (21) [7.8% (62 mmol/mol) and 8.5% (69 mmol/mol), respectively]. The higher CSII adoption (45 vs. 25%) and the use of hybrid closed loop infusion systems in all of our CSII patients might help explain our lower values compared with those published in 2017 by Rica et al. (20). Compared to international registries, our CSII adoption rate was lower than that published by the DPV (89%) and the T1D exchange (65%). However, the fact that most of their patients did not use integrated systems at the time of the study might account for part of the difference (22, 23).

The KIDMED questionnaire has been used previously to assess adherence to the Mediterranean diet in pediatric T1D patients (11, 17). In our population, the median KIDMED score was 8, with 59% of our patients following an "optimal Mediterranean diet" (score ≥ 8). These results are very similar to those reported by Dominguez et al. (11) and Rebollo et al. (24) for a pediatric population living in southern Spain, both regarding the quality of the diet and the

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TABLE 2 Summary of correlation analyses.

| Items analyzed | *R* | *p* value |
|---|---|---|
| HbA1c/KIDMED score | −0.23 | 0.016 |
| TIR/KIDMED score | 0.23 | 0.014 |
| enKID/Accelerometry | 0.38 | 0.00 |
| BMI/Body fat % | 0.7 | 0.00 |

TABLE 3 Models reflecting stepwise linear regression influencing metabolic control.

| Model 1 | Beta | *p* value | *R* | $R^2$ | *p* value |
|---|---|---|---|---|---|
| (Constant) | | 0.000 | 0.453 | 0.205 | 0.036 |
| Insulin delivery method | 0.270 | 0.008 | | | |
| Years with T1D | 0.295 | 0.006 | | | |
| Age (years) | −0.291 | 0.009 | | | |
| Total KIDMED | −0.216 | 0.036 | | | |
| **Model 2** | | | | | |
| (Constant) | | 0.000 | 0.525 | 0.276 | 0.007 |
| Insulin delivery method | −0.465 | 0.000 | | | |
| Years with T1D | −0.253 | 0.007 | | | |

Model 1: Step wise linear regression showing factors influencing HbA1c levels. Model 2: Step wise linear regression showing factors influencing time in range. The insulin delivery method used was multiple insulin injections. T1D, Type 1 diabetes.

correlation of the latter with HbA1c and time in the glucose target range. Antoniotti et al. reported a similar study of a pediatric population in northern Italy (17). They reported a lower KIDMED score (median of 6, with only 29% of patients presenting a score ≥ 8) and did not find a significant correlation between the KIDMED score and metabolic control, only with the consumption of sweets and fish. In our case, the only independently associated component of the KIDMED questionnaire was "not having breakfast." The difference in nutritional habits between the two populations might explain the difference in results. Levran et al. (25) recently reported an intervention targeting the quality of the diet in adolescents diagnosed with T1D in Israel in an attempt to improve the intake of these patients to better simulate the Mediterranean diet. They reported a significant improvement in metabolic control (TIR), as well as in other nutritional indicators, 6 months after the initiation of the intervention (25).

Regarding self-reported physical activity, the median enKid score was 5 in our sample, with only 35% of patients presenting an optimal score ≥ 7. On the other hand, the median number of hours of daily moderate-intense physical activity measured by accelerometry was 3.3 h (above the recommended 60 min/day). This difference is not surprising since the correlation between the enKid questionnaire score and activity measured with accelerometry was low, in agreement with the findings of other authors (26). A possible explanation could be that they probably measure different aspects of physical activity, and some authors recommend the complementary use of both strategies (27). With respect to the number of hours of data collected via accelerometry, we were surprised to find that, in our study, there were no significant associations between physical activity (measured by either accelerometry or the enKid questionnaire) and HbA1c. Nevertheless, our study is not the only one to do so. Shorey et al. (28) performed a meta-analysis to evaluate the impact of physical activity on metabolic control and reported a lack of effect on HbA1c. Watson et al. (29) reported a paradoxical relationship between physical activity and HbA1c, with increased physical activity relating to higher HbA1c values. The lack of significance in our study could be due to the small sample size, which was not large enough to detect a significant association. Additionally, there might have been confounding variables that were not considered. Third, the study may have been limited by the use of questionnaires and accelerometers, which can be subject to bias and inaccuracies. Additionally, simply, the relationship might not exist. On the other hand, other authors have reported a potential protective effect of exercise on β-cell health (30), as well as decreased HbA1c values in active children (10, 31) and adults (32) with T1D, with lower glucose values on active days, and through all type of structured exercises (aerobic, interval or resistance training). Apart from its debatable impact on metabolic control, exercise is highly recommended due to its positive effects on cardiovascular and overall health (33).

The effects of age and years with T1D on metabolic control have been widely studied. HbA1c values typically increase as puberty approaches and remain high until the beginning of the second decade for most patients with T1D (34, 35). Our results were slightly puzzling in the sense that the number of years with T1D was associated with higher HbA1c values, but age was inversely correlated with metabolic control. This difference was not explained by CSII use since further analysis revealed greater pump use in younger children. We think that the positive effect of age, along with the negative effect of the number of years with T1D, might be explained by selection bias, with older children with recent-onset T1D having greater participation.

A similar effect for time in range was found for the number of years after T1D and insulin delivery method. No relationship was found with age, hours of sleep, physical activity, or adherence to the Mediterranean diet.

Some of the strengths of our study are the randomization of patient selection (although self-selection cannot be ruled out), the number of patients studied and the simultaneous use of accelerometry and questionnaires to evaluate physical activity.

Some of the limitations of our study include the following: cross-sectional, retrospective study; possible self-selection, possibly with higher adherence to treatment and recommendations; and more hybrid closed-loop system users than our general population with T1D (45 vs. 35% of our total T1D pediatric population). Additionally, although the studied sample constitutes more than one-third of our total T1D population, the number of subjects might limit our ability to reflect all factors influencing metabolic control in our population.

In summary, our study evaluated the impact of body composition and nonpharmacological treatments on the metabolic control of our T1D population and revealed the significant effects of insulin delivery modality, adherence to the Mediterranean diet, age and years with T1D on HbA1c values. Body composition and physical activity, as measured by accelerometry or questionnaires (enKid), were not associated with HbA1c values. Our results highlight the need for

strategies to improve metabolic control in pediatric patients approaching puberty. These findings contribute to our understanding of the factors influencing glycemic control in pediatric patients. However, further research including a larger number of subjects in our study and other populations is needed to validate and expand upon these findings.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the YN-M, yeraynm@hotmail.com.

## Ethics statement

The studies involving humans were approved by Ethics Committee of Las Palmas University Hospital Dr. Negrín. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

## Author contributions

YN-M: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. AP-L: Investigation, Resources, Writing – review & editing. NS-R: Investigation, Resources, Writing – review & editing. MB-B: Investigation, Resources, Writing – review & editing. HF: Data curation, Formal analysis, Investigation, Resources, Software, Writing – review & editing. SL-L: Data curation, Writing – review & editing. SQ: Data curation, Writing – review & editing. AD: Data curation, Writing – review & editing. ML: Data curation, Writing – review & editing. MG: Data curation, Writing – review & editing. EC: Data curation, Writing – review & editing. AW: Conceptualization, Data curation, Formal analysis, Investigation, 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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# Energy imbalance gap was associated with body mass index and sex in Latin American adolescents—results from the ELANS study

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**Introduction:** Energy imbalance gap (EIG) is defined as the average daily difference between energy intake (EI) and energy expenditure (EE). This study aimed to examine the associations between EIG and sociodemographic and anthropometric variables in the adolescent population of eight Latin America countries.

**Methods:** A total of 680 adolescents aged 15 to 18 were included in this study. The estimation of EI was based on two non-consecutive 24-h dietary recalls. EE was predicted from Schofield equations using physical activity level obtained through the long version of the International Physical Activity Questionnaire. Sociodemographic data and anthropometric measurements were also obtained. A descriptive analysis and multilevel linear regression models were used to examine associations between variables.

**Results:** The mean EI, EE, and EIG were 2091.3 kcal, 2067.8 kcal, and 23.5 kcal, respectively. Argentina had the highest EI and EIG, whereas Chile had the lowest EI and EIG. Males had a higher EI (2262.4 kcal) and EE (2172.2 kcal) than females (1930.1 kcal and 2084.5 kcal), respectively ($p < 0.05$). Overweight subjects had a

lower EIG than did underweight and normal-weight subjects ($p < 0.05$). Subjects with low socioeconomic status (SES) had a lower EE (2047.0 kcal) than those with a high SES (2164.2 kcal) ($p < 0.05$).

**Conclusion:** Sex and BMI were associated with EIG in adolescents from Latin America.

KEYWORDS

energy balance, energy expenditure, energy intake, energy imbalance gap, underweight, overweight, Latin America

## 1 Introduction

Latin America (LA) is a region with several and complex health concern and the double burden of malnutrition is an important one. Globally, there has been an interest in adolescents as a group that is relevant for the future health of the population; thus, the World Health Organization (WHO) has included it among its prioritizing groups (1). A previous global report (2) established that overweight adolescents are increasing in LA, with a prevalence between 15 and 25% in most countries of the region. In contrast, the prevalence of moderate and severe underweight was below 10% for both girls and boys in all LA countries (2). On the other hand, a recent report (3) indicated that in both the LA and the Caribbean, approximately two-thirds of teenagers have insufficient physical activity. More than 40% of the participants were sedentary and more than 20% were completely inactive. These results were more frequent among girls than among boys. These constitute low energy expenditure (EE) indicators in adolescents in the region.

For around a hundred years, it has been thought that weight management is the result of small, persistent differences in energy intake (EI) and EE. The energy imbalance gap (EIG) is defined as the average daily difference between EI and EE (4). Therefore, a positive energy imbalance gap arises when EI is greater than EE, whereas a negative energy imbalance gap occurs when EE exceeds EI (5) by applying the First Law of Thermodynamics (energy conservation principle) (6). This approach is simple and easy to remember by the general population; therefore, it is commonly used for educational purposes in public health, especially in dietary guidelines (7, 8), and it represents a driver for the changes observed in BMI of overweight and obese individuals, and allow to follow epidemiologic trends within a given population (9).

Nevertheless, at the individual level, the energy balance model states that the brain serves as the primary organ responsible for regulating body weight through the integration of neuroendocrine-gastrointestinal signaling pathways that either increase or decrease overall EI (10). The current better understanding of the neuro-endocrine axis where environmental signals are to be integrated and translated into neuro-hormonal signals in the short term that regulate food intake via the hypothalamus, basal ganglia, through the release of ghrelin, peptide YY and GLP-1 and controls the appetite and satiety cycles (10), as demanded by external environmental stimulus including rewards cycle, have allowed to introduce the knowledge to accept the complexity of food intake and its impairments and consequences in the long term including leptin alterations that will run the changes over time, thus impacting the energy balance of an individual.

Additionally, environmental, economic, and social trends, which are external drivers and because of the behavior toward foods, excessive or inadequate intake, significantly impact EIG (11) and therefore translate into all these neuro-endocrine events, making the environmental factors important elements in the regulation of the food intake (10).

Owing to this complex system, an individual's energy balance can vary daily. Therefore, accurate measures of energy balance in humans are controversial. More precise methods are costly and challenging to perform in public health and epidemiological studies. Nevertheless, knowing the trends within a population is key to monitoring well-being and contributing to the prevention of chronic diseases (12).

The disparity between EI and EE, represents a significant global health challenge. Studies show that exceeding energy needs even by a small amount over time can significantly increase the risk of developing chronic diseases, including obesity, cardiovascular disease, type 2 diabetes, and certain cancers (13, 14). On the other hand, when there is an insufficient intake of energy compared to energy expenditure, it can lead to malnutrition and deficiencies in essential nutrients (15). This could weaken the immune system, impair growth and development, and increase the risk of infections and other health problems (16). Furthermore, energy imbalance can also impact mental health and well-being. Poor diet and lack of physical activity could contribute to feelings of fatigue, low mood, and decreased cognitive function (15). These factors can further exacerbate the risk of developing mental health disorders such as depression, anxiety and eating disorders, especially in adolescents (17).

To date, only a limited number of studies have examined EIG in a large population (4, 5, 9, 18), finding heterogeneity in EIG by ethnicity, sex, and body mass index (BMI) in adults. Fallah-Fini et al. (4) quantified the dynamics of the EIG among New Zealand adults over 3 decades using a new population-level system dynamics model. They found that there was an inconsistent pattern over time, especially in different ethnic, sex, and BMI subpopulations, i.e., higher BMI was associated with both a higher and a lower EIG. In Japanese adult population (18), the trend of EIG was studied by near 4 decades. They found that EIG was associated to sex and weight groups in this population. The EIG for men ranged from −3.5 kcal/day for a BMI of $\geq$30.0 kg/m$^2$ to 4.6 kcal/day for a BMI of 15.0 to 17.9 kg/m$^2$. In a Belgium population, Fallah-Fini et al. (9) found that there was some heterogeneity in the patterns by BMI class, and no consistent patterns emerged over time. These studies, while valuable, do not include data

from the Latin American population. Additionally, they are longitudinal rather than cross-sectional studies, which limits their applicability for direct comparison of results. On the other hand, the authors' previous experience with adults in LA (5), found that overall EIG was positive, meaning people consumed more energy than they were expended. This was more pronounced in men and people with higher socioeconomic status. People who were overweight or obese in Argentina, Costa Rica, Ecuador, Peru, and Venezuela had a significantly lower EIG than those who were underweight. These findings suggest high variability in the EIG and its correlates in the eight LA countries. For the age group of adolescents, much uncertainty still exists about the relationship between EIG and socioeconomic status, anthropometrics, and lifestyle.

This context highlights the relevance of studying the characteristics associated with maintaining a good balance between EI and EE in adolescents as a key component of overall regional prevention policies. Being overweight in adolescents can cause various health and emotional problems including hypertension, dyslipidemia, type 2 diabetes, metabolic syndrome, obstructive sleep apnea, eating disorders, and depression (19, 20). However, undernutrition can also increase the risk of other chronic health problems such as insulin resistance, lowered fat oxidation, increased risk of diabetes in adulthood, reduced energy expenditure, dyslipidemia, hypertension, and diminished manual worker capacity (21).

This study aimed to examine the associations between the EIG and sociodemographic and anthropometric variables in the adolescent population of the eight LA countries evaluated.

# 2 Materials and methods

## 2.1 Research design and participants

The Latin American Study of Nutrition and Health (Estudio Lationamericano de Nutrición y Salud; ELANS) is a multicenter cross-sectional nutritional and health surveillance study of a nationally representative sample of urban populations from eight Latin American countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Peru, and Venezuela). This study addressed EI, EE, and anthropometric data in 10,134 individuals ranging in age from 15 to 65 years, in a lapse between September 2014 and July 2015.

A multistage sampling process was used to select the sample, stratified by geographical location, sex, age, and socioeconomic status (SES), with a random selection of primary and secondary sampling units for the urban population in order to achieve an urban representative sample (22).

In this study, adolescents were considered to be between 15 and 18 years of age. This was because the minimum interview age for the ELANS study was 15 years and, for this study, after 18 years of age, the subjects were considered adults, and informed consent was no longer requested from parents. Healthy adolescents from the urban areas of each country were selected as participants. Excluded from the study were adolescents without parental or legal guardian consent, pregnant or lactating women, individuals residing in non-household settings like hospitals, regiments, and nursing homes, individuals with significant physical or mental impairments, such as musculoskeletal diseases, recent surgeries, severe asthma, dementia, major depression, and those unable to read. These subjects were excluded because their daily intake may be limited by the disability or the care of responsible persons, physical limitations may make body measurements difficult, and illiterates may have difficulty understanding survey instructions and forms, which could lead to errors in the data.

Of the partial sample of 9,680 participants, 462 were excluded because of inconsistencies, including duplicate observations or observations that did not pass the supervisor's quality check. Of the 9,218 subjects, only 937 were adolescents (15–18 years), and another 257 were excluded due to incomplete data. The final sample comprised 680 adolescents (Figure 1).

Additional details of the study design and protocol have been described elsewhere (22, 23). All parents or patient representatives signed informed consent forms. The Western Institutional Review Board (#20140605) approved the study protocol and was registered on the Clinical Trials website (#NCT02226627).

## 2.2 Socioeconomic and anthropometric variables

A sociodemographic questionnaire was developed to evaluate the sociodemographic characteristics of adolescents, such as country, sex, age, SES, educational level, and ethnicity. Household SES was measured using appropriate scales for each country and was classified as high, middle, or low. For educational level, the categories were basic, high school, and undergraduate. Ethnicity was obtained based on self-reported race or ethnicity and divided into five groups: Caucasian, Mestizo, Afro-American, Indigenous and Others.

After administering the questionnaire, adolescents' body weight and height were measured and recorded following the standard method, wearing light clothing and no shoes. The weight (kg) of the participants was determined using an electronic scale (Seca®, Hamburg, Germany) with a measurement precision of 0.1 kg. Height (cm) was measured using a portable stadiometer (Seca®, Hamburg, Germany) with an accuracy of 0.1 cm. Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the height in meters squared. The BMI for age and height for age were assessed based on the reference values provided by the WHO (24) as body mass index z-score (zBMI) and height-for-age z-score (HAZ), which was designed as a universal norm and takes into consideration the widely differing ethnic backgrounds and cultural settings (25). These indicators were classified as underweight (zBMI $<-2$), normal weight (zBMI $\geq -2$ to $\leq +1$), or overweight (zBMI $> +1$). Owing to the low frequency of obesity (zBMI $> +2$), it was grouped together in one category with "overweight." On the other hand, height was classified as low height (HAZ $< -2$), risk of low height (HAZ $\geq -2$ to $< -1$), and normal height (HAZ $\geq -1$). In this work, a classification for the risk of low height was also carried out, due to the current trend toward diagnosing not only established stunting, but also the risks of developing this nutritional privation, in accordance with local guidelines and references (26, 27), and the relevance of taking the window of opportunity for interventions in adolescents at risk.

## 2.3 Energy intake

A dietary assessment that involved two non-consecutive 24-h food recalls was used to estimate the EI. The Multiple Pass Method

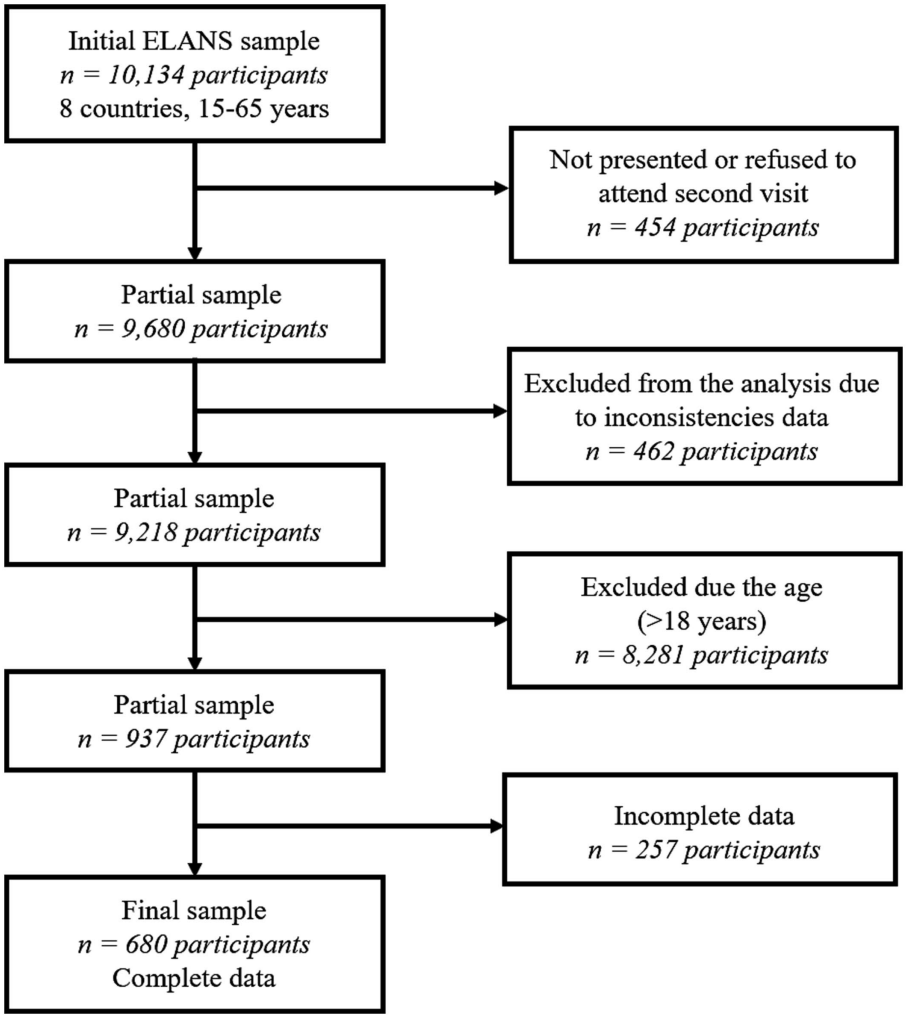


FIGURE 1
Selection process flowchart of adolescent participants.

was used to evaluate all foods and beverages consumed during the previous day (28). To estimate the portion sizes, photographic albums of common foods from each country and household utensils were used. The selected portions were transformed into grams or milliliters by a group of trained nutritionists.

In another step, macronutrients consumption was transformed into EI using the software Nutrition Data System for Research (NDS-R, Minnesota University, MN, United States). Version 2013. The Multiple Source Method (MSM), a web-based statistical modeling technique proposed by the European Prospective Investigation into Cancer and Nutrition (EPIC) (29), was employed to determine the typical daily EI, taking into account individual variations.

## 2.4 Energy expenditure

The EE was determined by multiplying the Basal Metabolic Rate (BMR) with Physical Activity (PA) utilizing the following formula:

$$EE = BMR \times PA$$

To estimate the BMR, the equations of the FAO/WHO report "Human Energy Requirements" (30) and the activity factors for physical activity (PA) published by Gerrior et al. (31) were used, which comprised variables such as sex, age, and weight.

PA was assessed using the International Physical Activity Questionnaire (IPAQ) in its extended Spanish version, which was validated for LA (32). The active transportation and leisure-time physical activity domains were incorporated into the study because of their higher significance in informing public health policies and programs (32) and the limited reliability of the IPAQ questions related to occupational and home-based physical activity among adolescents in LA countries.

Therefore, the data collected from the questionnaire regarding physical activity (PA) were expressed as the amount of time spent walking, moderate activity, and vigorous activity per day. The Compendium of Physical Activities was used to determine the metabolic equivalents (METs) for each physical activity, which were expressed as minutes/day and minutes/week (MET-min/day and MET-min/week, respectively) (33). Finally, the IPAQ protocol was used to classify participants into three categories: high, moderate, or low physical activity levels. The IPAQ has been validated through

objective methods, i.e., accelerometer (model GT1M) to evaluate PA in adolescents from different countries, with correlations ranging from 0.20 to 0.29 (34).

## 2.5 Energy imbalance gap

The EIG was defined as the average daily difference between EI and EE, using the formula:

$$EIG = EI - EE$$

Thus, if a negative number is obtained, it is because the EE exceeds the EI, whereas if the EI is above the EE, a positive number is obtained (5, 18).

## 2.6 Statistical analysis

The Kolmogorov–Smirnov test was used to confirm whether the data adhered to a normal distribution. The means, 95% confidence intervals (95% CI), specific percentiles (3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles), and percentages were calculated as required to describe the variables. The weighting process was carried out based on sociodemographic characteristics such as sex, SES, and country.

Multilevel linear regression models (with b coefficients and 95% confidence intervals) were employed to investigate the associations between sociodemographic characteristics (acting as independent variables) and EI, EE, and EIG (functioning as dependent variables) in each country and collectively. These models satisfied the assumptions of linearity, independence, homoscedasticity, and normality and included regions and cities as random effects. Furthermore, they were adjusted for sex, SES, education level, ethnicity, and BMI and provided unstandardized beta coefficients and 95% confidence intervals. A significance level of 5% was considered to be statistically significant.

All statistical analyses were conducted using IBM SPSS software version 26 (IBM Corp., Armonk, New York, United States).

# 3 Results

The total sample comprised 680 adolescents (mean age 16.5 ± 1.2 years). The features of the participants are listed in Table 1, which provides a comprehensive overview of their characteristics. Overall, the proportion of males was higher than that of females, except in Venezuela. About half (53.1%) were classified as having a low SES, 82.8% had a basic or lower educational level, and 48.7% were of the Mestizo ethnicity. More than 80% of the adolescents had normal BMI and height for age. The prevalence of low height was higher than the prevalence of overweight in this group of adolescents (7.5% vs. 6.2%, respectively).

Overall, the mean EI was 2091.3 kcal/day, while the mean EE was 2067.8 kcal/day, resulting in a small positive EIG of 23.5 kcal/day. Chile had the lowest average for daily EI (mean 1884.6 kcal; 95% CI: 1777.9; 1991.3) among all countries, while Argentina had the highest average for daily EI (mean 2323.1 kcal; 95% CI: 2202.7; 2443.6). The difference between the two countries was 438.5 kcal. For EE, the highest values were in Costa Rica (mean: 2172.2 kcal; 95% CI: 2047.0; 2297.3) and the lowest was in Peru (mean: 1963.7 kcal; 95% CI: 1882.7; 2044.7). The mean difference between the two countries was 208.5 kcal. Regarding the EIG, the mean difference between Argentina (highest energy balance) and Chile (lowest energy balance) was 489.1 kcal (Table 2).

In terms of sex differences, males had higher EI and EE than females, resulting in a negative EIG (−35.1 kcal/day) for males and a positive EIG (102.2 kcal/day) for females.

Socioeconomic status did not show significant differences in EIG, although those in the low SES group had a slightly higher EIG than those in the middle or high SES groups. Education level also did not show significant differences in EIG, although those with an undergraduate degree had a slightly larger negative EIG (−122.1 kcal/day) than those with only basic or high school education.

Ethnicity showed some differences in EIG, with Indigenous individuals having the largest negative EIG (−156.9 kcal/day) and Afro-American individuals having a small positive EIG (69.7 kcal/day). Finally, BMI by age showed significant differences in EIG, with underweight individuals having the largest positive EIG (346.2 kcal/day) and overweight individuals having the largest negative EIG (−353.1 kcal/day).

Among the EI percentiles (Figure 2A), Argentina consumed the most energy and Chile had the lowest caloric intake (2262.4 kcal and 1930.1 kcal). By sex, all percentiles for males were higher than those for females. In addition, subjects with high SES, underweight subjects, and people with normal height consumed more energy at the 50th percentile (see Supplementary Table S1).

EE (Figure 2B), in Chile was the highest, and Peru was the one with the lowest expenditure (2084.5 kcal and 1848.5 kcal, respectively). In addition, in all countries, males spent more energy than females, as did individuals with high SES, overweight, and normal height (Supplementary Table S2).

In Figure 2C, Ecuador had the highest positive EIG at the 50th percentile, while Chile had the highest negative EIG, with values of 144.9 kcal and − 291.5 kcal, respectively. By sex, males had a negative energy balance at the percentile 50th, and females had a positive balance (−33.4 kcal and 94.0 kcal, respectively). In addition, subjects with high SES had a negative energy balance compared to the rest of the group, as did the overweight subjects. In contrast, in terms of height for age, all categories had a positive EIG at the 50th percentile (Supplementary Table S3).

The associations between the correlates and the total EI, EE, and EIG are presented in Table 3. As expected, the results showed that males consume more energy than females and had a higher EE (433.0 kcal and 581.0 kcal, respectively; $p < 0.05$), therefore they had a negative energy balance in relation to the female sex (−148.1 kcal; $p < 0.05$). In the SES, the subjects with high SES spent more energy than those within low SES (110.1 kcal; $p < 0.05$). Regarding the BMI for age, it was observed that underweight adolescents and normal-weight subjects spent less energy than overweight subjects ($p < 0.05$), so these two groups had a positive energy balance (+979.6 kcal and + 394.1 kcal, respectively). Finally, in terms of height for age, the risk of low-and low-height subjects consumed and spent less energy than normal height subjects, but they had a positive energy balance; however, these results were not significant ($p > 0.05$).

TABLE 1 Distribution of adolescents according to sociodemographic variables by country.

| Variables n (%) | Argentina | Brazil | Chile | Colombia | Costa Rica | Ecuador | Peru | Venezuela | Overall |
|---|---|---|---|---|---|---|---|---|---|
| | 87 (12.8) | 123 (18.1) | 64 (9.4) | 73 (10.7) | 69 (10.2) | 73 (10.7) | 97 (14.3) | 94 (13.8) | 680 (100.0) |
| Sex | | | | | | | | | |
| Male | 57 (65.5) | 76 (61.8) | 35 (54.7) | 43 (58.9) | 42 (60.9) | 41 (56.2) | 51 (52.6) | 45 (47.9) | 390 (57.4) |
| Female | 30 (34.5) | 47 (38.2) | 29 (45.3) | 30 (41.1) | 27 (39.1) | 32 (43.8) | 46 (47.4) | 49 (52.1) | 290 (42.6) |
| Socio-economic status | | | | | | | | | |
| Low | 55 (63.2) | 48 (39.0) | 25 (39.1) | 49 (67.1) | 23 (33.3) | 34 (46.6) | 50 (51.5) | 77 (81.9) | 361 (53.1) |
| Middle | 29 (33.3) | 64 (52.0) | 32 (50.0) | 19 (26.0) | 38 (55.1) | 32 (43.8) | 31 (32.0) | 13 (13.8) | 258 (37.9) |
| High | 3 (3.4) | 11 (8.9) | 7 (10.9) | 5 (6.8) | 8 (11.6) | 7 (9.6) | 16 (16.5) | 4 (4.3) | 61 (9.0) |
| Educational level | | | | | | | | | |
| Basic | 83 (95.4) | 99 (80.5) | 60 (93.8) | 56 (76.7) | 65 (94.2) | 71 (97.3) | 52 (53.6) | 77 (81.9) | 563 (82.8) |
| High school | 3 (3.4) | 24 (19.5) | 3 (4.7) | 15 (20.5) | 4 (5.8) | 2 (2.7) | 44 (45.4) | 3 (3.2) | 98 (14.4) |
| Undergraduate | 1 (1.1) | 0 (0.0) | 1 (1.6) | 2 (2.7) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 14 (14.9) | 19 (2.8) |
| Ethnicity | | | | | | | | | |
| Caucasian | 59 (67.8) | 49 (39.8) | 24 (37.5) | 25 (34.2) | 36 (52.2) | 4 (5.5) | 7 (7.2) | 30 (31.9) | 234 (34.4) |
| Mestizo | 16 (18.4) | 22 (17.9) | 31 (48.4) | 38 (52.1) | 19 (27.5) | 65 (89.0) | 85 (87.6) | 55 (58.5) | 331 (48.7) |
| Afro-American | 1 (1.1) | 23 (18.7) | 0 (0.0) | 2 (2.7) | 0 (0.0) | 3 (4.1) | 1 (1.0) | 2 (2.1) | 32 (4.7) |
| Indigenous | 0 (0.0) | 4 (3.3) | 2 (3.1) | 2 (2.7) | 1 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9 (1.3) |
| Others | 11 (12.6) | 25 (20.3) | 7 (10.9) | 6 (8.2) | 13 (18.8) | 1 (1.4) | 4 (4.1) | 7 (7.4) | 74 (10.9) |
| Body mass index for age | | | | | | | | | |
| Underweight | 2 (2.3) | 5 (4.1) | 0 (0.0) | 1 (1.4) | 0 (0.0) | 2 (2.7) | 1 (1.0) | 1 (1.1) | 12 (1.8) |
| Normal weight | 80 (92.0) | 111 (90.2) | 59 (92.2) | 68 (93.2) | 62 (89.9) | 69 (94.5) | 89 (91.8) | 88 (93.6) | 626 (92.1) |
| Overweight | 5 (5.7) | 7 (5.7) | 5 (7.8) | 4 (5.5) | 7 (10.1) | 2 (2.7) | 7 (7.2) | 5 (5.3) | 42 (6.2) |
| Height for age | | | | | | | | | |
| Low | 5 (5.7) | 6 (4.9) | 0 (0.0) | 9 (12.3) | 3 (4.3) | 7 (9.6) | 13 (13.4) | 8 (8.5) | 51 (7.5) |
| Risk of low height | 5 (5.7) | 9 (7.3) | 8 (12.5) | 6 (8.2) | 11 (15.9) | 7 (9.6) | 15 (15.5) | 7 (7.4) | 68 (10.0) |
| Normal | 77 (88.5) | 108 (87.8) | 56 (87.5) | 58 (79.5) | 55 (79.7) | 59 (80.8) | 69 (71.1) | 79 (84.0) | 561 (82.5) |

Figure 3 shows a Scatter-dot plot of the energy imbalance gap as a function of body mass index in the study participants. The results showed a significant negative correlation between BMI and EIG ($r = -0.40$, $p < 0.001$), indicating that as BMI increased, EIG decreased. This suggests that individuals with normal BMI or overweight tend to have a smaller energy imbalance gap, potentially contributing to weight gain or maintenance. Furthermore, the analysis revealed a greater dispersion of EIG in men compared to women.

## 4 Discussion

This study examined first the gaps between EI and EE, and second, the associations between EIG and sociodemographic and nutritional status variables in the urban adolescent population of ELANS countries. The results showed that there was a positive energy balance in general, with EI values (2091 kcal) being higher than EE values (2068 kcal).

Growth and development have a significant impact on the energy requirements during adolescence. Adolescents typically need extra calories to fuel metabolic and physical activities, as well as to increase the amount of important body tissues such as bone, muscle, blood, and body organs (35). A positive energy balance is necessary for growth; however, it is also important for adolescents to maintain a healthy energy balance and avoid weight gain. A negative energy balance can prevent adolescents from growing properly, which is a public health concern (36).

The WHO (37) has strengthened its approach toward adolescence as a period in which rapid changes are manifested, and risks for diseases need to be addressed. According to the same source, adolescents between 10 and 14 years old are more at risk of experiencing diseases as a result of lack of sanitation; however, the risks associated with those between 15 and 19 years old are related to behaviors including diet, PA, substance misuse, and unsafe sex.

The positive EIG in most ELANS countries suggests that adolescents consume more energy than they expend, which could lead to weight gain over time. This is especially concerning in Argentina, Colombia, and Peru, where the EIG is higher than 100 calories. Previous studies have found that these three countries also have a positive energy balance in their adult populations (5). Additionally, a

TABLE 2 Energy imbalance gap and its components according to sociodemographic characteristics.

| Variables | n (%) | Mean (95% CI) of EI (kcal/day) | Mean (95% CI) of EE (kcal/day) | Mean (95% CI) of EIG (kcal/day) |
|---|---|---|---|---|
| Overall | 680 (100.0) | 2091.3 (2054.0;2128.6) | 2067.8 (2033.6;2102.1) | 23.5 (−16.9;63.8) |
| Country | | | | |
| Argentina | 87 (12.8) | 2323.1 (2202.7;2443.6) | 2116.9 (2026.1;2207.8) | 206.2 (91.9;320.5) |
| Brazil | 123 (18.1) | 2046.1 (1944.1;2148.1) | 2070.6 (1982.6;2158.6) | −24.5 (−129.9;80.9) |
| Chile | 64 (9.4) | 1884.6 (1777.9;1991.3) | 2167.5 (2053.6;2281.4) | −282.9 (−408.8;-156.9) |
| Colombia | 73 (10.7) | 2190.9 (2085.9;2296.0) | 2020.5 (1927.2;2113.7) | 170.5 (59.4;281.5) |
| Costa Rica | 69 (10.1) | 2003.8 (1895.3;2112.3) | 2172.2 (2047.0;2297.3) | −168.4 (−299.7;-37.0) |
| Ecuador | 73 (10.7) | 2177.0 (2081.0;2273.0) | 2103.1 (2010.3;2195.9) | 74.0 (−33.4;181.3) |
| Peru | 97 (14.3) | 2087.1 (2002.1;2172.1) | 1963.7 (1882.7;2044.7) | 123.4 (30.3;216.5) |
| Venezuela | 94 (13.8) | 2001.2 (1906.2;2096.1) | 1991.2 (1892.3;2090.1) | 10.0 (−96.3;116.2) |
| Sex | | | | |
| Male | 390 (57.4) | 2276.2 (2228.3;2324.0) | 2311.3 (2268.8;2353.7) | −35.1 (−93.7;23.5) |
| Female | 290 (42.6) | 1842.7 (1796.7;1888.6) | 1740.4 (1713.6;1767.3) | 102.2 (50.7;153.7) |
| Socio-economic status | | | | |
| Low | 361 (53.1) | 2102.6 (2051.0;2154.1) | 2047.3 (2003.2;2091.5) | 55.2 (0.3;110.1) |
| Middle | 258 (37.9) | 2067.9 (2007.0;2128.8) | 2073.7 (2015.6;2131.8) | −5.8 (−72.1;60.5) |
| High | 61 (9.0) | 2123.5 (2000.4;2246.5) | 2164.2 (2030.5;2297.9) | −40.8 (−180.7;99.2) |
| Education level | | | | |
| Basic | 563 (82.8) | 2113.7 (2071.9;2155.5) | 2084.8 (2047.3;2122.3) | 28.9 (−16.2;74.1) |
| High school | 98 (14.4) | 1966.9 (1880.0;2053.7) | 1946.5 (1867.3;2025.6) | 20.4 (−71.1;111.9) |
| Undergraduate | 19 (2.8) | 2069.2 (1855.8;2282.5) | 2191.3 (1867.9;2514.7) | −122.1 (−428.8;184.6) |
| Ethnicity | | | | |
| Caucasian | 234 (34.4) | 2092.6 (2028.8;2156.3) | 2127.3 (2060.9;2193.6) | −34.7 (−107.7;38.3) |
| Mestizo | 331 (48.7) | 2085.2 (2033.3;2137.1) | 2018.2 (1975.1;2061.3) | 67.0 (12.6;121.4) |
| Afro-American | 32 (4.7) | 2078.8 (1848.4;2309.1) | 2009.1 (1856.2;2162.0) | 69.7 (−156.4;295.8) |
| Indigenous | 9 (1.3) | 2006.9 (1808.8;2204.9) | 2163.8 (1840.8;2486.7) | −156.9 (−392.5;78.7) |
| Others | 74 (10.9) | 2130.1 (2008.3;2251.9) | 2115.5 (2003.2;2227.9) | 14.6 (−112.4;141.6) |
| Body mass index for age | | | | |
| Underweight | 12 (1.8) | 2233.5 (1949.6;2517.5) | 1887.3 (1736.0;2038.6) | 346.2 (70.2;622.2) |
| Normal weight | 626 (92.1) | 2086.7 (2048.2;2125.3) | 2044.2 (2011.6;2076.7) | 42.5 (2.7;82.4) |
| Overweight | 42 (6.2) | 2119.0 (1940.2;2297.8) | 2472.1 (2231.4;2712.9) | −353.1 (−595.5;-110.7) |
| Height for age | | | | |
| Low | 51 (7.5) | 2029.0 (1900.0;2157.9) | 1921.8 (1835.2;2008.4) | 107.2 (−10.5;224.8) |
| Risk of low height | 68 (10.0) | 2041.3 (1921.6;2160.9) | 2000.0 (1891.9;2108.1) | 41.3 (−84.7;167.3) |
| Normal | 561 (82.5) | 2103.0 (2061.6;2144.4) | 2089.3 (2050.8;2127.8) | 13.7 (−31.7;59.1) |

95% CI, confidence interval 95%; EI, energy intake; EE, energy expenditure; EIG, energy imbalance gap.

study of the anthropometric profiles of ELANS countries found that Argentina had the fourth highest prevalence of obesity (38).

In terms of the distribution of macronutrients, which are the nutrients that provide energy and constitute the EI, a previous ELANS study (39) found that in adolescents the 54.9% of their calories came from carbohydrates, 29.7% from lipids, and 15.4% from proteins. These percentages were consistent across different age groups and sexes. Peru had the highest percentage of energy derived from carbohydrates (62.9%), whereas Argentina and Colombia had the highest percentage of energy derived from fats (32.6 and 30.8%, respectively).

Argentina is a significant contributor to global beef production, accounting for approximately 5% of the total global output, and is one of the countries with the highest *per capita* meat consumption (40). In fact, animal-based proteins account for nearly 70% of the total daily protein intake (41). Additionally, it was the country with the highest processed food such as soft drinks, cookies and crackers, pizza, sugar and sweets, processed beef, cakes, salad dressing, and ice cream, many

TABLE 3 Adjusted multilevel linear regression models [b coefficient (95% CI)] for the relationships between independent variables and energy intake, energy expenditure and energy imbalance gap.

| Independent variables | Energy intake (kcal/day) | Energy expenditure (kcal/day) | Energy imbalance gap (kcal/day) |
|---|---|---|---|
| Sex | | | |
| Female[1] | Ref. | Ref. | Ref. |
| Male | 433.0 (364.6; 501.4) | 581.0 (529.8; 632.3) | −148.1 (−227.7; −68.4) |
| Socioeconomic status | | | |
| Low[2] | Ref. | Ref. | Ref. |
| Middle | −31.5 (−104.3; 41.3) | 16.5 (−37.1; 70.2) | −48.0 (−132.2; 36.1) |
| High | 20.1 (−104.0; 144.2) | 110.1 (22.4; 197.8) | −90.0 (−230.3; 50.3) |
| Body mass index for age | | | |
| Overweight[3] | Ref. | Ref. | Ref. |
| Normal weight | −40.4 (−180.7; 100.0) | −434.5 (−539.6; −329.3) | 394.1 (230.4; 557.8) |
| Underweight | −50.1 (−419.9; 319.7) | −1029.7 (−1319.0; −740.5) | 979.6 (518.6; 1440.6) |
| Height for age | | | |
| Normal[4] | Ref. | Ref. | Ref. |
| Risk of low height | −22.9 (−136.1; 90.3) | −40.9 (−125.6; 43.8) | 18.0 (−115.3; 151.3) |
| Low | −41.1 (−171.1; 88.9) | −95.4 (−192.4; 1.6) | 54.3 (−97.2; 205.7) |

Adjusted for [1]sex, [2]socio-economic status, [3]body mass index, and [4]height.

of which are sources of fat, in parallel it was country with the lowest consumption of fruits, legumes, rice, roots, and fish (39).

In Colombia, fat intake is mainly due to the use of oils for frying and the consumption of ultra-processed food products (42). The food groups that contributed the most to EI were fats, dairy products, eggs, nuts and seeds, roots, and alcoholic beverages, while the grains, pasta, bread, and soda drinks were the lowest contributors (39).

The agricultural industry in Peru has shown significant growth over the past decades, making it the second-largest economic sector in the country (43); thus, fresh food products are important in the Peruvian diet. In this case, grains, bread, pasta, potatoes, whole grain products, fruits, and vegetables were the principal contributors to the total EI (39), whereas poultry was the main protein source (41).

In terms of energy expenditure, Peru had the lowest value in this study, probably because of its low level of PA. A self-reported survey conducted in six South American countries showed that the highest levels of leisure physical inactivity (< 150 min/week) were in Peru (91.4%). A previous ELANS experience (44) noted that Peruvian adolescents and youth adults had the highest sitting time (556.8 min/day), which could explain their low EE. Wei et al. (45) described a model that suggests that Hispanic adolescents are likely to participate in less PA than others, which gives them a higher risk of obesity.

The higher EI and EE in male adolescents than in females was consistent with the results of previous studies. Silva et al. (46) studied 459 adolescents aged 10 to 17 in Portugal and found an energy imbalance gap of −50.7 kcal in males, with both EI and EE significantly higher than in females. Literature has consistently supported that male adolescents have a higher basal metabolic rate (BMR) and are more active than females (47, 48). Males have a greater BMR per unit of body than females because of body composition differences, including lean body mass (47). Additionally, males spend more time on high-intensity activities than females who spend more time on low-intensity activities (48). These findings suggest that biological and behavioral factors contribute to higher EI and EE in male adolescents.

The EE reported by adolescents in the present study was higher in subjects with a high SES than in those with a low SES. This is likely because adolescents from higher SES families are more likely to live in neighborhoods with parks, playgrounds, and other facilities that are conducive to PA, normally have the financial resources to purchase sports equipment and transportation for sports activities (45, 49), and are more likely to receive encouragement and support from their parents and peers to be physically active (50, 51). However, further studies are necessary to confirm this finding in the urban areas of Latin American.

Regarding BMI, there was a positive EIG in underweight and normal-weight adolescents compared to overweight adolescents. This is likely due to the compensatory strategies. Underweight adolescents had the lowest EE, which is likely due to a compensatory decrease in PA and a lower BMR due to their lower body weight. It is well established that underweight can induce reductions in EE and slow growth to favor subsequent body weight gain (52). Lazzer et al. (53) found that obese adolescents have a higher BMR due to their high weight, and higher EE compared to non-obese subjects. They also found that obese subjects spent more time on light physical activities, such as shopping or slow walking during the weekend, but much less time on moderate and sports activities than non-obese subjects. This could explain the results of Chile and Costa Rica, which had the lowest EIG values, with a higher EE than EI and a high prevalence of obesity by BMI (38). Therefore, despite a negative energy balance, they do not present high levels of malnutrition in their population. Thivel et al. (54) established that obese adolescents may spontaneously decrease EI after intensive exercise, an important compensatory theory, especially for this research because overweight adolescents had an EI very similar to that of the normal weight group.

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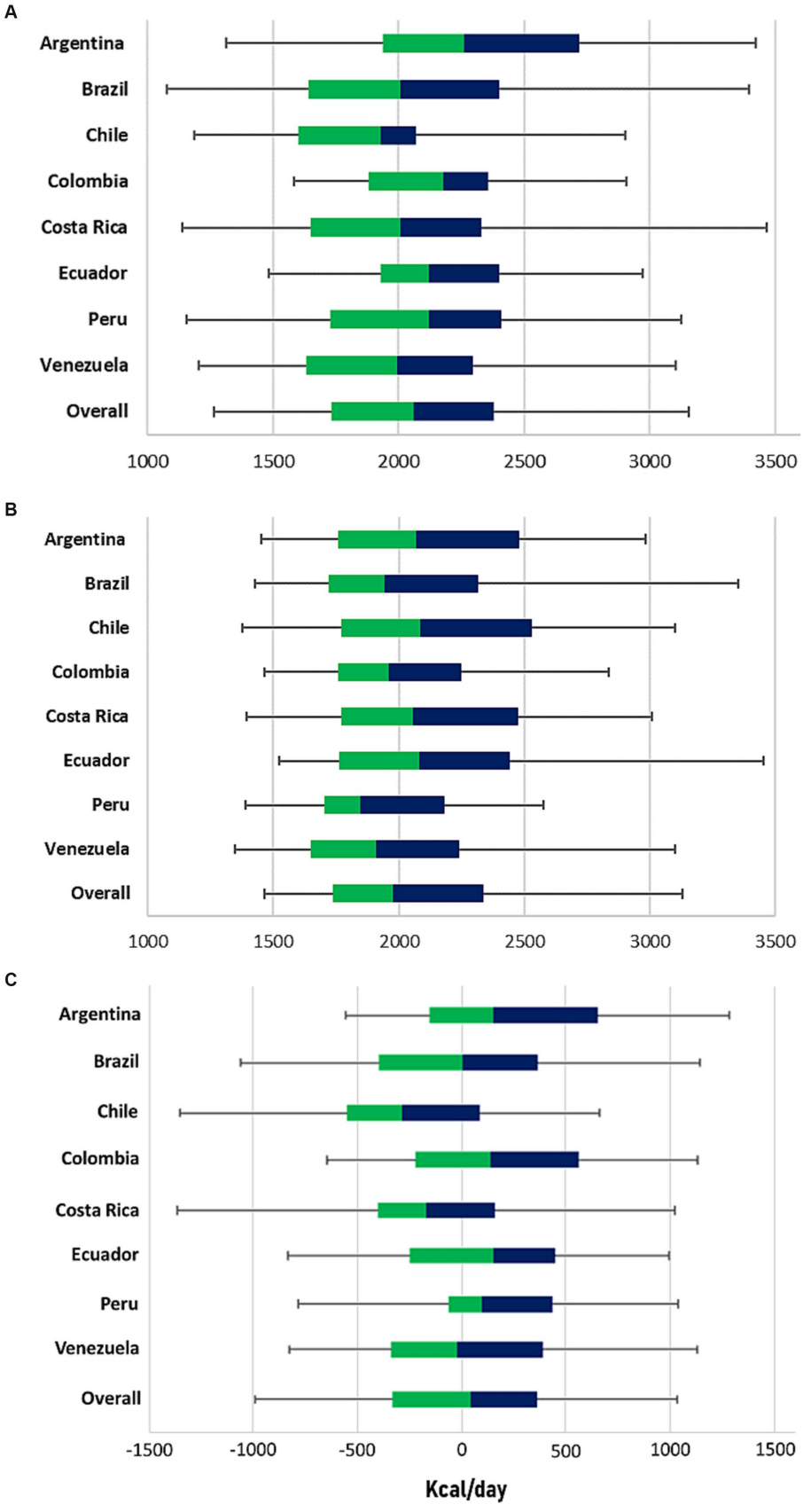


FIGURE 2
Boxplot of **(A)** energy intake, **(B)** energy expenditure, and **(C)** energy imbalance gap values by country. In the figure, the median is represented by the vertical line between the colors in the box. The part of the box above the median is shown in blue, and the part of the box below the median is shown in green.

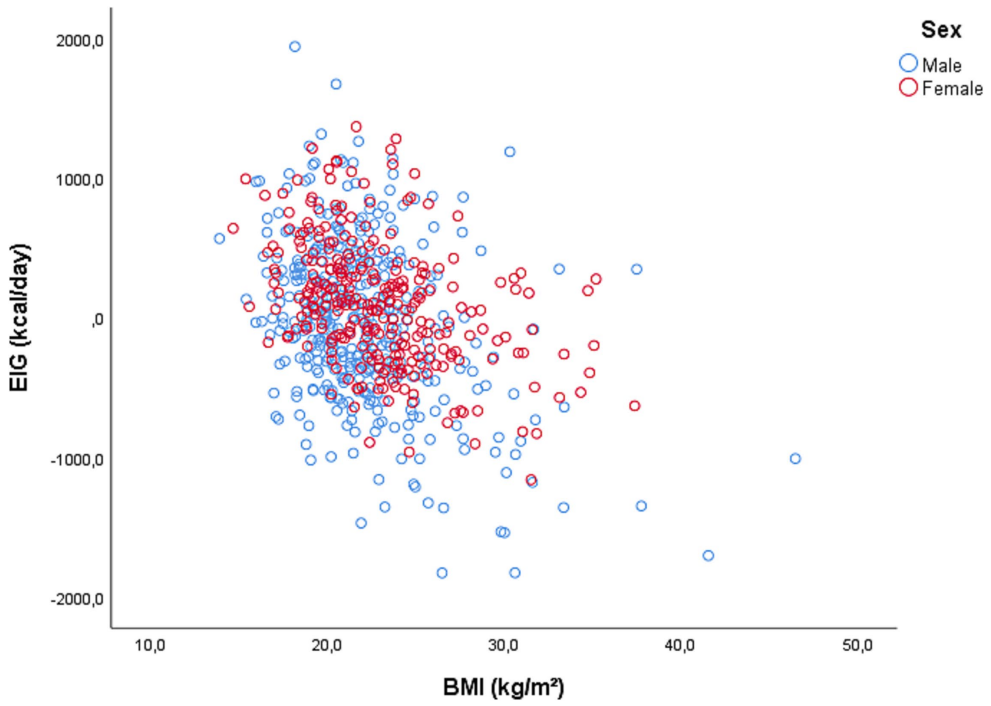


FIGURE 3
Scatter-dot plot of the energy imbalance gap as a function of body mass index in the study participants.

Burns (55), also revealed a discrepancy in the correlations between weight loss intent and the practice of specific energy balance-related health behaviors in adolescents. A cross-sectional study found that less movement does not necessarily imply lower energy expenditure (56). Thivel et al. (54) reported that energy intake (EI) in today's obesogenic environment may primarily be determined by non-homeostatic pathways that can override the body's energy and hormonal signals. This is because EI changes are not influenced by the amount of energy expended during activities, such as screen-based sedentary behaviors, which are more likely to stimulate food intake (regardless of appetite sensations) than non-screen sedentary behaviors. Therefore, accurately measuring energy balance and body changes remains challenging.

This study's innovative findings include identifying sex and BMI as factors associated with EIG among adolescents from Latin America. The inverse relationship between BMI and EIG is an interesting finding that should be studied in depth in the future. The study also highlights the variability in EIG across different countries in the region.

The authors' previous experience addressed the relationships between sociodemographic variables and nutritional status with EIG in LA adults. Nevertheless, this study has several strengths, including its focus on adolescent EIG, for which research is scarce. We also have used two non-consecutive 24-h recalls, the PA recall using the extensively validated IPAQ questionnaire, and the randomized multistage sampling. Additionally, a multilevel linear regression model was used to examine the individual and contextual factors that may contribute to the energy imbalance gap, providing a more comprehensive understanding of the issue.

However, this study has some limitations that need to be considered. First, this study was cross-sectional; therefore, it could not be used to establish causality. The data on EI and EE were self-reported, which may have introduced bias in the technique used. This study was conducted in a limited number of countries; therefore, the findings may not be generalizable to all LA regions. Moreover, BMI does not differentiate between excess fat, muscle, or bone mass, nor does it offer any insight into fat distribution in individuals. Longitudinal studies are needed to better understand how changes in BMI and EIG over time impact energy balance and weight management. Addressing these limitations in future research could enhance the understanding of the relationship between BMI and EIG, as well as gender-specific differences in energy balance regulation among adults.

On the other hand, the methodology used in this study to evaluate EIG has been controversially discussed as it goes away from direct and indirect calorimetry using a metabolic chamber and metabolic cart, respectively, and the doubly labeled water technique (57). However, these methods are costly or invasive to perform in epidemiological studies. Thus, the results of this study constitute a first step toward understanding the relationship between EI and EE in LA adolescents, and may constitute an input to promote public policies aimed at reducing the prevalence of obesity in urban areas of the LA region.

## 5 Conclusion

In conclusion, the findings of this study suggest that sex and BMI are associated with EIG among adolescents in ELANS countries. These factors should be considered when developing public health policies to prevent weight gain and promote healthy weight in this age group. The findings of this study also suggest first actions directed to raise

awareness on the EIG research in epidemiologic studies, and allocate funds to provide the resources to evaluate at least some neuro-endocrine markers that are involved in the mechanisms of energy intake, as usually funds are an important obstacle for not including those type of variables in an epidemiologic study. Second, policy makers and stake holders need to be aware that adolescents are a fundamental key pillar of societal wellbeing as is it during this life phase that future health and fertility are consolidated, and the window of opportunities for interventions during the period of growth and development goes to an end, therefore there is a need to implement public health interventions to address the issue of EIG in adolescents in LA, that translate into better health care actions, including screening, promoting healthy eating habits and better built environments less obesogenic and friendly for the practice of daily life physical activities.

## 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 study was conducted in accordance with the Declaration of Helsinki. Ethical approval was provided by the Western Institutional Review Board (#20140605), and by the ethical review boards of the participating institutions. This study is registered at Clinical Trials #NCT02226627. Written informed consent/assent was obtained from all individuals before commencement of the study.

## Author contributions

PH: Conceptualization, Visualization, Writing – original draft. MH-C: Data curation, Investigation, Methodology, Resources, Supervision, Writing – original draft. GF: Formal analysis, Writing – review & editing. RY: Formal analysis, Writing – review & editing. MY: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft. MV: Methodology, Writing – original draft. LC: Conceptualization, Investigation, Methodology, Resources, Writing – original draft. YS: Investigation, Resources, Supervision, Writing – original draft. ML-J: Investigation, Resources, Supervision, Writing – original draft. GG: Data curation, Investigation, Resources, Writing – review & editing. RM-R: Data curation, Investigation, Resources, Writing – review & editing. RP: Data curation, Investigation, Resources, Writing – review & editing. AR: Data curation, Investigation, Resources, Writing – review & editing. IK: Data curation, Funding acquisition, Investigation, Resources, Writing – review & editing. MF: Data curation, Funding acquisition, Investigation, Resources, 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.2024.1380315/full#supplementary-material

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# Adolescents' use of online food delivery applications and perceptions of healthy food options and food safety: a cross-sectional study in the United Arab Emirates

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**Introduction:** This cross-sectional study aimed to assess Online food delivery applications (OFDA) usage trends among adolescent users in the United Arab Emirates (UAE), focusing on their perceptions of healthy food options and food safety ($n = 532$).

**Methods:** Sociodemographic information, frequency of OFDA use, factors affecting food choices, and perceptions of healthy food and food safety were investigated. A total perception score was calculated for each participant;

**Results:** Most participants used OFDAs weekly (65.4%), favoring fast food (85.7%). Factors like appearance and price drove food choices (65.0%), while taste and cost hindered healthy food orders (29.7 and 28.2%). Younger and frequent users had lower scores for perceiving healthy food, while seeking healthy options was associated with higher scores ($p < 0.05$). Females and those seeking healthy food showed higher food safety scores ($p < 0.05$).

**Discussion:** The study suggests tailored interventions to promote healthier choices and improve food safety perceptions among adolescents using OFDAs in the UAE.

KEYWORDS

**food applications, digital food environment, food choices, consumer perception of healthy food, adolescence**

# 1 Introduction

Adolescence entails a critical period of physical, mental, and social growth as a child transitions toward adulthood (1). During this period, adolescents learn and adopt habits and choices that tend to persist into adulthood (2, 3). According to global statistics, the prevalence of overweight and obesity among children and adolescents who are 5–19 years old has more than quadrupled from 4% in 1975 to over 18% in 2016 (4). Most recent data in the UAE indicates a 29 and 35% prevalence of overweight and obesity among 4-13-year-old and 13-19-year-old children and adolescents, respectively (5, 6). Higher estimates of overweight and obesity have been reported in studies among 13-17-year-old adolescents in the national Global School-based Student Health Survey, reaching up to 55% (7). These numbers represent a serious public health issue that needs to be tackled to curb future health consequences that can persist into adulthood (8).

Numerous external factors leading to obesity have changed over the past few decades, with higher availability and accessibility of more processed and energy-dense food. The global economic landscape has significantly increased purchasing power and food availability at the individual level. The rapid proliferation of supermarkets and the exponential growth of the fast-food sector are central to this transformation, posing a dramatic impact on global eating habits (9, 10). This change has shifted diets toward a considerable reliance on ultra-processed foods high in sugars and saturated fats, effectively becoming the predominant energy source in many countries (9, 10). The flood of extensively advertised, convenient, and relatively inexpensive ultra-processed meals has significantly increased the energy level of the food supply far beyond actual population requirements (10). This surplus and a lack of nutritional alternatives encourages a diet heavy in calories, saturated fats, and added sweets, predisposing people to weight gain and the start of obesity (11). Furthermore, advancements in technology and its increasing use among the youth, and the increasingly sedentary nature of daily life have also contributed to these increasing rates (12).

Several studies in the UAE provide evidence of unhealthy food choices among this age group. One study showed that 30% of 4-13-year-olds exceeded their estimated energy requirements (5). Other studies showed that adolescents now consume more food away from home, consume fewer fruits and vegetables, and do not engage in physical activity (6, 13, 14).

Making food choices as an adolescent results from the interaction between external environmental factors and personal factors (15). This period is distinguished by increasing autonomy and a shift from spending more time with their parents to spending it with friends and peers away from home (16), resulting in a more significant influence of peers on their food choices (17). Nonetheless, profound evidence indicates that adolescents' exposure to the marketing of food and beverages that are high in energy, fat, and sugar and their engagement with unhealthy food products on social media could take a significant toll on increasing obesity rates (18, 19).

Food environments directly link to dietary habits and health consequences, including noncommunicable diseases and obesity (20, 21). In the modern world, the digitalization of food environments has led to novel forms of acquiring foods and beverages. These include online grocery shopping and food delivery through websites or smartphone applications (22). The extensive growth of information communication technology and smartphones and the development of mobile applications have indisputably penetrated people's lifestyles (23). Among the most popular mobile applications downloaded are mobile OFDA and statistics show that the number of users for OFDA has more than doubled from 2017 to 2022, reaching 1850 million users worldwide (24).

Smartphone applications can provide a robust medium for adolescents to acquire and adopt healthy or unhealthy food choices. Using such applications allows consumers to access and place orders from a wide range of food outlets at their convenience and to track their ordered meal till it reaches their chosen destination (25). Recent data shows that certain features of OFDA support consumers' intention to use them, including online reviews, restaurant ratings, tracking, and price value (26). Moreover, other factors extend to certain aspects of food safety and hygiene, referred to as food delivery hygiene, which can be defined as the ability of the delivery person or company to maintain the safety and cleanliness of food delivery services (27).

Although available data on OFDA use in the Middle East is scarce, limited data indicate that adult users exhibit unhealthy dietary practices (28) and that consumers perceive the online food environment as unhealthy (29).

With the influx of food delivery applications and their mere ease of use, especially among adolescents in the digital age, delving into their usage and perceptions could yield a deeper understanding of the potential factors that shape their food choices. This may further contribute to filling knowledge gaps on personal factors and perceptions of healthy food availability in the online food environment when accessibility to such platforms is especially easy for this group.

To the best of our knowledge, there is no available data on adolescents' OFDA usage and perceptions in the UAE, and as such, this study aims to assess the trends of OFDA usage among adolescents and investigate their perception of healthy food options and food safety through these apps.

# 2 Methods

## 2.1 Study design and participants

A cross-sectional, web-based study was carried out between January and June 2023, targeting adolescent OFDA users residing in the UAE. The inclusion criteria were adolescents aged 10 to 19 years as per the World Health Organization definition (1) and those who use OFDA at least once per month. The study participants were recruited using a convenience sampling method, allowing for better accessibility to people who satisfied the inclusion criteria within a restricted timeframe.

A sample size of 461 adolescents was determined based on the following formula with a confidence interval of 95%:

$$N = z^2 \times P \times (1 - P) / e^2$$

Where z = 1.96; P = (estimated proportion of the population that presents the characteristic) = 0.5; e (margin of error) = 0.05; N (sample size) = 384 participants. An additional 20% was added to the required sample size to account for any non-response bias or incomplete data, resulting in a target sample size of 461 participants.

Given the convenience sampling methodology employed in the study, 10 schools were contacted via email to request permission for data collection, ensuring the inclusion of at least one school in each of the seven Emirates. Of these, only three schools agreed to participate in the study (one in each of the three highly populated emirates: Abu Dhabi, Dubai, and Sharjah). A web link connecting to the online survey was sent to the administration and distributed to the students. While efforts were made to approach a wide array of schools, the participation of schools was voluntary, leading to variations in the distribution across emirates based on their willingness to participate and student and parent engagement. In addition, the web link was also shared via email invitations, with the contact lists being gathered from personal and professional contacts of the research team, including colleagues, friends, and family members, to disseminate among the target group to ensure a wider distribution and recruitment of participants from other emirates.

Parental consent was obtained through an online informed consent form, where parents were provided with detailed information about the study and asked if they agreed to their child's participation. Upon their approval, adolescents were provided with a simplified explanation of the study and asked to provide their consent assent before completing the survey. Participants were also informed that only one response would be accepted using the link. This restriction was enforced by the survey platform as only one response was allowed from each device to ensure data integrity. No personal information was collected during the survey to ensure confidentiality, and participants were assured that their responses would remain anonymous and would not affect their academic standing or relationships within the school community.

This study was conducted following the guidelines in the Declaration of Helsinki. All procedures involving human subjects/patients were approved by the University of Sharjah Research Ethics Committee (REC-22-02-16-09-S). The online form eased the consent process by presenting participants with an electronic consent form detailing the study's goal, methods, potential risks, and benefits. Before advancing to the survey questions, participants were requested to indicate their affirmative approval by clicking a marked 'I agree' button. All participants provided an electronic written informed consent before answering the survey questions.

## 2.2 Survey questionnaire and data collection

The survey used in this study was adapted from a previous tool developed by the research team and validated for use among adults (30). The original survey included 27 close-ended questions using Likert-scale, dichotomous, multiple choice, and checklist format (30). In the present study, some questions were omitted, while others were included to tailor the questionnaire for the present study population. These adjustments aligned the survey with the experiences and demographic characteristics pertinent to adolescents. For instance, some of the questions added were if the mother works outside the home and if, when using OFDA, a healthy or homemade meal is usually available at home. These questions were added to gain insights into the participants' experiences and the possible impact of having a mother working outside on the frequency of using the apps.

The final version of the survey used in this study consisted of five sections. The first section focused on sociodemographic information, asking about sex, age, the emirate of residence, daily allowance, and maternal employment status. The selection of these factors was essential to describe the study population and their influence on food habits and choices.

The second section inquired about OFDA usage trends and explored participants' behavior, inquiring about the frequency of OFDA use, most frequently used apps, the predominant type of food ordered (culinary styles or preferences), factors affecting food choices, and whether participants looked for healthy food options. The following section explored participants' perceptions of healthy food and their concerns when choosing healthy options. These questions were chosen for their direct relevance to understanding participants' decision-making when ordering meals online.

The last two sections comprised seven questions in each section and were employed to understand participants' perspectives on healthy food ordering, food safety, and delivery cleanliness using OFDA platforms. The questions used a 5-point Likert scale (response options: 1: strongly disagree, 2: disagree, 3: neutral, 4: agree, 5: strongly agree). Participant responses were recorded and were grouped into three categories (agree, neutral, and disagree) for descriptive analysis. In addition, a score ranging from 7 to 35 was calculated for each participant for inferential analysis.

## 2.3 Data analysis

Descriptive statistics, such as frequencies and percentages, were used to summarize the demographic characteristics of the participants, their OFDA use, perception of a healthy meal, and perceptions of healthy food ordering and food safety and hygiene via OFDA. Data distribution was assessed using the Shapiro–Wilk's test, which indicated a non-normal distribution ($p < 0.05$). Therefore, non-parametric tests and median and interquartile ranges (IQR) were used to analyze and describe the data. The frequency of using OFDAs was categorized into a dichotomous variable where frequent use corresponds to response options: daily, 4–6 times/week, and 2–3 times/week; infrequent use corresponds to response options: once/week and once/month. A total healthy food perception score was calculated for each participant based on their responses to the seven perception items by summing their responses. The score could range from 7 to 35, with a higher score indicating a more positive perception toward healthy food on OFDA. A reverse scale was used for negative-worded items "I often find it difficult to find healthy food choices on food apps,"

"I feel that ordering online from food apps has increased my food intake and appetite," and "Using online food delivery applications has changed my eating habits (for example: having late night meals, eating alone)." In addition, a total food safety score was calculated similarly, with a higher score indicating more food safety-inclined perceptions. During the data analysis, the score was transformed using a minimum-maximum scaling approach to normalize the data and convert it to a percentage (out of 100). Differences in the perception of healthy food on OFDA and food safety and hygiene according to sociodemographic characteristics and OFDA use were explored using the Mann–Whitney U and Kruskal-Wallis H tests. Pairwise comparisons were conducted to indicate which groups significantly differed from each

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TABLE 1 Sociodemographic characteristics of the study participants ($n = 532$).

| Characteristic | n | % |
|---|---|---|
| Age (years) | | |
| 10–13 | 129 | 24.2 |
| 14–16 | 187 | 35.2 |
| 17–19 | 216 | 40.6 |
| Sex | | |
| Male | 207 | 38.9 |
| Female | 325 | 61.1 |
| Emirate of residence | | |
| Abu Dhabi | 145 | 27.3 |
| Dubai | 113 | 21.2 |
| Sharjah | 174 | 32.7 |
| Northern Emirates[a] | 100 | 18.8 |
| Daily allowance (AED) | | |
| None | 143 | 26.9 |
| <25 AED | 201 | 37.8 |
| 25- < 50 AED | 111 | 20.9 |
| ≥50 AED | 77 | 14.5 |
| Mother work | | |
| Yes | 210 | 39.5 |
| No | 322 | 60.5 |

[a]Northern Emirates including Ajman, Um Al Quwain, Ras Al Khaimah, and Fujairah.

TABLE 2 Use of OFDA and healthy food ordering among the study participants ($n = 532$).

| Variable | n | % |
|---|---|---|
| Frequency of OFD use | | |
| Daily | 21 | 3.9 |
| 4–6 times/week | 51 | 9.6 |
| 2–3 times/week | 157 | 29.5 |
| 1 time/week | 191 | 35.9 |
| 1 time/month | 112 | 21.1 |
| Food at home when ordering | | |
| Yes | 160 | 30.1 |
| Sometimes | 227 | 42.7 |
| No | 145 | 27.3 |
| Look for healthy options on OFDA | | |
| Yes | 110 | 20.7 |
| Sometimes | 213 | 40.0 |
| No | 209 | 39.3 |
| The main concern about ordering healthy food | | |
| Taste | 158 | 29.7 |
| High price | 150 | 28.2 |
| Option availability | 92 | 17.3 |
| Small portion size | 69 | 13.0 |
| Low quality | 46 | 8.6 |
| Appearance | 17 | 3.2 |

other. A general linear model analysis was performed to investigate whether certain characteristics (independent variables) can predict the perceptions of healthy food perception and food safety and hygiene scores (score as dependent variable). $p$ values at <0.05 were considered statistically significant. Data were analyzed using SPSS software, version 26.0 (SPSS, Chicago, IL, United States).

# 3 Results

## 3.1 Study participants' characteristics

A total of 532 adolescents participated in the study comprised of 325 females (61.2%) and 207 (38.9%), as shown in Table 1. Most participants were between 17 and 19 years old (40.6%), followed by younger adolescents who were between 14 and 16 years old (35.2%). Most participants lived in Sharjah (32.7%), followed by Abu Dhabi (27.3%). Around a third of the participants had a daily allowance of <25 AED (~7 USD; 37.8%), and 60.5% of the participants reported that their mothers were not employed.

## 3.2 Use of OFDA and healthy food ordering

Most participants reported using OFDA once per week (35.9%) or 2–3 times per week (29.5%), as shown in Table 2. Approximately three-quarters of the participants reported that there is either always or sometimes food available at home when ordering through OFDA (30.1 and 42.7%, respectively). Figure 1 illustrates the trends of OFDA use among the study participants, where 447 participants reported using Talabat (84.0%), and 456 participants reported mostly ordering fast food (85.7%), followed by 229 participants ordering international cuisines (43.0%) and 190 participants preferring local cuisines (35.7%).

When asked about factors affecting their food choices, most participants were affected by appearance and price (~65%), followed by delivery time (44.7%). Only 20.7% of the participants reported always looking for healthy food options, while 40.0% reported sometimes doing so on OFDA. The most reported concern regarding healthy food ordering was taste (29.7%) and high price (28.2%). When asked about their perception of a healthy meal, almost half of the participants perceived a meal that is low in fat, low in calories, has a variety of vegetables, or is rich in protein (46.1–51.3%).

## 3.3 Perceptions of healthy food on OFDA

Figure 2 shows participants' agreement on seven statements about placing healthy food orders through OFDA. The participants' responses were grouped into agree, neutral, and disagree. Two hundred and eighty-four participants (53.4%) agreed on the difficulty of finding healthy food options on OFDA, 263 agreed that the OFDA increased their food intake and appetite (49.4%), while 258 agreed that their eating habits were affected by OFDA (48.5%), specifically in

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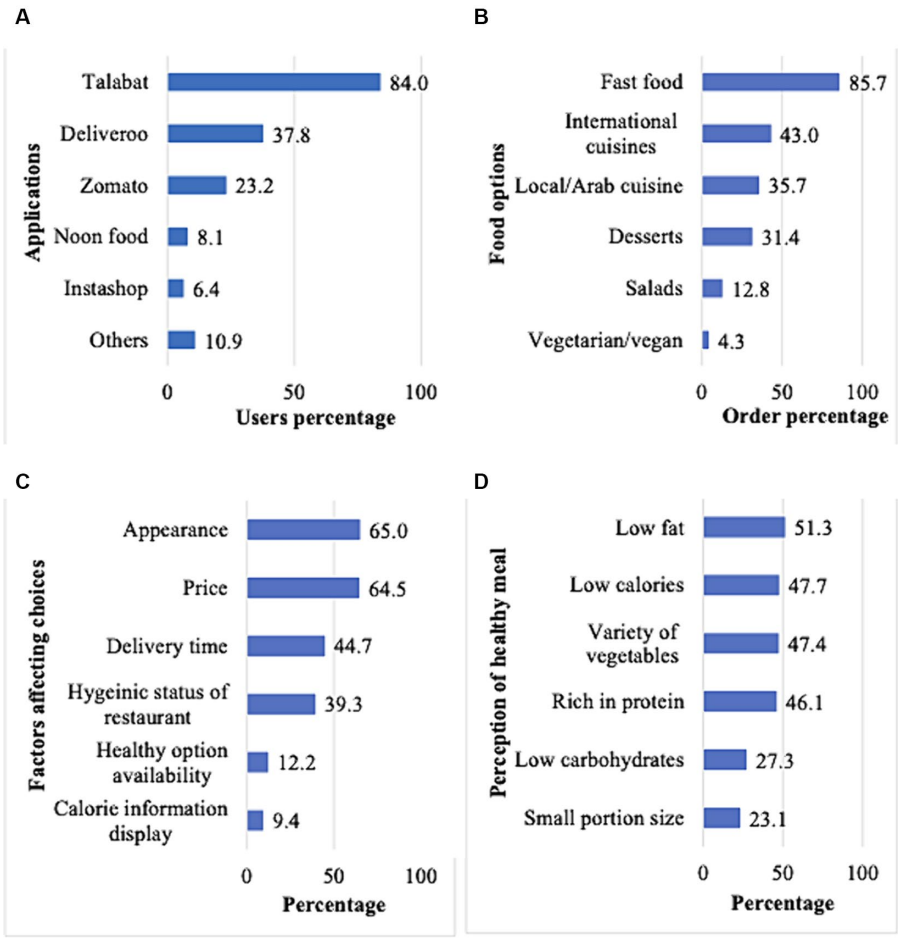


FIGURE 1
Trends of OFDA among study participants (**n** = 532). **(A)** Most OFDA used (Multiple responses were allowed; others include Uber Eats, Eat Clean me, EatEasy, Careem now, Carriage, and restaurant apps); **(B)** Most ordered cuisine. (Multiple responses were allowed); **(C)** Factors affecting food choice on OFDA among participants; **(D)** Perception of a healthy meal when using OFD applications among participants; Multiple responses were allowed.

terms of consuming more late-night snacks or eating alone. A lesser proportion of the participants agreed that OFDA made them aware of healthier food alternatives (31.0%), that having calorie and macronutrient content displayed on OFDA might affect their food choices (28.8 and 27.6%), and that they are willing to pay higher prices for healthier food options on OFDA (26.7%).

## 3.4 Perceptions of food safety and delivery hygiene

Figure 3 shows participants' agreement to several statements related to food safety and hygiene of food delivery. Most of the participants agreed that the temperature of the meal upon delivery is a good indicator of both the quality and safety of the food (86.8 and 72.3%, respectively). A similar proportion agreed hygiene ratings would be useful when ordering food (82.1%). Additionally, 68.8% of participants agreed that the driver's cleanliness and neatness impacted their perception of the meal's hygiene. Moreover, around 60% agreed that food available through the OFDA was prepared and delivered under sanitary conditions and that packaging influences food choices. Less than half of the participants (44.0%) agreed that using environmentally friendly packaging influences their food choices.

## 3.5 Differences in perception of healthy food and food safety on OFDA

Table 3 presents the differences in the study participants' perceptions of healthy food, food safety, and hygiene scores. The analysis indicated a significant difference in food safety and hygiene scores ($p < 0.001$), with females having higher scores than males. However, no significant difference in healthy food perception was observed. Moreover, individuals who actively look for healthy food have significantly higher perceptions of healthy food and food safety compared to those who do not actively seek healthy food. Specifically, those who actively seek healthy food have higher healthy food perception scores ($p < 0.001$) and higher food safety scores ($p = 0.012$). The pairwise comparisons further highlight the significance between different groups regarding healthy food perception and food safety scores, specifically emphasizing the impact of actively seeking healthy food on both perceptions.

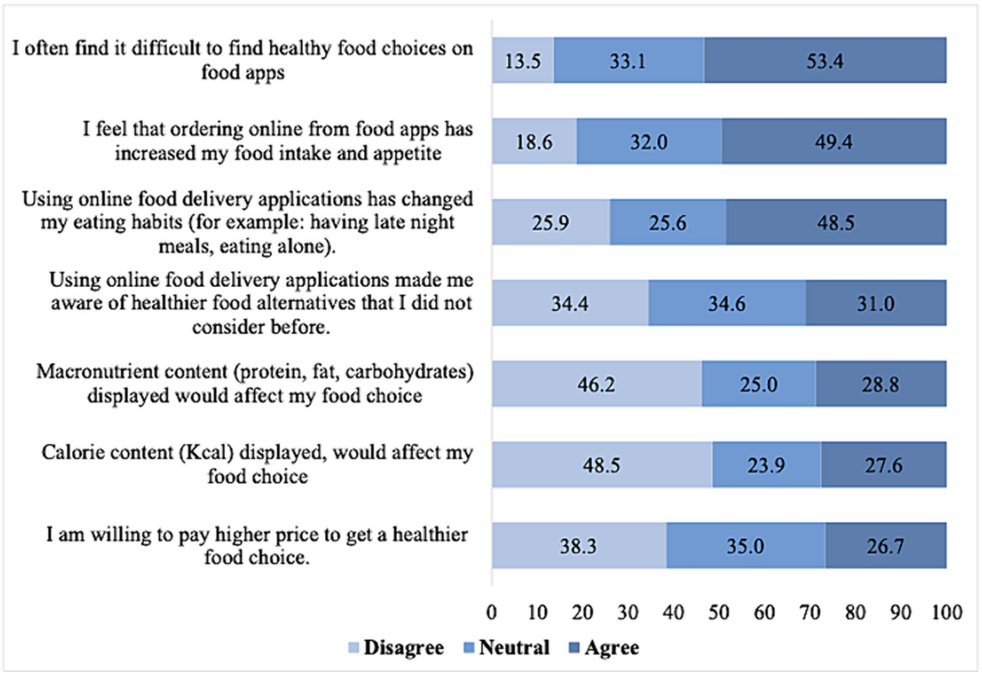


FIGURE 2
Perceptions of healthy food ordering through the OFD applications ($n$ = 532).

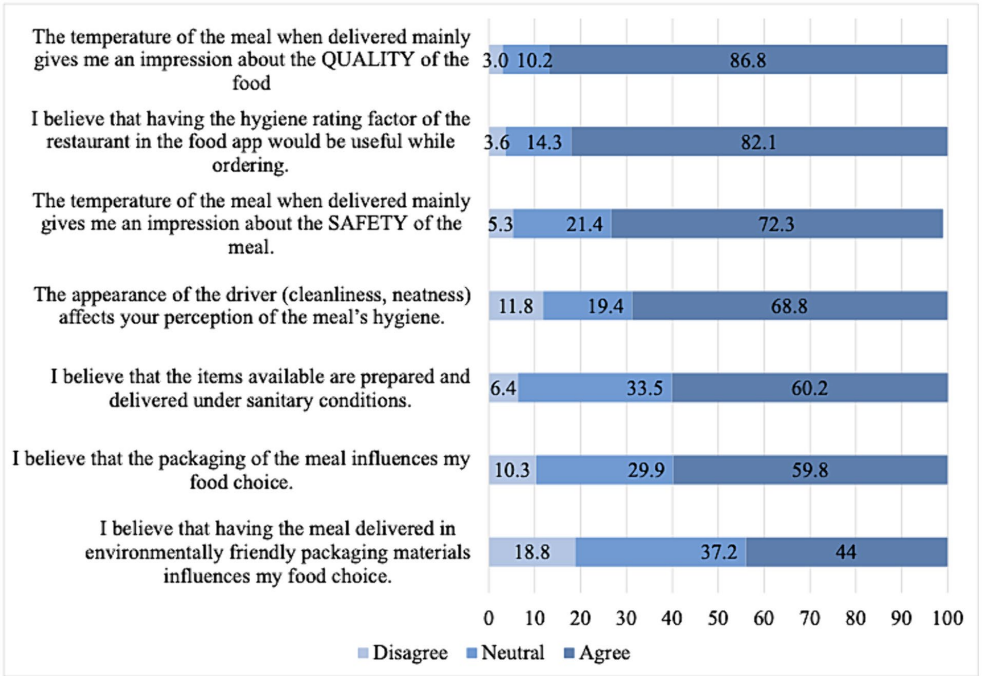


FIGURE 3
Perceptions of food safety and delivery hygiene through the OFD applications ($n$ = 532).

## 3.6 Association between the healthy food perception and food safety and hygiene scores and participants' characteristics

Table 4 shows the association between several sociodemographic and OFDA use and the healthy food perception score using general linear model analyses. The analysis revealed that the healthy food perception score was significantly lower by 2.6 and 1.9% among younger participants aged 10 to 13 years and frequent users ($B = -2.6$, 95% CI: −4.8–−0.3, $p = 0.026$) and ($B = -1.9$, 95% CI: −3.7–−0.1, $p = 0.038$) respectively. On the other hand, having a working mother and reporting looking for healthy food was associated with a 1.8 and

TABLE 3 The difference in perception of healthy food on OFDA and food safety and hygiene scores (out of 100) according to sociodemographic characteristics and OFDA use ($n = 532$).

| | | Healthy food perception score | | | Food safety and hygiene score | | |
|---|---|---|---|---|---|---|---|
| | n (%) | Median | IQR | *p* value | Median | IQR | *p* value |
| Total | | 28.6 | 14.3 | | 39.3 | 10.7 | |
| Age (years) | | | | | | | |
| 10–13 | 129 (24.2) | 25.0 | 14.3 | 0.054 | 42.9 | 10.7 | 0.447 |
| 14–16 | 187 (35.2) | 28.6 | 14.3 | | 39.3 | 10.7 | |
| 17–19 | 216 (40.6) | 28.6 | 17.9 | | 39.3 | 14.3 | |
| Sex | | | | | | | |
| Male | 207 (3.9) | 28.6 | 14.3 | 0.461 | 39.3 | 10.7 | **0.003** |
| Female | 325 (61.1) | 28.6 | 14.3 | | 42.9 | 10.7 | |
| Daily allowance (AED) | | | | | | | |
| None | 143 (26.9) | 28.6 | 14.3 | 0.598 | 42.9 | 17.9 | 0.687 |
| <25 AED | 201 (37.8) | 28.6 | 14.3 | | 39.3 | 10.7 | |
| 25- < 50 AED | 111 (20.9) | 28.6 | 14.3 | | 39.3 | 7.1 | |
| ≥50 AED | 77 (14.5) | 32.1 | 17.9 | | 39.3 | 14.3 | |
| Mother work | | | | | | | |
| Yes | 210 (39.5) | 28.6 | 10.7 | 0.126 | 39.3 | 10.7 | 0.804 |
| No | 322 (60.5) | 28.6 | 14.3 | | 42.9 | 14.3 | |
| Frequency | | | | | | | |
| Frequent | 229 (43.0) | 28.6 | 14.3 | 0.051 | 39.3 | 10.7 | 0.156 |
| Infrequent | 303 (57.0) | 28.6 | 17.9 | | 42.9 | 10.7 | |
| Look for healthy food | | | | | | | |
| Yes | 110 (20.7) | 28.6 [a] | 14.3 | **<0.001** | 46.4 [a] | 17.9 | **0.012** |
| Sometimes | 213 (40.0) | 32.1 [b] | 14.3 | | 39.3 | 10.7 | |
| No | 209 (39.3) | 25.0 [ab] | 14.3 | | 39.3 [a] | 10.7 | |

*$p$ value was based on the Mann Whitney U test and Kruskal Wallis K test at a 5% level of significance; [a]pairwise comparison significant difference between Yes and No. [b]pairwise comparison significant difference between Sometimes and No. Bold values represent significant values based on a $p < 0.05$.

5.8% significantly higher score ($B = 1.8$, 95% CI:0.1–3.6, $p = 0.043$) and ($B = 5.8$, 95% CI:3.5–8.2, $p < 0.001$) respectively.

Regarding the food safety and hygiene score, the analysis revealed that the score was significantly lower by 2.2% among males compared to females (B = −2.2, 95% CI: −3.8–−0.7, $p = 0.005$). On the other hand, looking for healthy food was associated with a 2.7% significantly higher score ($B = 2.7$, 95% CI:0.7–4.7, $p = 0.008$).

## 4 Discussion

The present study provided valuable insights into perceptions of healthy food and food safety and hygiene through OFDA among a sample of adolescent OFDA users in the UAE. Less than half (43.0%) of the participants were frequent users of OFDA (2 times or more/week). This frequency was higher than that of Jordanian adults (35.7%), college students in Malaysia (18.3%), and Brazilian adults (10.0%) (29–31). Among the several OFDA platforms available, Talabat was the most popular choice among our participants, perhaps due to its established popularity and performance in the country and the region (32). Moreover, in the current study, fast food was the dominant choice for orders via OFDA, highlighting adolescents' tendency toward palatable, convenient, and readily available choices. This is supported by studies in China and Australia, where fast-food outlets comprised 65 and 54% of the available food outlets through OFDA (33, 34).

Available literature points out the adverse impacts of an unhealthy food environment around schools and reveals increased discretionary food purchasing (35) and positive associations with children's weight status (36). Our findings highlight the need to consider not only food environments around schools but also the threats of the digital food environment, which has facilitated obtaining unhealthy food items with just a few clicks (37).

In the current study, visual appeal and affordability were key drivers for adolescents in making their food choices through OFDA. Similarly, a Polish study on food choices revealed that sensory appeal and price were the prominent drivers of food choice among adolescents (38). In our study, most adolescents reported looking for healthy food options either always or sometimes. This is a favorable find as it indicates a possible growing interest in healthy eating habits among this group. Taste and high prices emerged as key issues regarding healthy food ordering in our sample. This creates a paradox for adolescents, because while healthy food can be available on these apps, the prices are usually outside their budget (39), which can cost

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TABLE 4 Association between the healthy food perception and food safety and hygiene scores (out of 100%) and participants' characteristics ($n = 532$).

| Parameter | Healthy food perception score | | | |
|---|---|---|---|---|
| | | 95% CI | | |
| | B | Lower | Upper | *p* value |
| Intercept | 28.5 | 25.6 | 31.3 | **<0.001** |
| Sex (reference: female) | | | | |
| Male | −0.5 | −2.3 | 1.3 | 0.571 |
| Age category (reference: 17-19 years) | | | | |
| 10–13 years | −2.6 | −4.8 | −0.3 | **0.026** |
| 14–16 years | −1.0 | −3.0 | 1.0 | 0.337 |
| Allowance (reference: ≥50 AED) | | | | |
| None | −1.3 | −4.2 | 1.5 | 0.361 |
| <25 AED | −1.2 | −4.0 | 1.5 | 0.376 |
| 25- < 50 AED | −2.6 | −5.6 | 0.4 | 0.089 |
| Mother work (reference: no) | | | | |
| Yes | 1.8 | 0.1 | 3.6 | **0.043** |
| Frequency of use (reference: infrequent) | | | | |
| Frequent | −1.9 | −3.7 | −0.1 | **0.038** |
| Look for healthy food (reference: no) | | | | |
| Yes | 5.8 | 3.5 | 8.2 | **<0.001** |
| Sometimes | 5.7 | 3.7 | 7.6 | **<0.001** |
| Parameter | Food safety and hygiene score | | | |
| | | 95% CI | | |
| | B | Lower | Upper | *p* value |
| Intercept | 39.0 | 36.6 | 41.5 | **<0.001** |
| Sex (reference: female) | | | | |
| Male | −2.2 | −3.8 | −0.7 | **0.005** |
| Age category (reference: 17–19 years) | | | | |
| 10–13 years | 0.7 | −1.3 | 2.6 | 0.507 |
| 14–16 years | 1.0 | −0.7 | 2.8 | 0.246 |
| Allowance (reference: ≥50 AED) | | | | |
| None | 0.3 | −2.1 | 2.8 | 0.785 |
| <25 AED | 0.5 | −1.9 | 2.8 | 0.706 |
| 25- < 50 AED | 0.7 | −1.8 | 3.3 | 0.572 |
| Mother work (reference: no) | | | | |
| Yes | 0.4 | −1.1 | 1.9 | 0.611 |
| Frequency of use (reference: infrequent) | | | | |
| Frequent | −0.9 | −2.5 | 0.6 | 0.234 |
| Look for healthy food (reference: no) | | | | |
| Yes | 2.7 | 0.7 | 4.7 | **0.008** |
| Sometimes | 1.1 | −0.5 | 2.8 | 0.187 |

CI, Confidence interval; *p*-values based on a 5% level of significance following general linear model analyses; Dependent variable: Score %. Bold values represent significant values based on a $p < 0.05$.

up to twice as much as unhealthy food (40). When adolescents buy their food, individual budgetary limitations might influence their food choices, with many food selections being based on meal deals or special food offers (39).

A study published by Fleming et al., including over 600 adolescents from 18 countries globally, revealed that while adolescents were somewhat aware of what a healthy diet is, several factors shape their food options and compromise their intake. Identified factors included

taste, cost, and availability of healthy food options which remain barriers limiting their ability to make informed choices (41). Therefore, understanding these food choice drivers may help promote healthy food intake and limit the tendency toward unhealthy food options.

Research shows that adolescents perceive healthy eating to encompass moderation, balance, and variety (42). Perceptions of a healthy meal varied in the present study, with almost half of the participants associating healthiness with low fat, low calories, a variety of vegetables, and rich in protein. On the other hand, perceptions of small portion sizes and low carbohydrates as indicators of healthiness were less reported by our participants. These findings highlight the variable comprehension regarding healthy food among adolescent OFDA users, underscoring the importance of connecting how consumers view healthy eating and investigating their subsequent behaviors to advocate for improved dietary quality (43). Moreover, future research should also look into how adolescents perceive their body weight, which may impact how they eat and their food choices (44, 45).

In this study, perceptions of healthy food on OFDA were investigated, and the findings revealed that almost half of the participants agreed that it is difficult to find healthy options and that their food intake and eating habits have changed after using these apps. The findings point out the well-established lack of availability and the visibility of healthy options through these apps (33, 46).

Further analysis in our study revealed that actively seeking healthy food may positively impact perceptions of healthy food. Therefore, boosting the visibility and the number of healthy food options and implementing calorie declaration beside food items could be effective strategies to enhance the healthiness of people's food options. Moreover, educating the public on healthy eating can help mitigate the adverse impacts on eating habits associated with using these apps (37, 47). Moreover, in the present study, certain factors, such as older age, less frequent usage, and looking for healthy food options, aligned with a more positive perception of healthy food on OFDA. This suggests that with age, adolescents may gain a better understanding of healthy eating. In addition, given that less frequent users had more positive perceptions of healthy food on these platforms, calling for highlighting the negative impacts of frequent consumption of food away from home and the increased exposure to mostly nutrient-poor and energy-dense foods that may distort their perceptions of healthy food on these apps (48).

In this study, participants mostly agreed on the importance of the temperature of food when delivered as an indicator of the quality and safety of food and the importance of the driver's cleanliness and demeanor on their perception of the food's hygiene. These findings highlight the importance of these food delivery hygiene aspects among adolescents, consistent with other studies showing that consumers are concerned about these issues when eating away from home (49, 50). Further analysis in this study revealed that females and those who actively look for healthy options had higher food safety perception scores regarding food safety and hygiene. These findings are supported by research showing that females tend to be more aware and vigilant when choosing safe and hygienic restaurants (51). Moreover, from a restaurant/provider perspective, guaranteeing adherence to food safety regulations and translating this into all food delivery stages can help increase consumers' trust and recurring ordering (52).

The use of OFDA is becoming more prevalent, with increased use among the youth, given the advancements in technology and current ease of accessibility, raising concerns regarding their potential impact on public health outcomes and their alignment with Sustainable Development Goals (SDGs). While direct evidence linking OFDA to health and nutrition outcomes remains scarce, these platforms play an indirect role by providing convenient access to food (53). Existing research emphasizes the importance of examining the relationship between OFDA and the prevalence of non-communicable diseases (NCDs). Studies have revealed that many menu items available on OFDA fail to meet recommendations for healthy eating, with high levels of saturated fats, trans-fats, free sugars, and salt posing risks for NCDs (46, 54). Concerns are further raised by evidence showing that food options from OFDA tend to contain significantly more calories compared to retail products, potentially contributing to overconsumption and subsequent weight gain (20, 21). Moreover, from an environmental perspective, food ordered from OFDA often comes with high amounts of plastic packaging, such as containers, utensils, and bags, which are disposable and demand considerable energy and resources for production, transportation, and disposal contributing to environmental harm (55–57). However, amidst these concerns, to pave the way toward creating healthier digital food environments, it is suggested that these platforms provide and promote the purchasing of healthy and sustainable food options (58). In addition, researchers suggest collaborative efforts involving reforms in the food industry, coordinated public health communication, and ongoing monitoring of the expanding influence of OFDA could contribute to addressing various interconnected issues such as sustainability, environmental health, and health (59).

To our knowledge, this is the first study to investigate the trends of OFDA usage among adolescent users and their perceptions of healthy food ordering. Despite the cross-sectional design being suitable to fulfill the study objectives, several limitations should be acknowledged. The use of a self-reported questionnaire may lead to social desirability bias or misreporting of data. Moreover, the use of convenience sampling due to difficulties in accessing and recruiting this specific subset of adolescents within a limited timeframe may have limited the generalizability of findings beyond the subset of adolescents who already use OFDA regularly, potentially introducing sampling bias. In addition, the responses were dependent on voluntary participation, which may have led to variations in the representativeness of the different emirates. Moreover, the narrow focus on adolescents who use these apps more frequently may have limited the generalizability and understanding of OFDA use of the broader adolescent population in the country.

## 5 Conclusion

The study highlights the challenges in healthy food accessibility and the use of OFDA among young users. The findings highlight unfavorable food choices among adolescent users, with appearance and price as the main drivers for food choices. It also sheds light on their perceptions of healthy food and their concerns regarding healthy food ordering. These findings highlight critical links between OFDA usage patterns, food choice motivations, and views among adolescents, pushing for tailored interventions to promote healthier food choices and improve food safety perceptions. To date, the actual impact of

OFDA on health remains unclear. However, research is focusing on the digital food environment and how it can be used to improve people's dietary habits and overall well-being. Moreover, a holistic and sustainable approach is necessary, considering the SDGs, current environmental and economic constraints, and the complex influences on behavior. Collaboration among OFDA platforms, food vendors, and regulators can promote the availability of healthy, sustainable options, incentivize eco-friendly practices, and implement pricing strategies to enhance affordability. Education campaigns and regulatory measures can raise awareness and create a supportive environment for healthy choices. Ultimately, ongoing research and evaluation efforts are essential to understand the long-term impacts of these interventions and ensure their effectiveness in promoting sustainable dietary behaviors among adolescents.

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://figshare.com/s/9471b272877522041f79.

## Ethics statement

The studies involving humans were approved by University of Sharjah Research Ethics Committee (REC-22-02-16-09-S). 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

SS: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. TO: Conceptualization, Methodology, Writing – review & editing. AA-J: Writing – review & editing. HH: Writing – review & editing. MH: Writing – review & editing. MM: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SQ: Investigation, Writing – review & editing. HS: Writing – review & editing. RD: Investigation, Writing – review & editing. RR: Investigation, Writing – review & editing. EM: Formal analysis, Writing – review & editing. LS: Writing – review & editing. DP: Writing – review & editing. AZ: Writing – review & editing. AD: Writing – review & editing. HK: Investigation, Writing – original draft. LCI: Conceptualization, 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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# Associations of micronutrients and lipids with prediabetes and glycemic parameters in adolescent girls of the rural DERVAN cohort (DERVAN-9)

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**Background:** We investigated the associations of micronutrients and lipids with prediabetes, glycemic parameters, and glycemic indices among the adolescent girls of the DERVAN (aDolescent and prEconception health peRspectiVe of Adult Non-communicable diseases) cohort study from rural India.

**Methods:** We recruited 1,520 adolescent girls aged 16–18 years. We measured glycemic parameters (glucose, insulin and $HbA_1C$), lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides), and micronutrients (vitamin $B_{12}$, folate, and vitamin D). Prediabetes was defined using American Diabetes Association criteria (fasting glucose ≥100 mg/dL or HbA1C ≥5.7%). Glycemic indices (insulin resistance, insulin sensitivity, and β cell function) were calculated using the homeostasis model. Associations of prediabetes, glycemic parameters and glycemic indices with micronutrients and lipids were analyzed by multiple logistic regressions.

**Results:** The median age and Body Mass Index (BMI) were 16.6years and 17.6kg/$m^2$, respectively. Overall, 58% of girls had a low BMI. Median vitamin $B_{12}$, folate, and vitamin D concentrations were 249.0pg/mL, 6.1ng/mL, and 14.2ng/mL, respectively. The deficiencies observed were 32.1% for vitamin $B_{12}$, 11.8% for folate, and 33.0% for vitamin D. Median total cholesterol, LDL, HDL, and triglyceride concentrations were 148.0mg/dL, 81.5mg/dL, 50.8mg/dL, and 61.5mg/dL, respectively. Elevated total cholesterol, LDL, and triglycerides were observed in 4.8, 4.0, and 3.8%, respectively, while low HDL was observed in 12.8%. Prediabetes was observed in 39.7% of the girls. Among lipids, total cholesterol and LDL were higher in girls with prediabetes ($p$<0.01 for both). In a multivariate model containing cholesterol and vitamin $B_{12}$/folate/vitamin D, prediabetes was associated with high cholesterol. Prediabetes was also associated with high LDL, independent of folate and vitamin D. Poor insulin secretion was high in those with low vitamin $B_{12}$. Elevated insulin resistance was associated with low HDL. The likelihood of high insulin sensitivity was reduced in those with high triglycerides. The likelihood of poor β cell function was high in those with high LDL. Statistical interactions between micronutrients and lipids for prediabetes and glycemic outcomes were not significant.

**Conclusion:** There was a substantial deficiency of micronutrients and an absence of dyslipidemia. Our results indicate the need for lipid and micronutrient-based

interventions in adolescence to improve glycemic outcomes. Maintaining adequate storage of not only micronutrients but also lipids in adolescent girls is likely to reduce diabetes risk in adulthood.

KEYWORDS

micronutrients, lipids, prediabetes, undernutrition, India, adolescents, rural

## Introduction

Non-communicable diseases (NCDs) like diabetes and hypertension are on the rise in India (1). At the same time, the burden of cardiovascular diseases (CVD) is also increasing (2). An unhealthy diet, sedentary lifestyle, and substance abuse (smoking, tobacco chewing, and alcohol consumption) have been identified as major contributing factors. The rise in NCDs is very evident in urban India. Over the last few years, many rural communities have also started witnessing a rise, not only in CVD and coronary heart disease (CHD) (3, 4) but also in NCDs (5, 6). South Asians develop CHD earlier than white Caucasians (7). Lipid abnormalities have been identified as major risk factors for CVD as well as CHD (8, 9). The INTERHEART study (10) identified elevated levels of total cholesterol (CHOL) and low-density lipoprotein cholesterol (LDL) as risk factors for CHD in South Asians. Studies from India have shown increased CHOL levels not only in urban subjects but also in rural subjects (4, 11). According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, seeds of CHD, CVD, and NCDs are sown in early life, covering the intrauterine period as well as early childhood and adolescence (12–14). There are reports from Europe and China on early life undernutrition leading to dyslipidemia (15–17) as well as diabetes (18, 19) in adult life. Though dyslipidemia has been interconnected to the pathophysiology of CVD, it is also a modifiable dominant risk factor if detected early in life (20). Dyslipidemia is uncommon in adolescence, but if it exists then it is expected to intensify the risk of CVD in adulthood (21). Lipid levels in adolescence are known to strongly correlate with those in later life (22, 23). High levels of LDL and low levels of high-density lipoprotein cholesterol (HDL) in adolescence are precursors for atherosclerosis in adulthood (24). There are very few studies regarding undernutrition and dyslipidemia in Indian adolescents (25–27). Between the years 2016–18, the Indian government carried out a Comprehensive National Nutrition Survey (CNNS) of adolescents aged 10–19 years, covering the entire nation with a sample size of >35,000 (28). It found increased lipid burden (21) as well as prediabetes (29). Over the last decade, the role of undernutrition in the development of diabetes has also been under investigation (30–33). Also, there are many reports investigating the role of micronutrients, which are biomarkers of nutrition, in the development of NCDs, especially diabetes (34–36).

BKL Walawalkar Hospital was established in the year 1996 in the village of DERVAN situated in the coastal region of Konkan in the western Indian state of Maharashtra. Since its inception, women's health has been a prime area of interest. The hospital runs various holistic programs encompassing newborns, children, adolescent girls, newly married girls, and pregnant women. Comprehensive health education is provided, and various investigations are carried out. Counseling, holistic education, and medical treatment, if needed, are provided free of charge. Various hospital- and community-based cross-sectional, as well as observational, studies have demonstrated the presence of undernutrition across the entire life cycle (37–39). In addition, this region has also observed a rising prevalence of NCDs (diabetes and hypertension) (40). We have also demonstrated a high incidence of gestational diabetes among undernourished women in our region (41). This suggests an intergenerational link between an undernourished mother and her offspring.

The DERVAN cohort, a prospective longitudinal study of adolescent girls from the region, was set up in 2019 (42). Its objective was to test the hypothesis that poor physical growth and poor nutrition in adolescent girls increase the risk of NCDs, in particular the risk of diabetes in adulthood and in their offspring. Adolescent girls (16–18 years of age) were recruited between June 2019 and February 2023. The study is expected to continue for the next 20 years with an annual follow-up of adolescent girls.

Our recent report on this cohort showed a high prevalence of prediabetes (PD) among adolescent girls (43). Prediabetes precedes type 2 diabetes (T2D) and is marked by glucose levels above normal but below the diabetic threshold.

Baseline measurements of micronutrients, which are biomarkers of nutrition, as well as those of lipids, provided us the opportunity to investigate the role any of them may have in the development of PD in adolescence and diabetes in later life.

## Methods

The detailed protocol of the study is already reported (42). In short, 16–18-year-old adolescent girls born in Konkan, staying with parents with no history of any major illness (e.g., heart, kidney, liver disease, cancer, and psychiatric disorders), as well as with no history of mental, intellectual, or physical disability, were recruited. We recruited 1,520 girls at baseline. They were brought to the institute in groups of 5–7. They had an overnight stay at the hostel to ensure their fasting status. The detailed protocol for blood collection has already been reported (44).

Anthropometric measurements of height, weight, waist circumference, and hip circumference were made using a standardized protocol. Body fat was measured using a bioimpedance analyzer (MC-780, TANITA Corporation, Japan).

### Laboratory methods

A fasting blood sample was drawn from adolescent girls and further processed to measure micronutrients, lipids, and glycemic

parameters. Blood samples were centrifuged (4°C, 3,000 rpm, 15 min) within 1 h of collection and stored at −80°C for further investigations.

Blood glucose was measured on the ERBA 200, Trans Asia, Mumbai, India. The intra- and inter-batch coefficients of variation (CVs) were < 5%. HbA1c was measured using high performance liquid chromatography (Bio-Rad D10; Bio-Rad Laboratories, Hercules, CA, USA) calibrated against the National Glycosylated Standardization Program with a CV of 2.8%. Fasting insulin was measured on an Abbott Architect i1000SR with a CV of 2.0%. Vitamin $B_{12}$ (VitB12), folate, and vitamin D (VitD) were measured on the Abbott Architect i1000SR. The intra- and inter-batch CVs were 7.1% for VitB12, 7.7% for folate, and 5.3% for VitD. Total cholesterol, HDL, and triglycerides (TG) were measured on Trans Asia ERBA 200. The intra- and inter-batch CVs were 3.7% for CHOL, 5.2% for HDL, and 4.0% for TG.

## Calculations and classifications

Stunting and underweight (low Body Mass Index, BMI) were defined using World Health Organization (WHO) criteria (45) and thinness using International Obesity Task Force (IOTF) criteria (46), respectively. The Friedewald formula was used to calculate LDL (47). Prediabetes was defined using American Diabetic Association (ADA) criteria, i.e., fasting glucose ≥100 mg/dL or HbA1C ≥5.7% (48). Glycemic indices of insulin resistance (HOMa-IR), insulin sensitivity (HOMA-S) and beta cell function (HOMA-β) were estimated using the homeostasis model (49).

Elevated CHOL, LDL, and TG concentrations were defined as ≥ 200 mg/dL, ≥ 130 mg/dL, and ≥ 130 mg/dL, respectively, and low HDL was defined as < 40 mg/dL (28). Deficiency of vitB12 and folate was defined as <203 pg/mL and < 4.0 ng/mL (50), respectively. Deficiency of VitD was defined as <12 ng/mL (28).

## Statistical methods

Data has been represented by median and 25th–75th quartiles as well as by mean and standard deviation for continuous variables and by percentages for categorical variables. All the micronutrients (VitB12, folate, and VitD), lipids (CHOL, HDL, LDL, and TG), and all the glycemic variables (fasting glucose, fasting insulin, HOMA-IR, HOMA-S, and HOMA-β) were tested for normality. Except for fasting glucose, all the variables were skewed and appropriately transformed for normality. The transformation function to normalize was a natural logarithm for CHOL, HDL, TG, VitB12, HOMA-IR, and HOMA-S. The cube root function was used to normalize LDL and VitD. Folate and fasting insulin were normalized using hyperbolic arcsin functions. HOMA-β was normalized by subtracting the reciprocal of its square root from 1. Prediabetes, fasting insulin, and glycemic indices (HOMA-IR, HOMA-S, and HOMA-β) were treated as glycemic outcomes. Exposures refer to micronutrients (VitB12, VitD, and folate) and lipids (CHOL, LDL, HDL, and TG). Univariate associations between continuous glycemic outcomes and continuous exposures, as well as those between various continuous exposures (micronutrients and lipids), are shown by partial correlation. Comparison of exposures between normoglycemic and prediabetic girls was done by the analysis of variance for continuous and normally distributed exposures, by Mann–Whitney test for those not normally distributed and by chi-square test for those categorical. Prediabetes was a categorical outcome. Other categorical outcomes were defined using the presence of individuals in risk quartiles for each outcome. The risk quartiles for outcomes were the 1st quartile for fasting insulin and HOMA-β representing a group with poor insulin secretion and poor β cell function, respectively, and the 4th quartile for HOMA-IR and HOMA-S representing the most insulin resistant and most insulin-sensitive groups, respectively. We also categorized the exposures (micronutrients as well as lipids) by creating the quartiles of each exposure. The 4th quartile was used as a reference for VitB12, folate, and VitD, which represent high vitamin concentrations. Except for HDL, the 1st quartile was used as a reference for lipids (CHOL, LDL, and TG), representing low lipid levels. For HDL, the 4th quartile was used as a reference, indicating high or better HDL. Univariate as well as multivariate associations of the categorical outcomes with the categorical exposures were analyzed using logistic regression. Odds ratios (ORs) relative to the reference quartile for each exposure and 95% confidence intervals (CIs) for the outcomes were calculated. We also tested the interaction of various micronutrient and lipid exposures for various outcomes by including relevant product terms as appropriate. BMI representing the anthropometric markers of undernutrition and age of adolescent girls, was divided into quartiles and used as covariates. In the case of BMI, the 4th quartile was further divided into two groups: non-obese and overweight/obese, thus creating five groups. The overweight/obese group was treated as the reference. We also carried out the analysis for prediabetes using micronutrients and lipids as scale variables. Two-tailed significance was calculated at a 5% level. Analysis was performed using Statistical Package for the Social Sciences (SPSS) 25.0 and STATA 11.0 (STATA, College Station, TX, USA).

## Ethics

The study was approved by the Institute Ethics Committee of BKL Walawalkar Rural Medical College and Hospital. The committee is registered with the Department of Health Research (DHR), Government of India, with registration number EC/NEW/INST/2023/MH/0361. Appropriate written informed consent was obtained from those who were 18 years old at the time of the recruitment. For those below 18 years of age, written informed consent was obtained from the parents of the adolescent girl, and written informed ascent was obtained from the adolescent girl.

# Results

We recruited 1,520 adolescent girls in the cohort. Body composition measurements were done on 1,400 girls. Of this, five girls were diagnosed with diabetes. Out of the remaining normoglycemic ($n = 1,395$) cases, lipid and micronutrient measurements were available on 1,387 girls. Our final sample number for the data analysis is 1,387.

Anthropometry, body composition, micronutrients, lipids, and glycemia (Table 1).

The median age of the subjects was 16.6 years. Median height, weight, BMI, waist circumference, hip circumference, and waist circumference to hip circumference ratio were 151.7 cm, 40.7 kg,

TABLE 1 Anthropometry, body composition, micronutrients, lipids, and glycemia in adolescent girls ($n = 1,387$).

| Parameters | Median (25th – 75th percentile) or n (%) | Mean (SD) |
|---|---|---|
| Body composition | | |
| Age (yrs) | 16.6 (15.8–17.3) | 16.6 (0.9) |
| Height (cm) | 151.7 (148.2–155.6) | 151.8 (5.5) |
| Stunted[$] | **421 (30.4)** | |
| Weight (kg) | 40.7 (36.7–46.0) | 42.1 (8.1) |
| Underweight[$] | **400 (28.8)** | |
| BMI (kg/m$^2$) | 17.6 (16.0–19.8) | 18.2 (3.3) |
| **Thinness[@] (< − 1 SD)** | **805 (58.0)** | |
| **Overweight/obese[@] (> + 1 SD)** | **60 (4.3)** | |
| Waist circumference (cm) | 62.2 (58.5–67.2) | 63.5 (7.3) |
| Hip circumference (cm) | 83.2 (79.6–87.9) | 84.2 (7.1) |
| WHR | 0.75 (0.72–0.78) | 0.75 (0.05) |
| Fat mass (kg) | 8.9 (6.7–12.3) | 10.2 (5.3) |
| Body fat % | 22.5 (18.6–27.7) | 23.4 (6.9) |
| **Body fat % > 25** | **504 (36.3)** | |
| Lean mass (kg) | 29.5 (27.4–31.6) | 29.6 (3.2) |
| **Vitamins** | | |
| VitB12 (pg/mL) | 249.0 (182.5–340.1) | 287.3 (155.9) |
| **VitB12 < 203 pg/mL** | **445 (32.1)** | |
| Folate (ng/mL) | 6.1 (4.7–7.8) | 6.5 (2.6) |
| **Folate < 4 ng/mL** | **164 (11.8)** | |
| VitD (ng/mL) | 14.2 (10.8–17.4) | 14.6 (5.3) |
| **VitD ≤ 12 ng/mL** | **462 (33.3)** | |
| **Lipids** | | |
| CHOL (mg/dL) | 148.0 (131.0–165.0) | 149.9 (27.3) |
| **CHOL ≥ 200 mg/dL** | **66 (4.8)** | |
| LDL (mg/dL) | 81.5 (68.5–98.6) | 84.5 (23.6) |
| **LDL ≥ 130 mg/dL** | **55 (4.0)** | |
| HDL (mg/dL) | 50.8 (43.9–58.5) | 51.7 (10.9) |
| **HDL < 40 mg/dL** | **177 (12.8)** | |
| TG (mg/dL) | 61.5 (47.0–82.7) | 68.5 (29.6) |
| **TG ≥ 130 mg/dL** | **53 (3.8)** | |
| **Glycemia** | | |
| Fasting glucose (mg/dL) | 95.4 (88.9–101.6) | 95.1 (9.8) |
| **IFG** | **433 (31.2)** | |
| $HbA_1C$ (%) | 5.3 (5.0–5.5) | 5.2 (0.4) |
| **Elevated $HbA_1C$** | **191 (13.8)** | |
| **Prediabetes** | **551 (39.7)** | |
| Fasting insulin (μIU/mL) | 8.6 (6.9–11.1) | 9.3 (3.8) |
| HOMA-IR | 1.2 (0.9–1.5) | 1.2 (0.5) |
| HOMA-S | 86.0 (66.5–108.5) | 90.8 (36.3) |
| HOMA-β | 94.5 (79.4–113.6) | 100.4 (33.3) |

[$]As per WHO (36); [@]As per IOTF (International Obesity Task Force) (37); WHR, waist circumference to hip circumference ratio; SD, Standard Deviation; IFG, Impaired Fasting Glucose (fasting glucose ≥ 100 mg/dL); elevated $HbA_1C$ (>5.7%).

17.6 kg/m$^2$, 62.2 cm, 83.2 cm, and 0.75, respectively. Using the WHO standard, 30.4% of girls were found to be stunted, and 28.8% were underweight. Using the IOTF standard, 58% were thin. Median body fat% was 22.5 and 36.3% girls had body fat% > 25. Median concentrations of VitB12, folate, and VitD were 249.0 pg/mL, 6.1 ng/mL, and 14.2 ng/mL, respectively. Deficiencies of VitB12, folate, and VitD were observed in 32.1, 11.8, and 33.3%, respectively. Median levels of CHOL, LDL, HDL, and TG were 148.0 mg/dL, 81.5 mg/dL, 50.8 mg/dL, and 61.5 mg/dL, respectively. Elevated levels were observed in 4.8% of CHOL, 4.0% of LDL, and 3.8% of TG. Low HDL was observed in 12.8%. Median concentrations of fasting glucose and fasting insulin were 95.4 mg/dL and 8.6 μIU/ml, respectively. Median values for glycemic indices were 1.2, 86.0, and 94.5 for HOMA-IR, HOMA-S, and HOMA-β, respectively. Prediabetes was observed in 39.7% of girls.

Micronutrients, lipids, and prediabetes (Table 2).

We compared micronutrient concentrations and lipids between prediabetic and normoglycemic girls. Among lipids, CHOL and LDL were higher in girls with PD ($p < 0.01$) for CHOL and ($p < 0.001$) for LDL.

Univariate and continuous associations of micronutrients and lipids with glycemic outcomes and BMI (Supplementary Table 1).

Folate was inversely associated with fasting insulin, HOMA-IR ($p < 0.05$ for both), and HOMA-β ($p < 0.001$). Total cholesterol and LDL were positively associated with fasting glucose ($p < 0.05$ for both). Total cholesterol, LDL, and TG were positively associated with fasting insulin and HOMA-IR and inversely with HOMA-S ($p < 0.01$ for all). HDL was inversely associated with fasting insulin and HOMA-IR and positively with HOMA-S ($p < 0.001$) for all. Triglyceride was positively associated with HOMA-β and HDL was inversely associated ($p < 0.001$ for both). All three micronutrients and HDL were inversely associated with BMI, and CHOL, LDL and TG were positively associated.

Univariate and continuous associations between micronutrients and lipids (Supplementary Table 2).

Vitamin $B_{12}$ was positively associated with CHOL, LDL, and HDL but inversely with TG ($p < 0.001$ for all). Folate was inversely associated with LDL ($p < 0.001$) and positively with HDL ($p < 0.05$). Vitamin D was inversely associated with both CHOL and LDL ($p < 0.01$ for both).

Univariate analysis of micronutrients, lipids, BMI, and age as predictors of glycemic outcomes (Table 3).

We carried out univariate logistic regressions using quartiles of each micronutrient and each lipid parameter, as well as 5 groups of increasing BMI and quartiles of age with PD and risk quartiles of fasting insulin and glycemic indices as outcomes.

Prediabetes: The OR for the 2nd quartile of VitB12 and the 3rd quartile of VitD were significantly reduced (<1) to the upper quartile, representing relatively high levels of respective vitamins. Among lipids, PD was predicted by high CHOL (4th quartile) and high LDL (2nd and 3rd quartiles) to the 1st quartile, representing low levels of respective lipids. There was no association of PD with HDL and TG.

Poor insulin secretion (1st quartile of fasting insulin): Having poor insulin secretion was associated inversely with high CHOL (4th quartile), low HDL (1st quartile), and high TG (3rd and 4th quartiles), with the 1st quartile representing low levels of CHOL, TG, and the 4th quartile representing high HDL. The OR for poor insulin secretion increased with decreasing BMI. Those who were the oldest (4th quartile) had a higher likelihood of poor insulin secretion than those who were the youngest.

TABLE 2 Micronutrients and lipids between girls with PD and normoglycemia ($n = 1,387$).

| Parameters | PD ($n = 551$) | Normal ($n = 836$) | $p$ value |
|---|---|---|---|
| Micronutrients | | | |
| VitB12 (pg/mL) | 256.0 (183.0–362.0) | 244.9 (182.0–333.0) | 0.118 |
| <203 pg/mL | 170 (30.9) | 275 (32.9) | 0.425 |
| Folate (ng/mL) | 6.0 (4.7–7.8) | 6.1 (4.7–7.7) | 0.877 |
| <4 ng/mL | 63 (11.4) | 101 (12.1) | 0.715 |
| VitD (ng/mL) | 14.0 (10.6–17.8) | 14.2 (10.9–17.0) | 0.952 |
| ≤12 ng/mL | 189 (34.3) | 273 (32.7) | 0.525 |
| Lipids | | | |
| CHOL (mg/dL) | 150.0 (132.0–169.0) | 146.8 (130.0–164.0) | 0.013* |
| ≥200 mg/dL | 30 (5.4) | 36 (4.3) | 0.330 |
| LDL (mg/dL) | 85.1 (70.1–100.6) | 79.8 (67.5–96.9) | 0.004* |
| ≥130 mg/dL | 26 (4.7) | 29 (3.5) | 0.243 |
| HDL (mg/dL) | 51.2 (43.3–58.5) | 50.6 (44.1–58.4) | 0.855 |
| <40 mg/dL | 74 (13.4) | 103 (12.3) | 0.545 |
| TG (mg/dL) | 63.7 (47.7–84.3) | 60.7 (46.3–82.3) | 0.199 |
| ≥130 mg/dL | 26 (4.7) | 27 (3.2) | 0.157 |

Median (25th – 75th percentile) or $n$ (%); *statistically significant ($p < 0.05$) by Man–Whitney Test for non-normal variables and chi-square test for categorical variables.

Most insulin resistant (4th quartile of HOMA-IR): Among micronutrients, being most insulin resistant was inversely associated with folate (3rd quartile) and directly with VitD (2nd quartile). Among lipids, being most insulin resistant was associated with high CHOL (4th quartile), high LDL (2nd, 3rd, and 4th quartiles) low HDL (1st quartile), and high TG (3rd and 4th quartiles). The OR for being most insulin resistant decreased with decreasing BMI. Those who were oldest (4th quartile) had less likelihood of having most insulin resistance than those who were younger.

Most insulin sensitive (4th Quartile of HOMA-S): Protective associations were observed for high CHOL (4th quartile), low HDL (1st quartile), and high TG (3rd and 4th quartiles). The decreasing BMI increased the OR for being highly insulin sensitive. Those who were the oldest (4th quartile) had a high likelihood of being most insulin sensitive.

Poor β cell function (1st Quartile of HOMA-β): Poor β cell function was associated protectively with low folate (2nd and 1st quartile), low HDL (2nd and 1st quartile), and high TG (4th quartile). The OR for poor β cell function increased with decreasing BMI. Those who were the oldest (4th quartile) had a high likelihood of poor β cell function.

Multivariate analysis of micronutrients and lipids as predictors of glycemic outcomes.

We ran logistic regression models for each glycaemic outcome, containing a single micronutrient (VitB12/folate/VitD) and a single lipid (CHOL/LDL/HDL/TG) as independent variables and BMI and age as covariates. Thus, for each of the 3 micronutrients, 4 lipids, and 5 glycaemic outcomes, we ran 4 models for each of the 5 glycaemic outcomes. We also included relevant micronutrient and lipid interaction terms in the analysis.

Vitamin $B_{12}$ and lipids as predictors of PD (Table 4).

In Model-M1 containing CHOL, PD was independently associated only with relatively high CHOL (4th quartile). In the remaining 3 models (M2, M3, and M4) containing each of the remaining lipids, PD was associated with only VitB12 (2nd quartile) and that too with protective effects (ORs < 1).

Folate and lipids as predictors of PD (Table 5).

In Model-1 containing CHOL, PD was independently associated only with relatively high cholesterol (4th quartile). In the remaining models, there was an independent association of PD only with relatively high LDL (3rd and 4th quartiles) in Model-2.

Vitamin D and lipids as predictors of PD (Table 6).

In all 4 models, PD was independently associated with VitD (3rd quartile) and protective OR. PD was also independently associated with high cholesterol (4th quartile) in Model-1 and with high LDL (3rd and 4th quartiles) in Model-2.

We repeated the analysis described in Tables 4–6 for the remaining glycemic outcomes, i.e., poor insulin secretion, being most insulin resistant, being most insulin sensitive, and having poor β cell function. We have summarized these in Supplementary Tables 3–5 containing vitamin $B_{12}$, folate, and vitamin D, respectively.

Vitamin $B_{12}$ and lipids as predictors of poor insulin secretion (Supplementary Table 3).

Having poor insulin secretion was independently associated with poor VitB12 status (1st quartile) in all 4 models. The ORs were significant and >1 in all. Additionally, in Model-4 containing TG, there was also an independent association with elevated TG (4th quartile), but the effect was protective as OR was significant and <1.

Folate and lipids as predictors of poor insulin secretion (Supplementary Table 4).

Only in Model-4 containing TG was there an independent association with elevated TG (4th quartile), but the effect was protective as OR was significant and <1.

Vitamin D and lipids as predictors of poor insulin secretion (Supplementary Table 5).

Only in Model-4 containing TG was there an independent association with elevated TG (4th quartile), but the effect was protective as OR was significant and <1.

Vitamin $B_{12}$ and lipids as predictors of being most insulin resistant (Supplementary Table 3).

The only association observed was in Model-3 with low HDL (1st quartile), and the OR was significant and >1.

Folate and lipids as predictors of being most insulin resistant (Supplementary Table 4).

There was a protective effect of low folate (3rd quartile) in all 4 models, as ORs were significant and <1. Additionally, there was a positive effect of low HDL (1st quartile) in Model-3.

Vitamin D and lipids as predictors of being most insulin resistant (Supplementary Table 5).

The only significant positive effect observed was that of low HDL (1st quartile) in Model-3.

Vitamin $B_{12}$ and lipids as predictors of being most insulin sensitive (Supplementary Table 3).

Only in Model-4, a significant but protective effect of high TG (4th quartile) was observed.

Folate and lipids as predictors of being most insulin sensitive (Supplementary Table 4).

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TABLE 3 Association of PD and other glycemic outcomes with micronutrients, lipids, BMI, and age (univariate logistic regressions).

| Exposures ↓ | Prediabetes | Poor insulin secretion (Q1 of fasting insulin) | High HOMA-IR (Q4 of insulin resistance) | High HOMA-S (Q4 of insulin sensitivity) | Poor HOMA-β (Q1 of β cell function) |
|---|---|---|---|---|---|
| VitB12 Q1 | NS | NS | NS | NS | NS |
| Q2 | 0.708 (0.522–0.960) 0.026 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS | NS |
| Q4 (ref) | 1 | 1 | 1 | 1 | 1 |
| Folate Q1 | NS | NS | NS | NS | 0.705 (0.499–0.997) 0.048 |
| Q2 | NS | NS | NS | NS | 0.710 (0.506–0.996) 0.047 |
| Q3 | NS | NS | 0.602 (0.410–0.884) 0.010 | NS | NS |
| Q4 (ref) | 1 | 1 | 1 | 1 | 1 |
| VitD Q1 | NS | NS | NS | NS | NS |
| Q2 | NS | NS | 1.494 (1.050–2.127) 0.026 | NS | NS |
| Q3 | 0.687 (0.506–0.933) 0.016 | NS | NS | NS | NS |
| Q4 (ref) | 1 | 1 | 1 | 1 | 1 |
| CHOL Q4 | 1.513 (1.117–2.049) 0.008 | 0.626 (0.438–0.895) 0.010 | 1.661 (1.163–2.373) 0.005 | 0.564 (0.396–0.805) 0.002 | NS |
| Q3 | NS | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 | 1 |
| LDL Q4 | NS | NS | 1.915 (1.329–2.735) 0.000 | NS | NS |
| Q3 | 1.379 (1.016–1.872) 0.039 | NS | 1.554 (1.070–2.255) 0.020 | NS | NS |
| Q2 | 1.412 (1.041–1.916) 0.027 | NS | 1.251 (0.853–1.835) 0.251 | NS | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 | 1 |
| HDL Q1 | NS | 0.640 (0.452–0.906) 0.012 | 1.902 (1.320–2.740) 0.001 | 0.684 (0.484–0.966) 0.031 | 0.668 (0.475–0.941) 0.029 |
| Q2 | NS | NS | NS | NS | 0.706 (0.502–0.993) 0.045 |
| Q3 | NS | NS | NS | NS | NS |

*(Continued)*

TABLE 3 (Continued)

| Exposures ↓ | Prediabetes | Poor insulin secretion (Q1 of fasting insulin) | High HOMA-IR (Q4 of insulin resistance) | High HOMA-S (Q4 of insulin sensitivity) | Poor HOMA-β (Q1 of β cell function) |
|---|---|---|---|---|---|
| Q4 (ref) | 1 | 1 | 1 | 1 | 1 |
| TG Q4 | NS | 0.370 (0.254–0.537) 0.000 | 1.934 (1.351–2.767) 0.000 | 0.380 (0.263–0.549) 0.000 | 0.612 (0.428–0.874) 0.007 |
| Q3 | NS | 0.645 (0.461–0.904) 0.011 | 1.539 (1.066–2.220) 0.021 | 0.580 (0.413–0.815) 0.002 | NS |
| Q2 | NS | NS | NS | NS | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 | 1 |
| BMI Q1 | NS | 36.393 (4.983–265.798) 0.000 | 0.047 (0.025–0.091) 0.000 | 36.840 (5.044–269.059) 0.000 | 33.791 (4.626–246.852) 0.001 |
| Q2 | NS | 27.021 (3.696–197.566) 0.001 | 0.078 (0.041–0.146) 0.000 | 27.384 (3.746–200.208) 0.001 | 24.224 (3.311–177.214) 0.002 |
| Q3 | NS | 15.719 (2.142–115.372) 0.007 | 0.096 (0.052–0.179) 0.000 | 16.268 (2.217–119.365) 0.006 | 18.844 (2.572–138.091) 0.004 |
| Q4 – Normal | NS | NS | 0.235 (0.128–0.433) 0.000 | NS | 8.462 (1.137–62.975) 0.037 |
| Q4 – ovwt/obese (ref) | 1 | 1 | 1 | 1 | 1 |
| Age Q4 | NS | 1.686 (1.193–2.383) 0.003 | 0.638 (0.458–946) 0.024 | 1.709 (1.210–2.414) 0.002 | 1.550 (1.108–2.169) 0.010 |
| Q3 | NS | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 | 1 |

Values represent OR with 95% CI and an exact *p* value (<0.05); NS: Statistically not significant; Q1, Q2, Q3, and Q4 are quartiles of respective exposures; ovwt: Overweight; BMI Q4 is further divided into two groups: those with a normal BMI and those who are overweight/obese; ref: reference.

: represents the odds ratio < 1.

: represents the odds ratio > 1.

The protective effect of high CHOL (4th quartile) in Model-1 was observed. A significant but protective effect of high TG (4th quartile) was also observed in Model-4.

Vitamin D and lipids as predictors of being most insulin sensitive (Supplementary Table 5).

The protective effect of high CHOL (4th quartile) and high TG (4th quartile) was observed in Model-1 and Model-4, respectively.

Vitamin $B_{12}$ and lipids as predictors of poor β cell function (Supplementary Table 3).

There was a positive effect of high LDL (4th quartile) in Model-2 and a protective effect of low HDL (2nd quartile) in Model-3.

Folate and lipids as predictors of poor β cell function (Supplementary Table 4).

Folate (2nd quartile) had a protective effect on poor β cell function in all models. There was a positive effect of high LDL (4th quartile) in Model-2 and a protective effect of low HDL (2nd quartile) in Model-3.

Vitamin D and lipids as predictors of poor β cell in Model-3 function (Supplementary Table 5).

The likelihood of poor β cell function was not associated with any of the lipids.

Interactions of micronutrients and lipids with prediabetes, poor insulin secretion, and glycemic indices.

None of the interactions between each micronutrient and each lipid were found to be statistically significant for PD and other glycemic outcomes.

We also carried out multivariate logistic regression of PD, including independent variables such as lipids and micronutrients as scale variables (Supplementary Tables 6–8) without using quartiles. The results were very similar. Prediabetes was associated with CHOL and LDL.

## Discussion

We have reported micronutrients (VitB12, folate, and VitD) and lipid levels (CHOL, LDL, HDL, and TG) in 16–18 year-old adolescent girls of the DERVAN cohort. Among micronutrients, more than

TABLE 4 Multivariate association of PD with vitamin $B_{12}$ and lipids with BMI and age as covariates (logistic regression).

| Outcomes → | Prediabetes | | | |
|---|---|---|---|---|
| Exposures ↓ | $M_1$ | $M_2$ | $M_3$ | $M_4$ |
| VitB12 Q1 | NS | NS | NS | NS |
| Q2 | NS | 0.732 (0.538–0.996) 0.047 | 0.708 (0.521–0.962) 0.027 | 0.697 (0.514–0.947) 0.021 |
| Q3 | NS | NS | NS | NS |
| Q4 (ref) | 1 | 1 | 1 | 1 |
| CHOL Q4 | 1.45 (1.06–1.98) 0.020 | | | |
| Q3 | NS | | | |
| Q2 | NS | | | |
| Q1 (ref) | 1 | 1 | 1 | 1 |
| LDL Q4 | | NS | | |
| Q3 | | NS | | |
| Q2 | | NS | | |
| Q1 (ref) | 1 | 1 | 1 | 1 |
| HDL Q1 | | | NS | |
| Q2 | | | NS | |
| Q3 | | | NS | |
| Q4 (ref) | 1 | 1 | 1 | 1 |
| TG Q4 | | | | NS |
| Q3 | | | | NS |
| Q2 | | | | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 |
| BMI Q1 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS |
| Q4 – Normal | NS | NS | NS | NS |
| Q4 – ovwt/obese (ref) | 1 | 1 | 1 | 1 |
| age Q4 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 |

Values represent OR with 95% CI and an exact $p$ value (<0.05); NS: Statistically not significant; Q1, Q2, Q3, and Q4 are quartiles of respective exposures; ovwt: Overweight; BMI Q4 is further divided into two groups: those with a normal BMI and those who are overweight/obese; ref: reference.
$M_1$: Model-1 (VitB12, CHOL, BMI and age).
$M_2$: Model-2 (VitB12, LDL, BMI and age).
$M_3$: Model-3 (VitB12, HDL, BMI and age).
$M_4$: Model-4 (VitaB12, TG, BMI and age).
: represents the odds ratio < 1.
: represents the odds ratio > 1.
: variable not in the model.

TABLE 5 Multivariate association of PD with folate and lipids with BMI and age as covariates (logistic regression).

| Outcomes → | Prediabetes | | | |
|---|---|---|---|---|
| Exposures ↓ | $M_1$ | $M_2$ | $M_3$ | $M_4$ |
| Folate Q1 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS |
| Q4 (ref) | 1 | 1 | 1 | 1 |
| CHOL Q4 | 1.507 (1.106–2.052) 0.009 | | | |
| Q3 | NS | | | |
| Q2 | NS | | | |
| Q1 (ref) | 1 | | | |
| LDL Q4 | | 1.140 (1.026–1.911) 0.034 | | |
| Q3 | | 1.382 (1.015–1.881) 0.040 | | |
| Q2 | | NS | | |
| Q1 (ref) | | 1 | | |
| HDL Q1 | | | NS | |
| Q2 | | | NS | |
| Q3 | | | NS | |
| Q4 (ref) | | | 1 | |
| TG Q4 | | | | NS |
| Q3 | | | | NS |
| Q2 | | | | NS |
| Q1 (ref) | | | | 1 |
| BMI Q1 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS |
| Q4 – Normal | NS | NS | NS | NS |
| Q4 – ovwt/obese (ref) | 1 | 1 | 1 | 1 |
| Age Q4 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 |

Values represent OR with 95% CI and an exact $p$ value (<0.05); NS: Statistically not significant; Q1, Q2, Q3, and Q4 are quartiles of respective exposures; ovwt: Overweight; BMI Q4 is further divided into two groups: those with a normal BMI and those who are overweight/obese; ref: reference.
$M_1$: Model-1 (Folate, CHOL, BMI, and age).
$M_2$: Model-2 (Folate, LDL, BMI, and age).
$M_3$: Model-3 (Folate, HDL, BMI, and age).
$M_4$: Model-4 (Folate, TG, BMI, and age).
: represents the odds ratio < 1.
: represents the odds ratio > 1.
: variable not in the model.

TABLE 6 Multivariate association of PD with vitamin D and lipids with BMI and age as covariates (logistic regression).

| Outcomes → | Prediabetes | | | |
|---|---|---|---|---|
| Exposures ↓ | $M_1$ | $M_2$ | $M_3$ | $M_4$ |
| VitD Q1 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q3 | 0.669 (0.491–0.911) 0.011 | 0.667 (0.493–0.909) 0.010 | 0.671 (0.493–0.913) 0.011 | 0.664 (0.487–0.904) 0.009 |
| Q4 (ref) | 1 | 1 | 1 | 1 |
| CHOL Q4 | 1.523 (1.117–2.017) 0.008 | | | |
| Q3 | NS | | | |
| Q2 | NS | | | |
| Q1 (ref) | 1 | | | |
| LDL Q4 | | 1.405 (1.028–1.920) 0.033 | | |
| Q3 | | 1.403 (1.029–1.910) 0.032 | | |
| Q2 | | NS | | |
| Q1 (ref) | | 1 | | |
| HDL Q1 | | | NS | |
| Q2 | | | NS | |
| Q3 | | | NS | |
| Q4 (ref) | | | 1 | |
| TG Q4 | | | | NS |
| Q3 | | | | NS |
| Q2 | | | | NS |
| Q1 (ref) | | | | 1 |
| BMI Q1 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS |
| Q4: Normal | NS | NS | NS | NS |
| Q4: ovwt/obese (ref) | 1 | 1 | 1 | 1 |
| age Q4 | NS | NS | NS | NS |
| Q3 | NS | NS | NS | NS |
| Q2 | NS | NS | NS | NS |
| Q1 (ref) | 1 | 1 | 1 | 1 |

Values represent OR with 95% CI and an exact *p* value (<0.05); NS: Statistically not significant; Q1, Q2, Q3, and Q4 are quartiles of respective exposures; ovwt: Overweight; BMI Q4 is further divided into two groups: those with a normal BMI and those who are overweight/obese; ref: reference.
$M_1$: Model-1 (VitD, CHOL, BMI, and age).
$M_2$: Model-2 (VitD, LDL, BMI, and age).
$M_3$: Model-3 (VitD, HDL, BMI, and age).
$M_4$: Model-4 (VitD, TG, BMI, and age).

: represents the odds ratio < 1.

: represents the odds ratio > 1.

: variable not in the model.

1/3rd of girls were deficient in VitB12 and VitD. This was very similar to those reported in a national survey of adolescents (28). Folate deficiency was very low. Elevated CHOL, LDL, and TG were observed in <5%, but low HDL was observed in 12.8%. This was despite household chores and walking long distances to school (51). The prevalence of PD was close to 40%. Abnormality in lipids using the conventional cutoffs was itself very low. Prediabetes was not associated with micronutrient deficiencies when we used conventional cutoffs. Unlike other reports from India (21), the proportion of lipid abnormalities between prediabetics and normal was similar and very low. Cutoffs for micronutrient deficiencies are also facing challenges in Indian settings (52). Hence, we decided to use a quartile approach for both sets of exposures to test the associations of glycemic outcomes with micronutrients as well as lipid exposures. Other than PD, there are no specific cutoffs for insulin and various glycemic indices; hence, we also categorized all the outcomes other than PD as belonging to either the lowest or highest quartiles.

In the multivariate analysis using a quartile approach, relatively low VitB12 and VitD status were protective against PD. Among lipids, the likelihood of PD was high in those with relatively high CHOL, and it was much stronger in those with relatively high LDL. The likelihood of poor insulin secretion increased in those with relatively low VitB12, while it decreased in those with relatively high TG. Relatively low folate status was protective against high insulin resistance, while a high likelihood of insulin resistance was observed in those with relatively low HDL. Those with relatively high TG were less likely to have high insulin sensitivity, and those with relatively high LDL and low HDL were more likely to have poor β cell function. It is noteworthy that despite the very low prevalence of those with abnormal CHOL and LDL, there was still a graded association of PD with those having relatively high CHOL and LDL, independent of all three micronutrients.

Interactions between micronutrients and lipids have been reported for PD in another report from India on school-going young children of 5–9 years of age (53). It found significant interaction probabilities for PD among those with VitB12 deficiency with high CHOL, Sufficient VitD with high CHOL, and high VitD with high LDL. We used the odds ratio approach and found high likelihood of PD among those with relatively high CHOL, and relatively low VitD with high CHOL. The interesting thing in our data was the absence of statistical interactions between micronutrients and lipids for various glycemic outcomes. Beyond PD, the measurement of insulin and glycemic indices provided the opportunity to explore their associations with micronutrients and lipids. We could not find any reports that investigated such associations and interactions.

There are few studies reporting data on micronutrients, lipids, prediabetes, and diabetes in adolescent populations. A study from Italy (54) found an association between poor vitamin $B_{12}$ and high insulin resistance. A study from Saudi Arabia (55) found a significant association of vitamin D deficiency with T2D. The prevalence of overweight/obesity in these studies was 34 and 68%, respectively. The proportion of those overweight/obese in our study was miniscule (only 4.3%). Both studies have measured lipids, but none of them have reported the associations of diabetes or prediabetes with micronutrients and lipids together. Unlike our study, these studies have measured only a single micronutrient.

The prevalence of various lipid abnormalities that contribute to dyslipidemia was very low in our cohort. Lipids in non-pregnant adult populations always receive much attention due to their known associations with CVD as well as NCDs, but they are also known to play an important role as fuels in pregnancy (56). Our cohort consists of adolescent girls. Lipid levels in adolescence are known to track with those in later life (22, 23). Thus, our girls are likely to begin the pregnancy with inadequate levels of fuel/lipids. In 1980, Freinkel introduced the concept of 'Fuel-mediated teratogenesis,' (56) where the mixture of maternal nutrients/fuels (glucose and lipids) affects not only fetal growth but also the risk of future obesity and diabetes. Maternal lipids (CHOL and TG) are essential for fetal development (57, 58) and their low levels during pregnancy have been associated with delayed prenatal growth (59, 60). Low birthweight and stunting continue to be high in our region (61, 62). Studies from the US (63) and Europe (64–66) have shown associations between maternal lipids in pregnancy and birth weight. A study among undernourished rural pregnant Indian women has also shown a strong association between maternal glucose and lipids and fetal growth (67). The high prevalence of PD in our cohort (43) has already put our girls at risk of developing gestational diabetes. Thus, our adolescent girls are likely to enter pregnancy with risks of hyperglycemia, micronutrient deficiencies, and poor fuel storage. Prediabetes in our girls is driven by poor insulin secretion and poor β cell function. Based on our findings, improving vitB12, maintaining adequate TG, and reducing LDL in adolescence may help improve insulin secretion as well as β-cell function, leading to a reduction in PD. This indicates the need for lipid and micronutrient-based interventions in adolescents to improve glycemic outcomes. Maintaining adequate storage of micronutrients as well as fuels preconceptionally could reduce NCD risks. However, caution is warranted, as excess lipids may contribute to future obesity and diabetes-related insulin resistance.

The strengths of our study are the large sample size and measurements of detailed glycemic parameters beyond glucose. We measured micronutrients as well as lipids in a region known for widespread undernutrition across the life course. The prevalence of overweight/obesity in our sample was extremely low. There are some limitations, too. Our cohort consists only of girls. We did not measure other vitamins, like $B_2$ and $B_6$.

There are many lipid-based nutrient supplementation (LNS) studies in young malnourished children (68–70), but LNS studies among undernourished women with a life-course approach spanning from adolescence to pregnancy and adulthood are needed to assess their impact on diabetes risks in individuals as well as in the next generation.

To summarize, our report on adolescent girls has attempted to shed some light on the possible role of not only micronutrients but also lipids in undernourished adolescent girls on the development of NCDs in adulthood as well as in the next generation.

## Conclusion

In short, we have shown the existence of micronutrient deficiencies and poor lipid stores among rural Indian adolescent girls. We have also demonstrated their link to prediabetes. A link between micronutrient undernutrition in early life and diabetes in adulthood is well studied. Lipids play an important role as fuel in pregnancy. The persistence of poor lipid stores in adolescent girls, together with prediabetes, is likely to result in poor birth outcomes, like low birth weight. Lipid-based supplementation in adolescence together, with micronutrients, may offer a window of opportunity to reduce the subsequent risks of poor birth outcomes and diabetes in later life.

## Data availability statement

The datasets presented in this article are not readily available because the datasets generated are available from the corresponding author on reasonable request with necessary permissions from Institutional Ethics Committee and Government of India HMSC. Requests to access the datasets should be directed to SP, dr.suvrnanpatil@gmail.com. Institutional Ethics Committee and Government.

## Ethics statement

The studies involving humans were approved by Institute Ethics Committee of BKL Walawalkar Rural Medical College and Hospital. Registration number is (EC/NEW/INST/2023/MH/0361). 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

SP: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Project administration, Writing – review & editing. OD: Data curation, Formal analysis, Software, Writing – original draft. PH-B: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft. CJ: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. RB: Validation, Writing – review & editing. NP: Funding acquisition, Resources, Writing – review & editing. AY: Project administration, Investigation, Methodology, Writing – review & editing.

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## Conflict of interest

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

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1380777/full#supplementary-material

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# Evaluation of micronutrient and nutritional status among preschool children in Jordan: results from a Nationwide survey

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**Background:** Jordan faces various malnutrition challenges, including undernutrition, micronutrient deficiencies, overweight, obesity, and diet-related non-communicable diseases. The country has shifted from issues of undernutrition to rising rates of overweight and obesity, while still dealing with micronutrient deficiencies. The 2010 national survey revealed high rates of iron and vitamin D deficiencies among preschool children, with about 20% experiencing vitamin A deficiencies. The goals of the 2019 Jordan National Micronutrient & Nutrition Survey (JNMNS) include assessing feeding practices of infants and young children, determining the frequency of consuming micronutrient-rich foods, evaluating causes of anemia, assessing the health status of specific subgroups, and comparing findings to the 2010 survey.

**Methods:** JNMNS 2019 was a comprehensive national cross-sectional survey structured across four strata. Within each stratum, 40 primary sampling units were chosen in proportion to their size based on the 2015 Jordan census. Subsequently, the Department of Statistics conducted household listings in each PSU. Separate response rates were assumed for households and target groups, encompassing interviews, anthropometric measurements, and specimen collection. The survey aimed to collect data from 2,210 households, including interviews and anthropometry for 1,232 preschool children, with blood samples obtained from 992 of them.

**Results:** The findings revealed no severe anemia cases, but 11% of preschoolers aged 12–59 months were anemic. Iron deficiency affected 22.4%, with 5% having iron deficiency anemia. Vitamin D deficiency increased to 22.9% in 2019. Stunting and wasting rates improved slightly to 6.3 and 0.1%, respectively. Overweight and obesity rates remained stable at 6.2 and 2.1%. Anemia decreased by 5–6%, but iron deficiency rose by 7%. Vitamin A deficiency decreased, but iron deficiency anemia remained largely unchanged. Undernutrition was rare, but vitamin D deficiency affected 27.7% of preschoolers, impacting growth and immunity. Iron deficiency, affecting 25% of children, poses a risk to cognitive development. Overweight or obesity affected 9% of children, a medium public health issue according to the WHO. While malnutrition rates are low, the persistent issues of vitamin D deficiency, iron deficiency, and childhood obesity require focused attention.

**Conclusion:** The study highlights ongoing nutritional challenges among Jordanian preschoolers. Although severe anemia was rare, 11% were anemic, and

22.4% had iron deficiency, including 5% with iron deficiency anemia. Vitamin D deficiency affected 22.9%, impacting growth and immunity. While stunting and wasting improved, childhood overweight and obesity rates remained steady. Anemia decreased, but iron deficiency rose by 7%. Despite reduced vitamin A deficiency, stable iron deficiency anemia rates indicate ongoing concerns. Overall, undernutrition is uncommon, but vitamin D and iron deficiencies, along with childhood obesity, need sustained attention and targeted interventions to improve children's health in Jordan.

KEYWORDS

micronutrients deficiency, nutritional status, preschool children, feeding indicators, national survey

# 1 Introduction

Nutrition has significantly improved in the Hashemite Kingdom of Jordan in recent years. Between 1990 and 2012, the prevalence of childhood stunting decreased by roughly two-thirds, and levels of wasting among young children under 5 years old were maintained at a low level, indicating progress in the fight against child undernutrition (1). Since 1996, the ministry of health has implemented a national salt iodization program to combat the burden of micronutrient deficiencies. A survey carried out in 2010 revealed a significant improvement in iodine nutrition among school-age children (2). Additionally, since 2002, wheat flour has been fortified with iron and folic acid. Since then, the program has been expanded to include zinc, vitamins A, and a number of B vitamins (B1, B2, B3, and B12), as well as vitamin D. These changes have significantly decreased the prevalence of severe anemia (3, 4).

Jordan suffers from multiple forms of malnutrition, including undernutrition, micronutrient deficiencies, overweight, obesity and diet-related non-communicable diseases (NCDs). The country has witnessed a rapid nutrition transition due to changing diets and lifestyles, with a shift from undernutrition — but with persistent problems of micronutrient deficiencies — toward greater prevalence of overweight/obesity and diet-related NCDs (5).

These issues now coexist with persistent pockets of undernutrition, low levels of exclusive breastfeeding, alarming levels of low birth weight, and ongoing issues with micronutrient deficiencies (4). Furthermore, Jordan's food security and malnutrition have been impacted by the COVID-19 pandemic (5). Food security and nutritional health are now in even greater danger due to recent increases in food prices around the world and the conflict in Ukraine (5). Therefore, there is a significant opportunity to improve the health and standard of living for both Jordanians and the numerous refugees who are hosted in the nation.

Jordan has experienced uneven progress in reducing micronutrient deficiencies despite consistent economic growth and declines in some forms of malnutrition. The national micronutrient survey of 2010 found that preschool children and women of childbearing age had high prevalence rates of iron (6) and vitamin D (7), and that about one-fifth of preschoolers had vitamin A deficiency (8). There are conflicting reports regarding the prevalence of anemia.

The prevalence of anemia among preschoolers in Jordan has shown varied reports over time. While the 2010 national survey indicated that about one fifth of preschoolers were affected by anemia, subsequent Population and Family Health Surveys in 2012 and 2017–18 reported that over one third of preschoolers were affected (8, 9). There is inconsistency in anemia prevalence data, with the 2010 national survey reporting one fifth affected, while later surveys in 2012 and 2017–18 found over one third affected (8, 9). Regarding other indicators among preschool age children, stunting exists to a certain extent but is categorized as a 'low' public health concern. Wasting and underweight are relatively infrequent occurrences (10). The prevalence of overweight and obesity has been characterized as stable, albeit at slightly elevated levels (11).

Furthermore, our study aims to align with global objectives such as the Sustainable Development Goal (SDG) of achieving zero hunger. By elucidating the severity of micronutrient deficiencies and assessing the double burden of malnutrition, the study findings will contribute directly to the global effort to improve nutrition and food security. By highlighting the socio-economic and geographical frameworks specific to Jordanians, we underscore the significance of our research in addressing local nutritional challenges and informing policy intervention.

Therefore, the Jordan National Micronutrient & Nutrition Survey (JNMNS) 2019 aimed to compare its results with the national micronutrient survey conducted in 2010 and gain a better understanding of the severity of micronutrient deficiencies. The survey also collected simultaneous data on under- and overnutrition to determine the extent of the double burden of malnutrition. Additionally, survey results were contrasted with those of a national survey conducted in 2010 to assess changes in selected key micronutrient intake among preschool children (12). The findings presented in this article are derived from the Jordan National Micronutrient Survey (JNMNS), which was conducted among both Jordanians and Syrian refugees.

# 2 Methods

## 2.1 Sampling approach and sample size determination

The JNMNS 2019 was a national cross-sectional survey with four independent strata. In each of these strata, 40 clusters were selected with equal probability from the list of primary sampling units from the 2015 Jordan census as a result, the entire survey sample will have 160 clusters. In each cluster, a household listing exercise was

conducted. In order to achieve sufficient sample size for sub group analyses of Jordanian nationals and other nationalities, different numbers of households were randomly selected in the Northern governorates stratum (20 households) than in the Central, Southern and refugee camps strata (15 households). This resulted in the attempted recruitment of 2,600 households. Given the expected household response rate of 85%, the JNMNS 2019 sample should contain of 2,210 households overall. These 2,210 consenting households have 1,296 eligible preschool children, 1,232 of whom have anthropometry measured and 992 blood specimens collected taking individual response rates into account. The Fisher's formula for estimating the minimum sample size for prevalence descriptive studies was used as follows:

$$n = \frac{Z^2_{a/2} P(1-P)}{d^2} * DEFF * \frac{100}{RR}$$

Where:

n = minimum sample size, expressed as number of units of analysis,

Zα/2 = Z value corresponding to 95% confidence intervals.

P = the assumed prevalence.

d = the allowable sampling error, or ½ the desired confidence interval.

DEFF = design effect.

RR = response rate expressed as a decimal.

## 2.2 Study participants

The study participants were randomly chosen from households within selected primary sampling units. Table 1 outlines the inclusion criteria for survey enrollment, broken down by the target population group. No explicit exclusion criteria were employed, except for the absence of the specified inclusion criteria.

## 2.3 Training of survey teams and field work

The team members were thoroughly trained, and all survey instruments were pre-tested during the training. The training consisted of classroom instruction and practice, and of field testing of all survey procedures. 2 days field pilot testing in non-selected clusters (1 urban cluster, one rural cluster) where each team completed 4–6 households during field testing. In total, 11 teams were deployed to collect data. Each team was composed of one team leader, two interviewers, two phlebotomists, two anthropometrists, and one driver. Additionally, there was a regional supervisor for each stratum who supported coordination of centralization of blood and food specimens at a selected lab.

Two types of questionnaires were distributed to the designated households:

(a) A household questionnaire is administered to gather information on demographics, socio-economic status, and food purchasing habits within the household.

(b) An individual questionnaire is utilized for preschool children, with the caregiver serving as the respondent. This questionnaire succinctly captures data on individual health and vaccination status, consumption of micronutrient supplements, knowledge of micronutrients, appropriate feeding practices for infants and young children. Additionally, it records the results from blood collection, encompassing details such as hemoglobin concentration, collection time, and the estimated amount of blood collected through phlebotomy.

TABLE 1 Inclusion criteria by targeted population group.

| Target population | Inclusion criteria |
|---|---|
| Households | - Consent for survey data collection is obtained through oral agreement from the household head, spouse, or another adult member. |
| Children 0–59 months | - Participants must fall within the age range of 0–59 months during the survey (6–59 months specifically for blood sample collection).<br>- Individuals need to be recognized as household members by the adults residing in the household.<br>- For children within the specified age range, written consent for survey participation must be provided by either the mother or caretaker. |

## 2.4 Anthropometry and phlebotomy

Anthropometric measurements for children were conducted using established protocols. A scale, capable of subtracting the mother's weight, was utilized for measuring the children's weight. In cases where children could not stand quietly on the scale, their weight was taken in the mother's arms. The height or length of the children was measured using a standardized height board. Additionally, individual data was gathered through interviews and anthropometric measurements. Furthermore, the JNMNS 19 obtained blood specimens from participants who provided their consent during the survey. Experienced phlebotomists collected blood via venipuncture for preschool and school-age children, a 2 mL EDTA-coated tube and a 6 mL trace-element certified tube was used; a complete blood count was done on fresh whole blood, and after centrifugation and aliquoting, serum was shipped to predominantly national and some international laboratories for measurement of the concentrations of various micronutrients and detection of hemoglobinopathies and thalassemia. In preschool children, blood specimens was collected from children aged 6–59 months. Participants identified with severe acute malnutrition or severe anemia were referred for necessary treatment at the nearest health hospital or clinic (13). For more in-depth information, additional details can be referenced in another publication (14).

## 2.5 Measurement and definition of outcomes

The principal nutrition outcomes measured in preschool children are presented in Table 2. Comprehensive information can be found in another publication (14).

TABLE 2 Principal nutrition outcomes measured in preschool children.

| Condition measured | Indicator | PSC[a] |
|---|---|---|
| Anemia | Hemoglobin concentration[b] | ✓ |
| Iron deficiency | Serum ferritin, markers of inflammation (AGP and CRP) | ✓ |
| Iron deficiency anemia | Concurrent anemia and iron deficiency measured using ferritin | ✓ |
| Vitamin A deficiency | RBP and retinol | ✓[c] |
| Zinc deficiency | Serum zinc | ✓ |
| Blood disorders | Sickle cell and α-and β-thalassemia | ✓ |
| Vitamin D deficiency | Serum 25[OH]D | ✓ |
| Wasting/thinness | Weight-for-height z-score BMI-for-age z-score | ✓ |
| Stunting/shortness | Height-for-age z-score Height | ✓ |
| Overweight and obesity | Weight-for-height z-score BMI-for-age z-score BMI | ✓ |

[a]PSC, preschool children (0–59 months for anthropometry, 6–59 for blood biomarkers).
[b]A complete blood count was conducted, comprising 22 parameters (e.g., MCV, hematocrit, etc.)
[c]For PSC, serum retinol was measured from all samples.

TABLE 3 Clinical cut-off points and classifications for biomarker indicators.

| | Adequate | Mild | Moderate | Severe |
|---|---|---|---|---|
| Hemoglobin (18) PSC: Children 6–59 months | ≥ 110 g/L | 100–109 g/L | 70–99 g/L | <70 g/L |
| | Deficiency cut-offs | | | |
| RBP and retinol (19, 20) | ≤0.7 μM/L* | | | |
| Serum ferritin (21) | < 12 μg/L* | | | |
| α1-acid-glycoprotein (22) | >1 g/L | | | |
| C-reactive protein (23) | >5 mg/L | | | |
| 25[OH]D (24) | <12 ng/mL, deficiency; <20 ng/mL, insufficiency | | | |
| Serum zinc (25) Children 6–59 months | Morning, non-fasting: 65 μg/dL, afternoon, non-fasting: 57 μg/dL | | | |

*Adjusted for sub-clinical inflammation using suitable algorithms (26, 27), it is important to highlight that there are no established thresholds for Retinol-Binding Protein (RBP). Nevertheless, given the strong correlation between serum retinol and RBP, the same threshold was applied.

### 2.5.1 Anthropometric indicators

In preschool children aged 0–59 months, the assessment of undernutrition (including wasting, stunting, and underweight) and overnutrition followed the criteria outlined in World Health Organization (WHO) Child Growth Standards (15). The z-scores were used to classify children based on specific indicators (16, 17):

- *For wasting*
- Wasting: Z-score less than −2.0 for weight-for-height.
- Moderate wasting: Z-score less than −2.0 but greater than or equal to −3.0.
- Severe wasting: Z-score less than −3.0.
- *For stunting*
- Stunting: Z-score less than −2.0 for height-for-age.
- Moderate stunting: Z-score less than −2.0 but greater than or equal to −3.0.
- Severe stunting: Z-score less than −3.0.
- *For underweight*
- Underweight: Z-score less than −2.0 for weight-for-age.
- Moderate underweight: Z-score less than −2.0 but greater than or equal to −3.0.
- Severe underweight: Z-score less than −3.0.
- *For overweight*
- Overnutrition: Z-score greater than +2.0 for weight-for-height.
- Overweight: Z-score greater than +2.0 but less than or equal to +3.0.
- Obesity: Z-score greater than +3.0

### 2.5.2 Blood specimens

The cut-off values for biomarkers measured in the JNMNS 2019 are presented in Table 3.

The cut-off defining normal hemoglobin concentrations was adjusted for altitude of residence (Table 4).

### 2.5.3 Blood specimens

The methods of hemoglobin, serum ferritin, C-reactive protein and alpha-1 acid glycoprotein, Retinol, Retinol binding Protein (RBP), Vitamin D and Zinc analysis have explained in details elsewhere (14).

### 2.5.4 Data management and analysis

Data collection was executed electronically, employing tablet computers equipped with the Open Data Kit (ODK) software. Continuous monitoring of the data was undertaken to ensure frequent quality control. Descriptive statistics for key indicators were computed, stratified by different characteristics and strata.

### 2.5.5 Ethical considerations

To ensure adherence to principles safeguarding survey participants and minimizing potential risks, ethical approval for this study was secured from the Institutional Review Board at Jordan University of Science & Technology. Selected caregivers of children were required to furnish written informed consent for themselves and their wards. In cases where participants could not read or write, the consent form was read aloud, and a thumbprint or fingerprint was obtained as proof of

TABLE 4 Adjustments in cut-off defining anemia, by altitude of residence (18).

| Altitude (meters) | Increase in cut-off point defining anemia (g/L) |
|---|---|
| < 1,000 | No adjustment |
| 1,000–1,249 | + 2 |
| 1,250–1749 | + 5 |
| 1750–2,249 | + 8 |

agreement, serving as a substitute for a signature. Alternatively, participants could designate an alternative to sign on their behalf. It was clearly communicated to respondents that they retained the freedom to withdraw from the survey at any stage, even after providing written consent.

Rigorous confidentiality measures were precisely maintained throughout the entire process of data collection, processing, and analysis. For infants below 6 months, no blood samples were collected to avoid causing unnecessary discomfort. Participants diagnosed with severe acute malnutrition were promptly referred to a nearby health facility.

## 2.6 Data analysis

Data analysis was done using SPSS version 26. Data analysis included calculation of proportions to derive the prevalence of dichotomous outcomes and calculation of mean and median averages for continuous outcomes. Nationwide prevalence estimates were calculated by using weighted analysis to account for the unequal probability of selection in the 3 strata. The statistical precision of all estimates was assessed using 95% confidence limits. All measures of precision, including confidence limits and chi square *p* values for differences, were calculated accounting for the complex cluster and stratified sampling used by the JNMNS 2019.

# 3 Results

## 3.1 Characteristics

Table 5 provides an overview of the demographic attributes of preschool children engaged in the JNMNS. The majority of these children are situated in the Northern stratum. Approximately half of the children are male, and an overwhelming 85% of them inhabit urban households.

TABLE 5 Description of sampled preschool age children (0–59 months), settled population, Jordan.

| Characteristic | *n* | %[a] | (95% CI)[b] |
|---|---|---|---|
| Age Group (in months) | | | |
| 0–5 | 91 | 11.7 | (9.1, 14.8) |
| 6–11 | 77 | 9.7 | (7.3, 12.8) |
| 12–23 | 156 | 20.4 | (17.1, 24.1) |
| 24–35 | 172 | 22.0 | (18.5, 26.0) |
| 36–47 | 150 | 17.1 | (14.0, 20.8) |
| 48–59 | 164 | 19.1 | (16.3, 22.2) |
| Sex | | | |
| Male | 399 | 50.1 | (44.7, 55.4) |
| Female | 411 | 49.9 | (44.6, 55.3) |
| Residence | | | |
| Urban | 647 | 85.0 | (73.2, 92.2) |
| Rural | 161 | 15.0 | (7.8, 26.8) |
| Stratum | | | |
| Central | 187 | 23.1 | (16.0, 32.2) |
| Northern | 355 | 43.8 | (33.5, 54.7) |
| Southern | 268 | 33.1 | (23.9, 43.7) |

The n's are un-weighted numbers in each subgroup; the sum of subgroups may not equal the total because of missing data.
[a]Percentages weighted for unequal probability of selection.
[b]CI, confidence interval calculated taking into account the complex sampling design.

## 3.2 Anemia, iron deficiency, and iron deficiency anemia

Nationally, approximately 12% of preschool children were found to be anemic, with all cases classified as moderate or mild; no instances of severe anemia were identified (refer to Table 6). According to the WHO standards (18), this level of anemia prevalence is considered a mild public health concern. Significant associations with anemia were observed for age group and wealth quintile, with a notably higher prevalence among male children and those aged 6–11 months. The distribution of hemoglobin values for children, illustrated in Figure 1, is roughly symmetric, with the majority of values above the 110 g/L cutoff point. The mean hemoglobin concentration among settled children aged 6–59 months was 122.2 g/L (95%CI 121.8, 123.6 g/L).

Iron deficiency was noted in approximately 26% of preschool children, and significant associations with age group and wealth quintile were observed for this condition as well. Five percent of preschool children exhibited concurrent anemia and iron deficiency, commonly known as iron deficiency anemia (IDA). Variations were noted by age group, particularly with children aged 6–11 months showing significantly higher proportions of IDA (17.0%) compared to other age groups (2–7%).

Figures 2–4 show the prevalence of anemia, iron deficiency, and iron deficiency anemia in children aged 6–59 months, categorized by various demographic characteristics within the settled population.

## 3.3 Vitamin A deficiency

Approximately 4–8% of preschool children were identified as having vitamin A deficiency, with the prevalence depending on the indicator used—either serum retinol or RBP. Regardless of the chosen indicator, the observed prevalence of vitamin A deficiency is considered a mild public health concern on a national level, as per the World Health Organization (WHO) criteria (28). Significant variations were noted based on age and wealth quintile (Figure 5).

TABLE 6 Severity of anemia in children 6–59 months, by various demographic characteristics, settled population, Jordan.

| Characteristic | Mild anemia[b] | | | Moderate anemia[b] | | | Severe anemia[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | %[a] | 95% CI[c] | *n* | %[a] | 95% CI[c] | *n* | %[a] | 95% CI[c] |
| Total | 44 | 9.5 | (6.4, 13.8) | 13 | 2.4 | (1.1, 5.2) | 0 | 0.0 | – |
| Age (in months) | | | | | | | | | |
| 6–11 | 6 | 26.8 | (11.3, 51.3) | 3.0 | 11.7 | (2.8, 38.1) | – | – | – |
| 12–23 | 12 | 9.8 | (4.7, 19.5) | 5.0 | 5.1 | (1.4, 17.2) | – | – | – |
| 24–35 | 12 | 9.3 | (4.4, 18.5) | 1.0 | 0.6 | (0.1, 4.7) | – | – | – |
| 36–47 | 10 | 9.1 | (3.8, 20.0) | 1.0 | 0.4 | (0.0, 2.6) | – | – | – |
| 48–59 | 4 | 4.8 | (1.3, 15.9) | 3.0 | 1.5 | (0.4, 5.3) | – | – | – |
| Sex | | | | | | | | | |
| Male | 22 | 12.2 | (7.3, 19.6) | 8.0 | 3.7 | (1.3, 9.8) | – | – | – |
| Female | 22 | 6.9 | (4.0, 11.5) | 5.0 | 1.2 | (0.5, 3.1) | – | – | – |
| Residence | | | | | | | | | |
| Urban | 38 | 9.4 | (6.1, 14.2) | 12 | 2.7 | (1.2, 5.9) | – | – | - |
| Rural | 6.0 | 10.1 | (5.6, 17.4) | 1 | 0.6 | (0.1, 4.6) | – | – | – |
| Stratum | | | | | | | | | |
| Central | 7 | 7.8 | (3.8, 15.3) | 2 | 2.2 | (0.6, 8.3) | – | – | – |
| Northern | 20 | 11.9 | (7.6, 18.2) | 3 | 1.8 | (0.6, 5.4) | – | – | – |
| Southern | 17 | 11.5 | (6.8, 18.8) | 8 | 5.4 | (2.7, 10.5) | – | – | – |
| Wealth quintile | | | | | | | | | |
| Poorest | 20 | 12.3 | (6.9, 21.0) | 10 | 6.3 | (2.7, 14.1) | – | – | – |
| Second | 9 | 9.6 | (4.7, 18.6) | 3 | 3.3 | (0.7, 15.4) | – | – | – |
| Middle | 5 | 5.1 | (2.2, 11.5) | | 0.0 | – | – | – | – |
| Fourth | 6 | 5.1 | (1.4, 16.5) | | 0.0 | – | – | – | – |
| Wealthiest | 4 | 19.6 | (7.7, 41.6) | | 0.0 | – | – | – | – |

The "*n*'s" represent the numerators for a particular sub-group.
[a]All percentages, excluding region-specific estimates, are weighted to account for unequal probability of selection among strata.
[b]Mild, moderate, and severe anemia are defined as hemoglobin levels of 100–109 g/L, 70–99 g/L, and < 70 g/L, respectively.
[c]CI, confidence interval, calculated considering the complex sampling design.

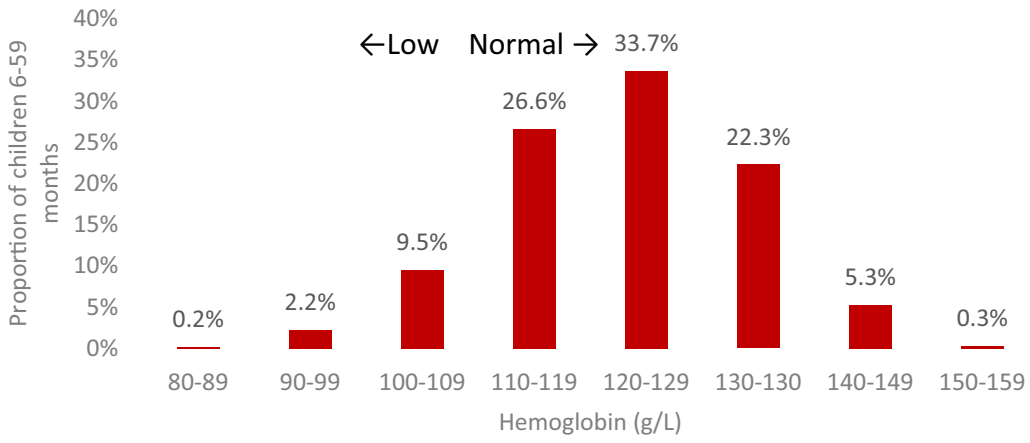


FIGURE 1
The distribution of hemoglobin concentrations (g/L) in children aged 6–59 months, residing in settled areas of Jordan. *Significantly significant difference ($p < 0.05$).

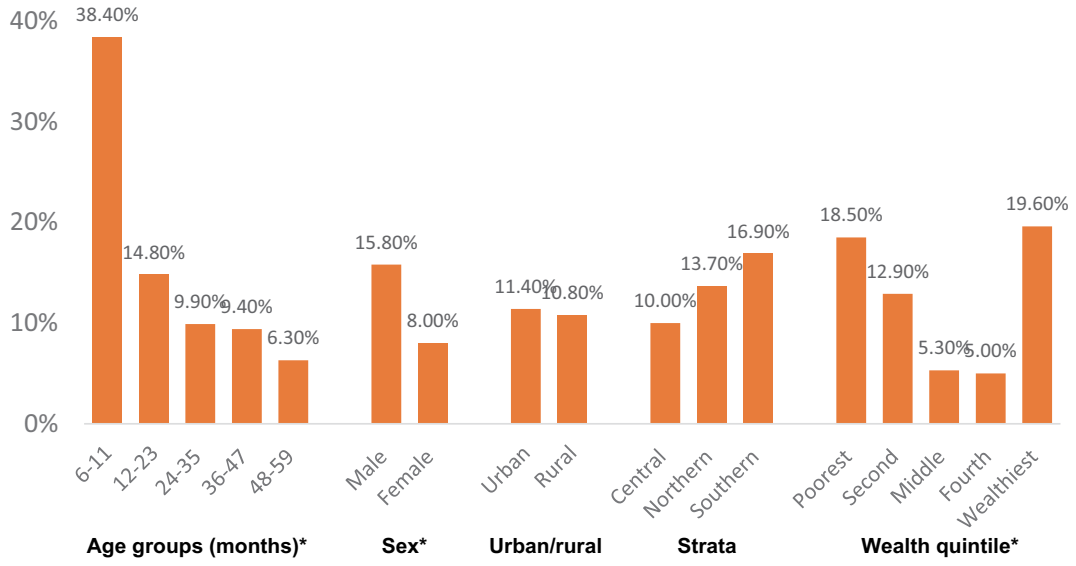


FIGURE 2
Prevalence of anemia Strata. *Significantly significant difference ($p < 0.05$).

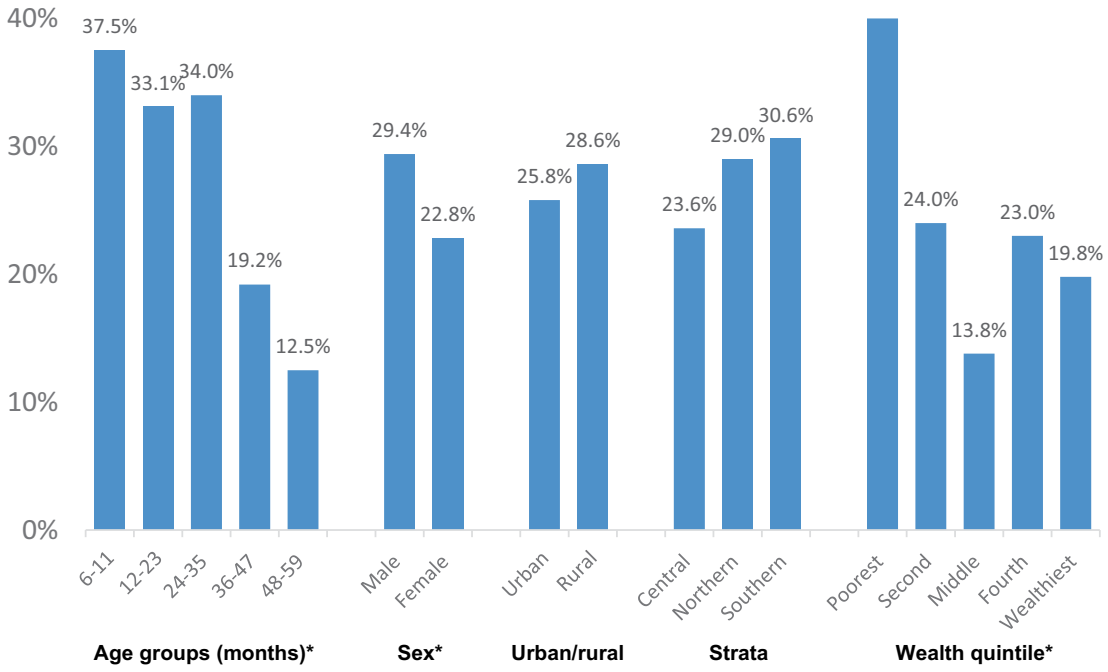


FIGURE 3
Prevalence of iron deficiency. *Significantly significant difference ($p < 0.05$).

Figure 6 illustrates the distribution of retinol binding protein (RBP) and serum retinol values for children in the settled population. Notably, the majority of values for both indicators surpass the threshold of 0.7 µmol/L. It's important to note that the histogram for RBP is not inflammation-adjusted, resulting in more cases falling below the threshold. The mean serum retinol concentration in this group was 1.13 µmol/L (95%CI: 1.08, 1.16), and the mean inflammation-adjusted retinol binding protein concentration was 1.13 µmol/L (95%CI: 1.09, 1.16).

## 3.4 Vitamin D deficiency and insufficiency

Approximately one-third of children aged 6–59 months within the settled population were found to be vitamin D deficient, while another third exhibited vitamin D insufficiency, resulting in nearly two-thirds of children having inadequate vitamin D status (refer to Figure 7). Apart from the 6–11 months' age group, which displayed a high prevalence of inadequate vitamin D status, a discernible pattern emerged, indicating an increasing prevalence with age. Additionally, a gender disparity was

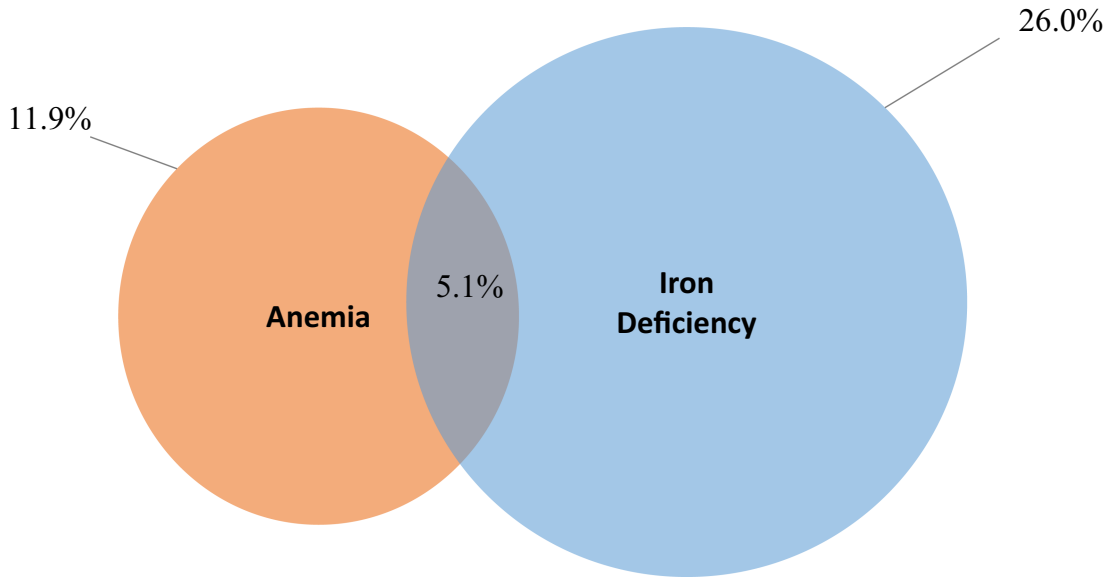


FIGURE 4
Prevalence of iron deficiency anemia.

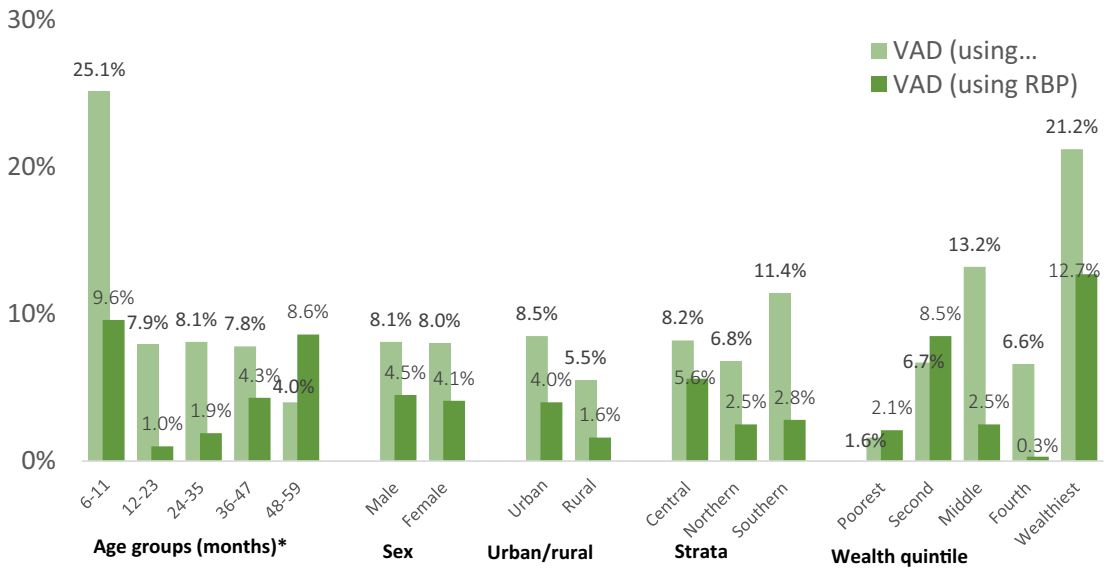


FIGURE 5
The prevalence of vitamin A deficiency in children aged 6–59 months within the settled population of Jordan is detailed across various demographic characteristics. *Significantly significant difference ($p < 0.05$).

observed, with a higher proportion of girls experiencing vitamin D deficiency compared to boys. Notably, children in the Southern stratum exhibited a lower frequency of vitamin D deficiency compared to those in the Central or Northern strata. Other demographic factors did not exhibit a clear association with vitamin D status.

The geometric mean of vitamin D concentration was 16.8 ng/mL (95%CI: 15.7, 17.9). Figure 8 illustrates the geographic distribution of vitamin D deficiency among preschool children in the settled population, revealing higher prevalence rates in the Northern and Central strata compared to the South. Karak stands out as an exception, with a prevalence below 10%.

## 3.5 Zinc deficiency

Zinc deficiency affected slightly more than 1 out of 10 preschool children in the settled population. Significant variations were observed by age, with older children exhibiting a significantly

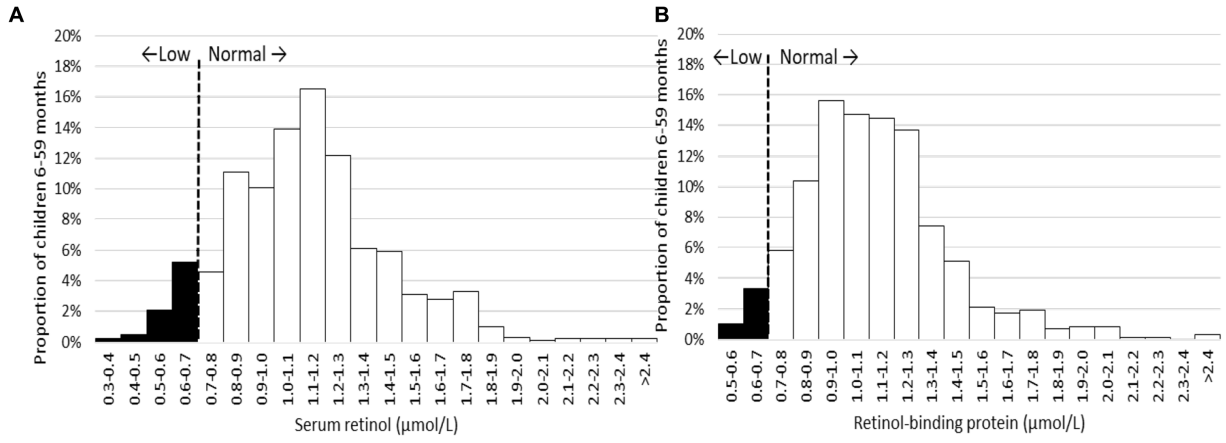


FIGURE 6
Distribution of serum retinol **(A)** and inflammation-adjusted retinol-binding protein **(B)** in children 6–59 months, settled population, Jordan.

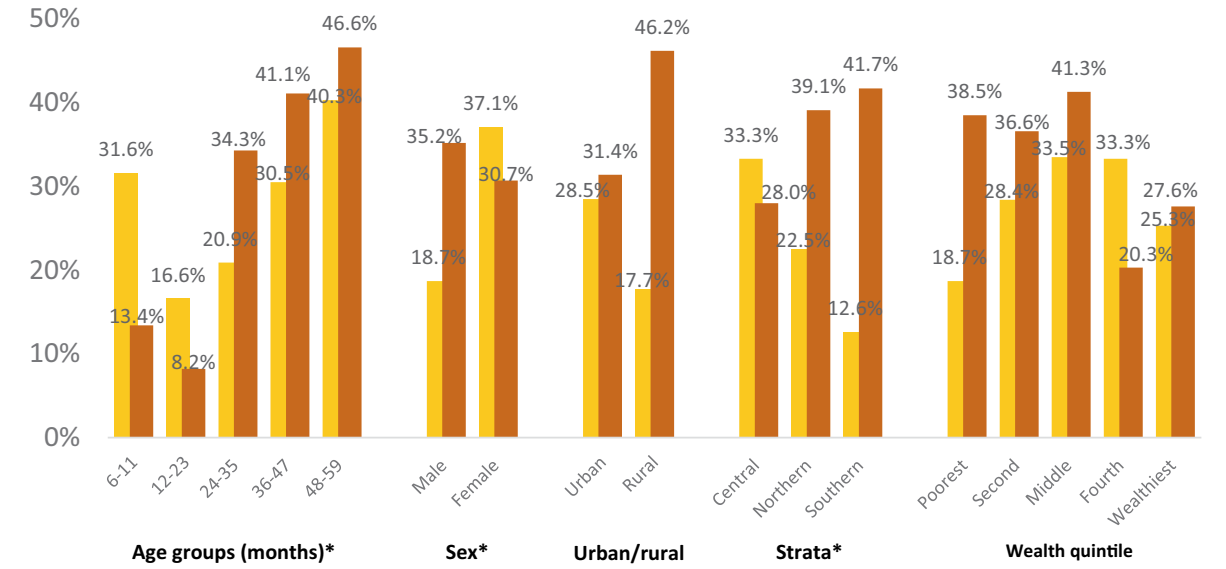


FIGURE 7
Vitamin D deficiency and insufficiency prevalence in children 6–59 months within the settled population of Jordan across different demographic characteristics. *Significantly significant difference ($p < 0.05$).

lower prevalence. However, no statistically significant differences in zinc deficiency were found between male and female children, or among children living in different residences, strata, or households with different wealth levels (refer to Figure 9). The mean serum zinc level in this group was 72.2 µg/dL (95%CI: 69.7, 74.7).

## 3.6 Stunting

Regarding stunting, the overall prevalence is 7.4% among preschool children in the settled population, as indicated in Table 7. This prevalence is relatively low, considering recently updated thresholds that define categories for stunting into public health relevance (29). Significant variations were noted by stratum, with fewer children affected in the Southern stratum. No other demographic subgroup analysis identified statistically significant differences. While not reaching statistical significance, children of mothers with short stature were twice as likely to be stunted and four times as likely to be severely stunted compared to children whose mothers had normal stature. The distribution of height-for-age z-scores, illustrated in Figure 10, is slightly shifted to the left. The mean height-for-age z-score was −0.33 (95% CI: −0.42, −0.24), with a standard deviation (SD) of 1.26.

## 3.7 Wasting and underweight

The prevalence of wasting among preschool children in the settled population was only 0.6% (95% CI: 0.2, 2.0). The small number of affected children limits the feasibility of conducting meaningful subgroup analyses (Figure 11).

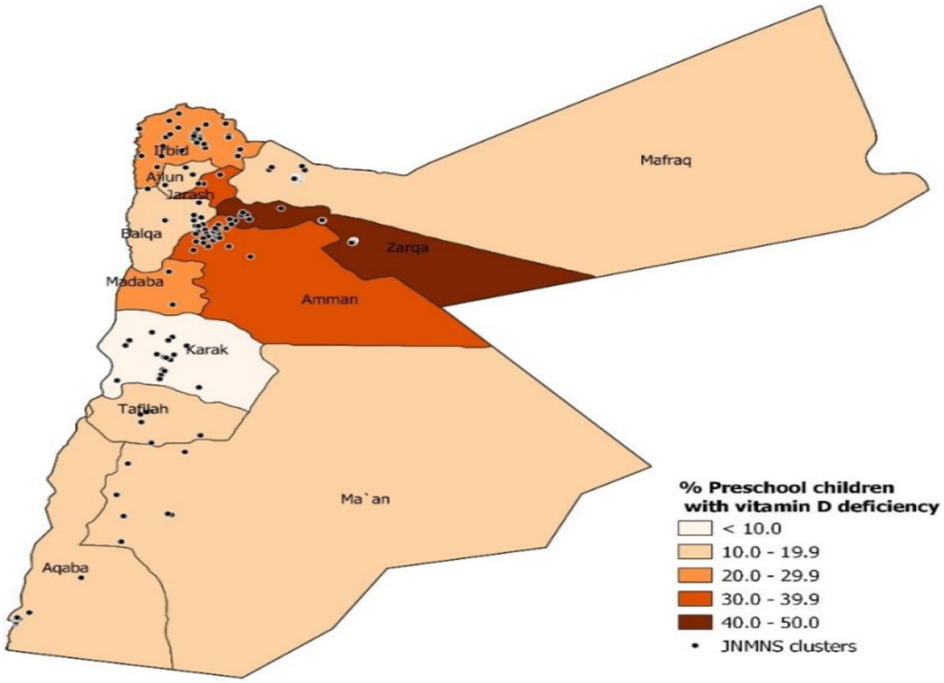


FIGURE 8
The prevalence of vitamin D deficiency (defined as <12 ng/mL) in preschool children within the settled population of Jordan defined by governorate.

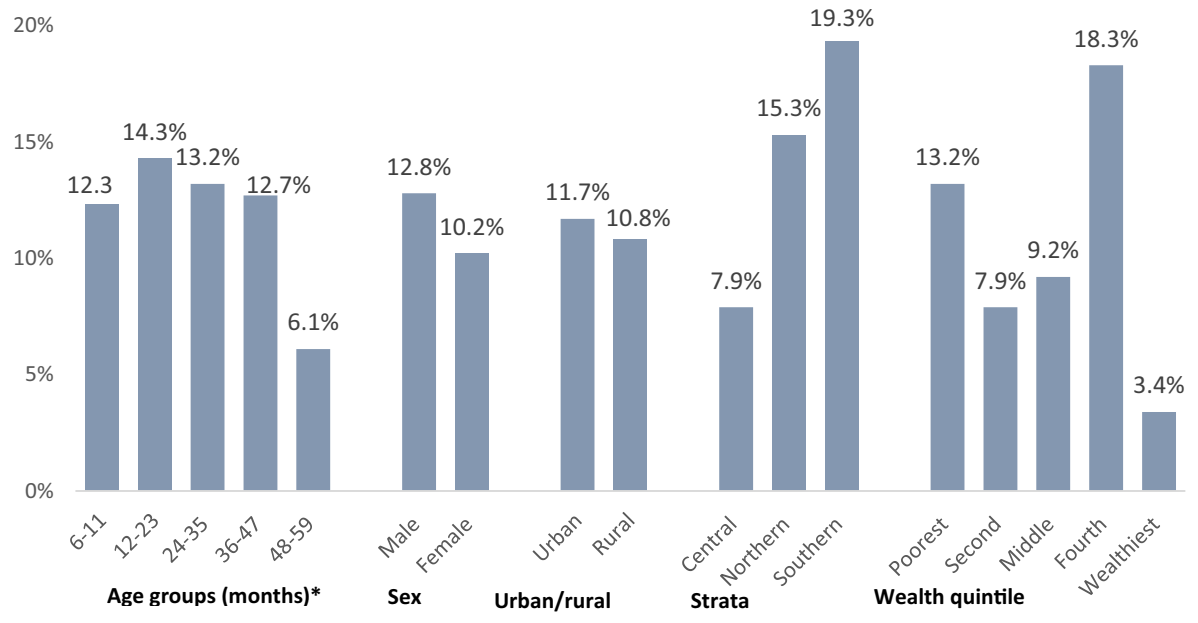


FIGURE 9
Zinc deficiency prevalence in children aged 6–59 months, categorized by various demographic characteristics within the settled population of Jordan. *Significantly significant difference ($p < 0.05$).

Similarly, the prevalence of underweight in this population group was very low, affecting 2.7% (95% CI: 1.6, 4.7) of children. Only 0.6% of children were identified with severe underweight. Due to the limited number of affected children, no subgroup analyses were performed.

## 3.8 Overweight and obesity

The Prevalence of overweight among children under 5 years was 9.2% in 2019 (2.2% with obesity). Prevalence was higher among boys (11.7%) than girls (6.7%), in urban and rural areas (10% vs. 5.2%) and

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TABLE 7 Prevalence of stunting in children 0–59 months, categorized by various demographic characteristics within the settled population of Jordan.

| | | Severely stunted[b] | | Moderately stunted[b] | | | Total stunted[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| Characteristic | *n* | %[a] | 95% CI | % | 95% CI | *p*-value [d] | % | 95% CI | *p*-value[d] |
| Total | 750 | 3.2 | (1.8, 5.8) | 4.2 | (2.7, 6.5) | | 7.4 | (5.1, 10.7) | |
| Age (in months) | | | | | | | | | |
| 0–11 | 155 | 6.6 | (2.7, 15.0) | 3.1 | (1.1, 8.6) | 0.491 | 9.7 | (5.1, 17.7) | 0.581 |
| 12–23 | 147 | 1.7 | (0.6, 4.6) | 2.8 | (0.8, 9.1) | | 4.4 | (1.9, 10.0) | |
| 24–35 | 157 | 3.1 | (0.8, 11.5) | 6.0 | (2.7, 12.6) | | 9.1 | (4.8, 16.8) | |
| 36–47 | 138 | 2.1 | (0.4, 11.2) | 6.1 | (2.6, 14.0) | | 8.2 | (3.0, 20.5) | |
| 48–59 | 53 | 2.3 | (0.5, 10.7) | 3.2 | (1.0, 9.6) | | 5.5 | (2.2, 13.2) | |
| Sex | | | | | | | | | |
| Male | 362 | 3.0 | (1.4, 6.4) | 4.0 | (2.1, 7.5) | 0.911 | 7.0 | (4.5, 10.8) | 0.699 |
| Female | 388 | 3.5 | (1.6, 7.5) | 4.4 | (2.6, 7.3) | | 7.9 | (4.7, 13.1) | |
| Residence | | | | | | | | | |
| Urban | 601 | 3.7 | (2.0, 6.7) | 4.1 | (2.5, 6.8) | 0.281 | 7.8 | (5.2, 11.6) | 0.493 |
| Rural | 147 | 0.9 | (0.2, 4.5) | 5.0 | (2.1, 11.2) | | 5.9 | (2.8, 11.9) | |
| Stratum | | | | | | | | | |
| Central | 172 | 4.7 | (2.3, 9.2) | 4.1 | (2.0, 8.0) | 0.042 | 8.7 | (5.2, 14.2) | 0.142 |
| Northern | 337 | 1.5 | (0.6, 3.4) | 4.7 | (2.8, 8.0) | | 6.2 | (3.9, 9.8) | |
| Southern | 241 | 0.8 | (0.2, 3.2) | 2.9 | (1.5, 5.5) | | 3.7 | (1.8, 7.4) | |
| Wealth quintile | | | | | | | | | |
| Poorest | 213 | 5.7 | (2.6, 11.9) | 6.6 | (4.0, 10.9) | 0.081 | 12.3 | (7.9, 18.7) | 0.103 |
| Second | 168 | 1.0 | (0.2, 4.0) | 2.2 | (0.6, 7.8) | | 3.2 | (1.2, 8.1) | |
| Middle | 165 | 0.6 | (0.1, 2.8) | 5.9 | (2.5, 13.7) | | 6.5 | (2.9, 14.1) | |
| Fourth | 126 | 6.4 | (1.8, 20.2) | 3.3 | (0.9, 11.0) | | 9.7 | (4.0, 21.7) | |
| Wealthiest | 78 | 2.5 | (0.4, 16.1) | 0.8 | (0.1, 5.5) | | 3.3 | (0.7, 14.7) | |
| Mother's stature | | | | | | | | | |
| Short (< 150 cm) | 24 | 16.6 | (4.6, 44.9) | 0.0 | -- | 0.112 | 16.6 | (4.6, 44.9) | 0.310 |
| Normal (> 150 cm) | 321 | 4.5 | (1.9, 10.2) | 3.8 | (1.8, 7.8) | | 8.3 | (4.7, 14.3) | |

The "*n*'s" represent unweighted numbers (denominator) for each subgroup; subgroups that do not sum to the total indicate missing data.

[a]Percentages are weighted to account for unequal probability of selection.

[b]Severe stunting is defined as having a height-for-age z-score below −3 standard deviations from the WHO Child Growth Standards population median; moderate stunting is defined as having a height-for-age z-score equal to or above −3 standard deviations and less than −2 SD from the WHO Child Growth Standards population median.

[c]Total stunting includes both severely and moderately stunted children.

[d]A p-value <0.05 indicates that at least one subgroup is significantly different from the others. Chi-square results are based on total stunting.

in wealthier households (14.2% vs. 4.8% in the wealthiest compared to the poorest income quintile) as shown in Table 8.

## 3.9 Infant and young child feeding indicators and supplements

According to WHO/UNICEF recommendations (16), Figure 12 summarizes the various infant and young child feeding indicators. Ever breastfeeding was widespread, but less than two thirds of parents initiated breastfeeding at an early age. In children under the age of 6 months, exclusive breastfeeding is very low below the WHO recommendations. Furthermore, continuing breastfeeding after 1 year and after 2 years is not very common. A relatively brief breastfeeding period is indicated by the median breastfeeding duration of 14 months among children under 24 months (data not shown).

The indicators of complementary feeding, such as the introduction of solid foods, the minimum requirements for dietary diversity, meal frequency, and dietary acceptability are reasonable but not ideal. As presented in Table 9, nearly two thirds of kids had consumed iron-rich foods or taken iron supplements within the previous day before data collection. Approximately two thirds of kids had food from a bottle in the previous 24 h, and breastfeeding that is age-appropriate and prevalent is relatively poor. Water, infant formula, and other non-human milks were the most frequently consumed liquids by infants younger than 6 months. In the previous 24 h, nearly half of kids aged 6 to 23 months had consumed sugary foods or drinks. A third of the 6-to 23-month-old children consumed fried or salty snacks.

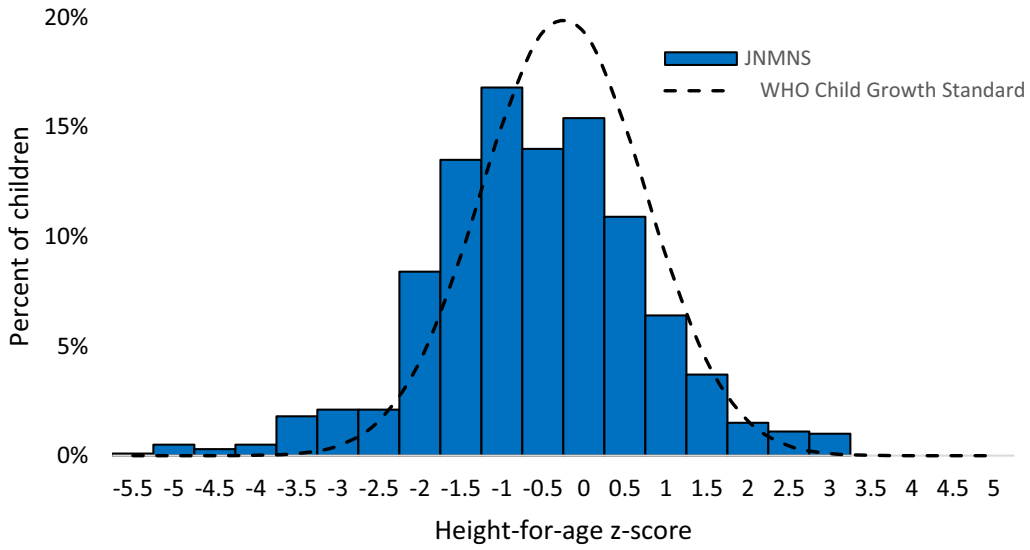


FIGURE 10
Height-for-age z-scores distribution in children <5 years of age, settled population, Jordan.

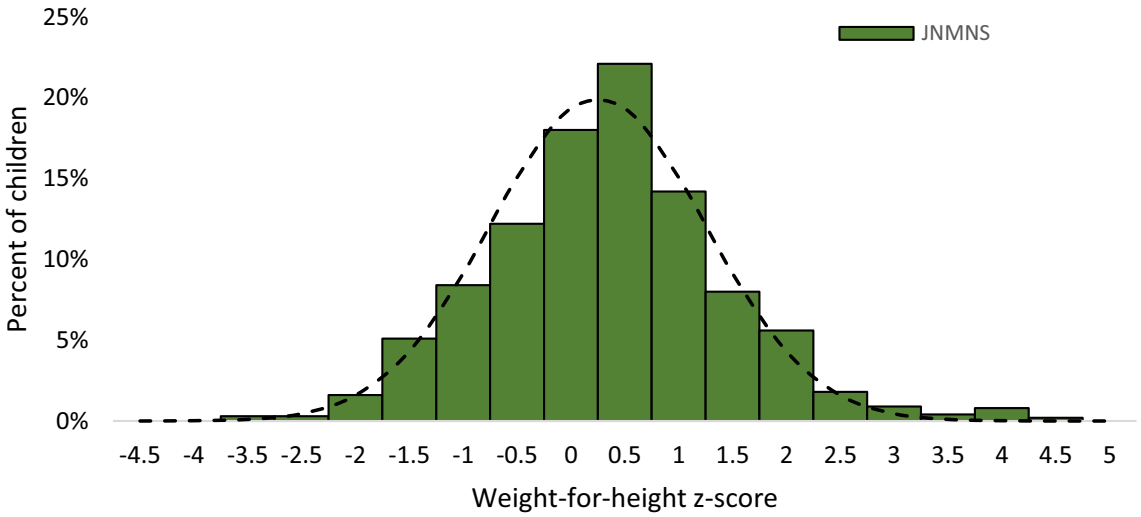


FIGURE 11
Weight-for-height z-scores distribution in children 6–59 months, settled population, Jordan.

Although almost one quarter of children consumed vitamin A supplements, supplement consumption in general and treatment with an anthelmintic drug in the preceding 6 months was low in this age group (Figure 13).

## 4 Discussion

The JNMNS 2019 aimed to compare its findings with the 2010 national survey to understand micronutrient deficiencies better. It also assessed the double burden of malnutrition by collecting data on both under-and overnutrition. Additionally, the survey evaluated changes in key micronutrient intake among preschool children compared to the 2010 survey.

Data from 2019 suggest that anemia among young children is a mild public health problem in the settled population. Among young children aged between 6 and 59 months, 11.9% were anemic. No children in this age group had severe anemia and 2.4% had moderate anemia. In the same age group, 26% were iron deficient and 5.1% had iron-deficiency anemia in 2019. Not all anemia in Jordan is due to iron deficiency. As children get older, there is less overlap between anemia and iron deficiency, suggesting that other causes of anemia are more significant. Overall, anemia prevalence in this age group decreased between 2010 and 2019, whereas iron deficiency prevalence

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TABLE 8 Prevalence of overweight and obesity in children 0–59 months, by various demographic characteristics, settled population, Jordan.

| | | Obesity[b] | | Overweight[b] | | | Total overweight or obesity[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| Characteristic | *n* | %[a] | 95% CI | % | 95% CI | *p*-value[c] | % | 95% CI | *p*-value[c] |
| Total | 747 | 2.2% | (1.2, 4.0) | 7.0% | (4.9, 9.7) | | 9.2% | (6.9, 12.1) | |
| Age (in months) | | | | | | | | | |
| 0–11 | 153 | 2.0% | (0.4, 9.4) | 10.6% | (5.9, 18.1) | 0.630 | 12.6% | (7.5, 20.4) | 0.328 |
| 12–23 | 147 | 3.3% | (1.1, 9.0) | 7.1% | (3.6, 13.4) | | 10.4% | (6.0, 17.4) | |
| 24–35 | 156 | 2.9% | (0.9, 9.2) | 7.6% | (3.8, 14.8) | | 10.5% | (5.7, 18.6) | |
| 36–47 | 138 | 1.7% | (0.6, 5.2) | 5.0% | (1.7, 14.0) | | 6.7% | (2.9, 15.1) | |
| 48–59 | 153 | 1.1% | (0.3, 4.3) | 3.8% | (1.3, 10.6) | | 4.8% | (2.0, 11.4) | |
| Sex | | | | | | | | | |
| Male | 363 | 2.3% | (1.1, 4.8) | 9.4% | (6.5, 13.5) | 0.072 | 11.7% | (8.6, 15.7) | 0.023 |
| Female | 384 | 2.1% | (0.8, 5.4) | 4.5% | (2.6, 7.7) | | 6.7% | (4.2, 10.5) | |
| Residence | | | | | | | | | |
| Urban | 596 | 2.5% | (1.4, 4.6) | 7.5% | (5.2, 10.6) | 0.286 | 10.0% | (7.5, 13.2) | 0.204 |
| Rural | 149 | 0.7% | (0.1, 4.6) | 4.5% | (1.5, 12.5) | | 5.2% | (1.8, 13.7) | |
| Stratum | | | | | | | | | |
| Central | 171 | 1.8% | (0.6, 5.2) | 5.8% | (3.2, 10.6) | 0.397 | 7.6% | (4.6, 12.3) | 0.266 |
| Northern | 333 | 3.3% | (1.8, 5.9) | 8.7% | (6.0, 12.5) | | 12.0% | (8.7, 16.3) | |
| Southern | 243 | 1.2% | (0.4, 3.9) | 7.4% | (4.2, 12.6) | | 8.6% | (5.1, 14.1) | |
| Wealth quintile | | | | | | | | | |
| Poorest | 213 | 1.3% | (0.4, 4.5) | 3.5% | (1.4, 8.3) | 0.477 | 4.8% | (2.3, 9.9) | 0.310 |
| Second | 165 | 3.1% | (1.0, 9.5) | 6.2% | (2.9, 12.8) | | 9.3% | (4.8, 17.0) | |
| Middle | 164 | 0.9% | (0.2, 3.6) | 9.3% | (5.2, 16.2) | | 10.2% | (5.8, 17.2) | |
| Fourth | 128 | 3.3% | (0.9, 11.0) | 7.4% | (3.3, 15.5) | | 10.7% | (5.6, 19.4) | |
| Wealthiest | 77 | 3.7% | (0.8, 15.3) | 10.5% | (4.4, 22.8) | | 14.2% | (6.7, 27.5) | |

The *n*'s are un-weighted numbers (denominator) for each subgroup; subgroups that do not sum to the total have missing data.

[a]Percentages weighted for unequal probability of selection.

[b]Overweight is defined as having a weight-for-height z-score greater than +2 but less than or equal to +3 standard deviations from the WHO Child Growth Standards population median; obesity is defined as having a weight-for-height z-score greater than +3 standard deviations from the WHO Child Growth Standards population median.

[c]*P* value <0.05 indicates that at least one subgroup is significantly different from the others.

increased and anemia caused by iron deficiency remained largely unchanged.

The observed declines in overall anemia and severe anemia may be attributed to some extent to the successful national wheat flour fortification program. Given the substantial difference in prevalence of anemia and iron-deficiency anemia in some groups, further research is needed to investigate the potential causes of anemia and iron deficiency. An analysis of these data will be able to inform policy responses and intervention. The most recent JNMNS 2019 looked into factors related to anemia and iron deficiency.

The 2010 Jordan Micronutrient Survey recorded a lower prevalence of iron deficiency. However, due to the incomplete correction for inflammation in serum ferritin concentrations, the computed values likely leaned toward higher levels, resulting in an underestimated prevalence of iron deficiency. A meta-analysis for the Middle East and North Africa region indicated that 35% of anemia can be attributed to iron deficiency (30). Our preliminary analysis of anemia risk factors suggests that both iron and vitamin A deficiency play significant roles, while the scarcity of α-and β-thalassemia minimizes their impact on public health.

The prevalence of vitamin A deficiency among young children under 5 is categorized as a mild public health issue in Jordan. According to 2019 data, the prevalence was 4.8% among preschool children, with variations depending on the indicator used (8.1% based on serum retinol and 4.3% based on RBP). This represents an improvement since 2010, possibly attributed to the intensified vitamin A supplementation program implemented since 2012. However, it's important to note that the 2010 survey excluded children aged 6 to 11 months, a group identified by the JNMNS as having a considerably higher prevalence of vitamin A deficiency compared to older children.

In Jordan, a substantial proportion of young children are vitamin D deficient. Studies in the Middle East and North Africa region reported varying prevalence rates for vitamin D deficiency in this age group, ranging from 12 to 60% (31).

The prevalence of zinc deficiency in preschool children within the settled population of Jordan is lower than the global levels reported by the WHO Vitamin and Mineral Nutrition Information System (VMNIS) (32, 33). The JNMNS found slight association between stunting and zinc deficiency, possibly attributable to the low prevalence of both zinc deficiency and stunting.

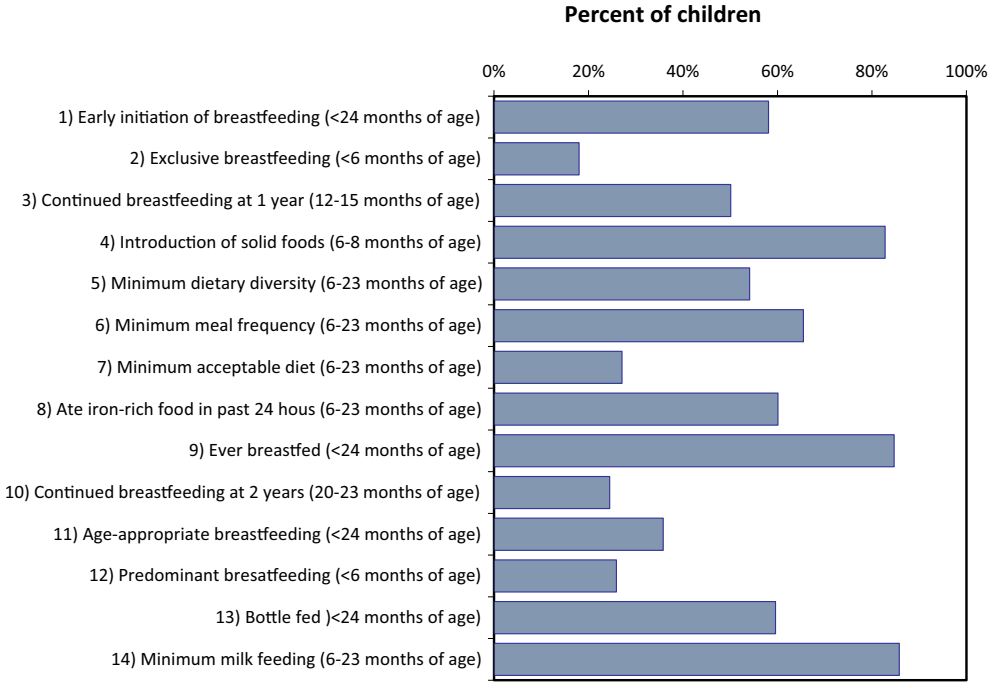


FIGURE 12
Prevalence of standard WHO/UNICEF infant and young child feeding indicators in children of various ages, settled population, Jordan.

TABLE 9 Additional dietary indicators in children less than 24 months of age, settled population, Jordan.

| Characteristic | *N* | %[a] | 95% CI[b] |
|---|---|---|---|
| Liquids other than breast milk consumed in past 24 h (<6 months of age) | | | |
| - Plain water | 42 | 49.7% | (35.5, 63.9) |
| - Infant formula | 37 | 42.0% | (27.2, 58.3) |
| - Tinned, powdered, or other non-human milk | 35 | 41.4% | (28.9, 55.1) |
| - Juice or juice drinks | 6 | 3.8% | (1.7, 8.3) |
| - Shourba or clear broth | 7 | 4.1% | (1.9, 8.6) |
| - Yogurt | 10 | 7.8% | (3.3, 17.3) |
| - Thin porridge | 4 | 4.0% | (1.0, 15.4) |
| - Other liquids | 9 | 4.6% | (2.3, 9.3) |
| Ate sugary foods in past 24 h (6–23 months of age) | | | |
| - Yes | 118 | 46.9% | (37.2, 56.9) |
| - No | 115 | 53.1% | (43.1, 62.8) |
| Consumed sugary drinks in past 24 h (6–23 months of age)[c] | | | |
| - Yes | 103 | 38.8% | (31.3, 46.9) |
| - No | 130 | 61.2% | (53.1, 68.7) |
| Ate salty/fried foods in past 24 h (6–23 months of age)[d] | | | |
| - Yes | 90 | 37.5% | (29.7, 46.0) |
| - No | 143 | 62.5% | (54.0, 70.3) |

The *n*'s are un-weighted numbers for each subgroup; subgroups that do not sum to the total have missing data.
[a]Percentages weighted for unequal probability of selection.
[b]CI = confidence interval calculated taking into account the complex sampling design.
[c]The question was about 'Sugar-sweetened beverages (soft drinks/fizzy drinks, chocolate drinks, malt drinks, yoghurt drinks, sweet tea or coffee with sugar, sweetened fruit juices and "juice drinks").
[d]The question was about 'Salty or fried snacks: Crisps and chips, fried dough or other fried snacks (e.g., Samposic).

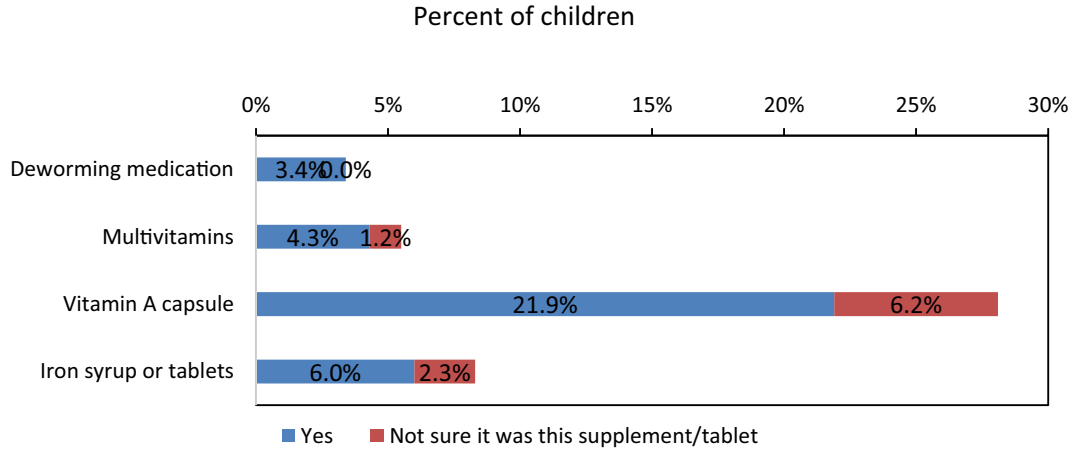


FIGURE 13
Percentages of children under 5 years of age who have taken different supplements in past 6 months, settled population, Jordan.

Overall, the prevalence of undernutrition in young Jordanian children is low, with a reduction in stunting between 2010 and 2019. Stunting prevalence in the settled population is considered low according to WHO cut-off values, constituting a moderate public health problem. The prevalence of overweight among children under 5 years was 9.2% in 2019 (2.2% with obesity), signifying a moderate public health issue that demands policy attention (34).

To mitigate overweight and obesity, WHO recommends limiting energy intake from fats and sugars and engaging in regular physical activity (35). In the JNMNS, almost half of children aged 6–23 months consumed sugary foods, one-third consumed sugary drinks, and over one-third consumed salty/fried snacks in the previous 24 h. Additionally, very few children participated in organized physical activity, though no association was found between physical activity and overweight/obesity in young children.

## 5 Strengths and limitations of the JNMNS

One of the study limitation is the response rate among preschool children which was notably lower than expected. This was primarily due to a relatively high rate of refusal among this age group and the challenges associated with performing phlebotomy on children under 2 years old. Although the study provided national estimates with confidence intervals deemed satisfactory for preschool children, the relatively small sample size of young children resulted in lower precision than expected for subgroup-specific estimates based on laboratory test results.

The trends in various nutrition indicators did not follow a consistent pattern. The prevalence of anemia decreased between 2010 and 2019 in both preschool children and non-pregnant women. However, during the same period, the prevalence of iron deficiency increased, and the prevalence of iron deficiency anemia remained stable. Additionally, there was a decline in the prevalence of vitamin A deficiency, while vitamin D deficiency remained persistently high without significant changes.

## 6 Conclusion and recommendations

Overall, stunting was less common in this age group between 2010 and 2019, with a low prevalence of under-nutrition among young Jordanian children in the settled population, which falls within the WHO's cut-off values for public health significance.

The following WHO recommendations should be enforced for feeding infants and young children (6–23 months): Continued breastfeeding, introduction of solid, semisolid, or soft foods at 6 months, ensuring food diversity (at least five food groups per day), maintaining appropriate meal frequency (two to three times per day between 6 and 8 months, increasing to three to four times per day between 9 and 23 months, with nourishing snacks offered once or twice a day as desired), safe food preparation, and responsive feeding based on infants' cues are all crucial.

For children aged 2–5 years, promoting a healthy and balanced diet in households, kindergartens, and schools, along with the activation of growth monitoring at Primary Health Centers (PHCs) and schools, is essential.

Anemia in Jordan has a complex etiology involving both nutritional and non-nutritional factors, making it a multifactorial condition. Addressing anemia should consider additional potential contributing factors beyond iron deficiency. While Jordan may not be on track to achieve the WHA and SDG goals, anemia is shifting from severe to moderate to mild among preschool children, which reflects the impact of the national flour fortification program.

The prevalence of vitamin A deficiency among young children under 5 is classified as a mild public health problem in Jordan. This reflects the diversity in the diets of this group, as well as the impact of wheat flour fortification. However, vitamin D deficiency remains a concern, and there is a need to encourage sun exposure and consider increasing the levels of vitamin D3 in flour fortification to align with WHO recommendations.

The implementation of the national nutrition strategy by the Ministry of Health (MOH) using a multisectoral approach in collaboration with significant stakeholders is expected to yield more effective results and outcomes. Additionally, it is essential to integrate comprehensive nutrition and health education for parents into the

national nutrition strategy to effectively enhance children's nutritional status. This education can empower parents with the knowledge and tools needed to make informed decisions about their children's diet and health.

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://www.moh.gov.jo/ebv4.0/root_storage/ar/eb_list_page/jnmns19_report_220207_printable.pdf.

## Ethics statement

The studies involving humans were approved by Ministry of Health, Jordan, Amman. 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

RB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. RT: Writing – original draft, Writing – review & editing. LA-M: Data curation, Formal analysis, Methodology, Resources, Writing – review & editing. BA-K: Conceptualization, Data curation, Methodology, Writing – review & editing. AJ: Writing – original draft, Writing – review & editing.

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## Conflict of interest

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

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# The association of vitamin D insufficiency with the prevalence of obesity in children: implications for serum calcium levels, alkaline phosphatase activity, and bone maturation

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**Background:** Vitamin D deficiency has been identified as a potential risk factor for various adverse health outcomes. However, its specific role in metabolic regulation and skeletal development in school-aged children is not fully understood. This study aimed to explore the correlation between vitamin D deficiency and childhood obesity rates, and its impact on serum calcium, alkaline phosphatase, and bone age in children.

**Methods:** The study analyzed clinical data from 159 school-aged children who underwent medical examinations. Participants were divided into the 25-hydroxyvitamin $D_3$ (25(OH)$D_3$) deficiency group and the 25(OH)$D_3$ normal group based on their serum levels. We compared body mass index (BMI), total cholesterol (TC), triglycerides (TG), Ca, ALP, bone age, fasting blood glucose (FBG), and hemoglobin A1c (HbA1c) between the two groups. Logistic regression and Spearman correlation analyses were performed to further investigate relationships between 25(OH)$D_3$ levels and metabolic and bone-related markers.

**Results:** This study showed that the 25(OH)$D_3$ deficiency cohort exhibited significantly higher BMI, TC, TG, and ALP levels, with lower Ca levels and delayed bone age compared to the normal group. Logistic regression analysis identified Ca, ALP, and bone age as significant predictors of 25(OH)$D_3$ deficiency. Subgroup analysis showed that in the 25(OH)$D_3$ deficient group, children with higher BMI had elevated TC, ALP levels, and delayed bone age, while Ca levels were lower. Correlation analysis confirmed the predictive value of these markers for 25(OH)$D_3$ deficiency.

**Conclusion:** Our findings demonstrate that 25(OH)$D_3$ deficiency is strongly associated with obesity in school-aged children and may negatively affect normal skeletal development. Regular monitoring of 25(OH)$D_3$ levels in school-aged children is essential for ensuring proper growth and development, especially in those at risk for obesity.

KEYWORDS

**vitamin D, school-aged children, obesity, bone age, BMI**

# 1 Introduction

Vitamin D, a lipid-soluble vitamin, is integral to a myriad of physiological processes, notably enhancing cellular proliferation, facilitating differentiation, and modulating immune responses (1). As an essential nutrient not endogenously produced by the human body, vitamin D must be acquired through dietary intake or sunlight exposure, such as fish liver, egg yolks, and certain dairy products. Once absorbed in the small intestine, dietary sources of vitamin D are transported via chylomicrons into the bloodstream and converted in the liver into 25(OH)$D_3$. This intricate physiological process is the principal form of vitamin D circulating in the bloodstream, serving a vital function in the facilitation of calcium absorption and bone mineralization.

Previous studies showed that infants, children, adolescents, and pregnant women require 400 IU/d of vitamin D, and inadequate dietary intake can lead to insufficiency in vitamin D, increasing the risk of conditions such as adult osteomalacia and childhood rickets (2–4).

Vitamin D insufficiency is a globally recognized public health challenge, affecting billions of individuals worldwide (5–7). In China, vitamin D deficiency poses an equally pressing concern, notably affecting school-aged children. Ongoing developmental processes in preschool-aged children may render them susceptible to a range of gastrointestinal disorders, potentially hindering efficient vitamin D absorption. Furthermore, selective eating behaviors in this age group increase their risk of vitamin D deficiency (8, 9). Research indicates that 34% of obese children are affected by this deficiency (10). Vitamin D deficiency has been alarmingly associated with a spectrum of severe health conditions, encompassing cardiovascular diseases, metabolic disorders, endocrine imbalances, and even childhood cancers (11). Overall, the issue of vitamin D insufficiency in school-aged children is increasingly gaining attention from various sectors of society.

TC, TG, FBG, and HbA1c are widely acknowledged in glucose and lipid metabolism for their diagnostic value. In clinical practice, the assessment of vitamin D status is conventionally conducted by detecting 25(OH)$D_3$ levels. Therefore, we aim to assess how variations in 25(OH)$D_3$ levels affect Ca levels, ALP activity, and bone age in this pediatric population. This study aims to investigate the risk of childhood obesity and foster optimal skeletal growth and development by addressing vitamin D deficiency in school-aged children. This study aims to examine childhood obesity and promote skeletal growth and development in school-aged children by addressing the deficiency of 25(OH)$D_3$.

# 2 Materials and methods

## 2.1 Subjects and data collection

We retrospectively analyzed clinical data collected from 159 school-aged children (aged 6–12 years) during health examinations at the Hainan Hospital of PLA General Hospital and Lingshui Li Autonomous County People's Hospital from April 2019 to April 2022. Baseline data were systematically collected using a standardized data collection form to ensure consistency and accuracy, which included demographic information such as age, gender, and residential location obtained through parental interviews and hospital records. Anthropometric measurements, including height and weight, were recorded using calibrated equipment, and BMI was calculated using the formula: BMI = weight (kg) /height$^2$ (m$^2$). Serum samples were collected to measure TC, TG, Ca, ALP, FBG and HbA1c in accordance with standard laboratory protocols. Data pre-processing involved detecting outliers using the interquartile range (IQR) method and handling missing values via multiple imputation techniques to ensure data integrity. To facilitate comparability between datasets from the two hospitals, *Z*-score normalization was performed on the biochemical parameters. The American Academy of Pediatrics' criteria for vitamin D deficiency were applied: <15 ng/mL as deficiency, 15–20 ng/mL as insufficiency, and ≥20 ng/mL as sufficiency. In this study, participants were categorized into two groups based on their 25(OH)$D_3$ serum levels: the deficiency group ($n$ = 56), including both deficient (<15 ng/mL) and insufficient (15–20 ng/mL) levels; the non-deficiency group ($n$ = 103), with sufficient levels (≥20 ng/mL).

## 2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) All participants were children undergoing routine health examinations. (2) Age range of 6 to 12 years. (3) Availability of complete clinical data for each participant.

The exclusion criteria were as follows: (1) Physical growth abnormalities or deformities. (2) A history of gastrointestinal, respiratory, or other system-related illnesses and recent medication use within the past 3 months. (3) Immunological disorders or uncontrolled infections. (4) Impaired heart, liver, or kidney functions.

Ethics approval and consent to participate: From 2019 until late 2022, clinical data collected from 159 school-aged children during health examinations and outpatient visits at the Hainan Hospital of PLA General Hospital and Lingshui Li Autonomous County People's Hospital. The Ethics Committee of Hainan Hospital of PLA General Hospital and the Ethics Committee of Lingshui Li Autonomous County People's Hospital was responsible for supervising and approving the course of the entire study.

## 2.3 Collection of clinical blood samples

A total of 5 mL of venous blood was obtained from each child through standard venipuncture techniques, ensuring aseptic conditions. Blood samples were processed within 2 h post-collection to maintain the integrity of the biochemical analyses.

## 2.4 Measurement of TC and TG

TC and TG levels were measured using a ADVIA 2400 automated biochemical analyzer (Siemens AG, Germany). Serum was separated from whole blood via centrifugation at 3000 rpm for 10 min at room temperature. Serum samples are mixed with the corresponding reagents as per the manufacturer's instructions, and the resulting TC and TG levels are assessed colorimetrically at 500 nm. All reagent kits are sourced from Roche (Shanghai, China).

## 2.5 Serum levels of FBG

FBG levels were assessed using the 7060 automated biochemical analyzer (Hitachi, Japan). Following serum preparation as described, the glucose oxidase method was utilized, wherein glucose is oxidized to gluconic acid and hydrogen peroxide. The resultant hydrogen peroxide is colorimetrically measured at 505 nm. The reagent kits are from Roche (Shanghai, China).

## 2.6 Serum levels of FBG

The levels of HbA1c were analyzed using the RT6000 microplate reader (Rayto, China). Whole blood was mixed with a buffer, incubated at room temperature for 15 min, and then centrifuged at 3,000 rpm. The supernatant was subsequently injected into the HPLC system, with measurements taken at an absorbance of 415 nm. Reagent kits were supplied by Roche (Shanghai, China).

## 2.7 Serum levels of calcium and ALP

Calcium and ALP levels were measured using the Hitachi 7060 automated biochemical analyzer. After centrifugation of serum at 4°C, serum samples were mixed with the reagents for calcium and ALP assays in accordance with Roche (Shanghai, China) instructions. The calcium levels were measured at 650 nm, while the ALP levels were assessed at 405 nm.

## 2.8 Measurement of 25(OH)$D_3$ levels

The measurement of 25(OH)$D_3$ levels was performed using an enzyme-linked immunosorbent assay (ELISA) by Roche (Shanghai, China). Serum samples were diluted in a buffer, followed by the addition of specific antibodies against 25(OH)$D_3$. After incubation and washing, a substrate solution was added to produce a color change proportional to the 25(OH)$D_3$ concentration in the sample. Absorbance was measured at 450 nm using the 680 microplate reader (Bio-Rad, United States).

## 2.9 Bone age assessment and calculation of body mass index

All children underwent a radiographic examination of the left wrist in the hospital after admission using a Shimadzu X-ray machine. During the radiographic examination, the palm and fingers were placed facing downwards on the detector. The children were instructed by the physician to extend their forearms and hands until the forearm axis aligned with the middle finger axis, with their fingers naturally spread apart. The central axis of the X-ray beam was aligned with the third metacarpophalangeal joint gap, and a perpendicular projection was taken, with the focal-film distance set at 90 cm. Furthermore, the BMI was calculated following the collection of admission statistics for the children, using the formula BMI = body weight (kg) /height$^2$ (m$^2$).

## 2.10 Statistical analysis

Data analysis was performed using SPSS 22.0. Continuous variables were assessed for normality using the Kolmogorov–Smirnov test. Independent sample *t*-tests were employed for normally distributed variables, while non-normally distributed data were analyzed using the Mann–Whitney *U* test. Categorical data were compared using the $\chi^2$ test. Spearman correlation analysis was performed to explore associations between 25(OH)$D_3$ levels and BMI, TC, TG, Ca, ALP, and bone age. Multivariate logistic regression analysis was conducted to assess the independent predictors of 25(OH)$D_3$ deficiency. ROC curve analysis was used to evaluate the predictive value of BMI, TC, TG, Ca, ALP, and bone age in diagnosing vitamin D deficiency. Statistical significance was set at $p < 0.05$.

# 3 Results

## 3.1 Basic information of the two groups and comparison of laboratory indices and bone age between the two groups

To explore the correlation between vitamin D deficiency and the prevalence of obesity in children, we conducted a retrospective analysis of the clinical data from 159 school-age children who underwent physical examinations (Figure 1). Among the participants, 109 were male and 50 were female, with ages ranging from 6 to 12 years and an average age of 9.27 ± 2.10 years. No significant differences were observed in gender, age, height (Figure 2A), FBG, and HbA1c between the two cohorts ($p > 0.05$). However, the group with 25(OH)$D_3$ deficiency showed significantly higher levels of weight, BMI, TC, TG, and ALP compared to the non-deficient group (Figures 2B–F). In contrast, Ca levels and bone age were significantly lower in the 25(OH)$D_3$ deficiency group (Figures 2G,H). The general characteristics of these patients are detailed in Table 1.

## 3.2 Comparison of left wrist normal-position X-rays in the two groups of children

In the present investigation, we collected anteroposterior radiographs of the left hand from a cohort of school-age children for bone age evaluation. Furthermore, we have featured a subset of exemplary radiographic findings. Figure 3A presents a standard anteroposterior X-ray image of the left wrist from a 9-year-old female participant in the non-25(OH)$D_3$ group. The radiographic R-series indicates a bone age advancement of 9 months relative to chronological age, while the C-series demonstrates a normal bone age alignment. Figure 3B likewise represents an anteroposterior radiograph of the left wrist from a 9-year-old male, the R-series suggests a bone age 5 months older than the actual age, and the C-series indicates a 1-year and 2-month difference. Figure 3C shows a radiograph from a 9-year-old male exhibiting 25(OH)$D_3$ insufficiency. The R series indicates a bone age 2 years younger than his actual age, while the C series suggests a bone age 1 year and 10 months older. Similarly, we found that school-aged children within the 25(OH)$D_3$ deficiency cohort exhibit lower R-series and C-series ages than their peers (Figure 3D).

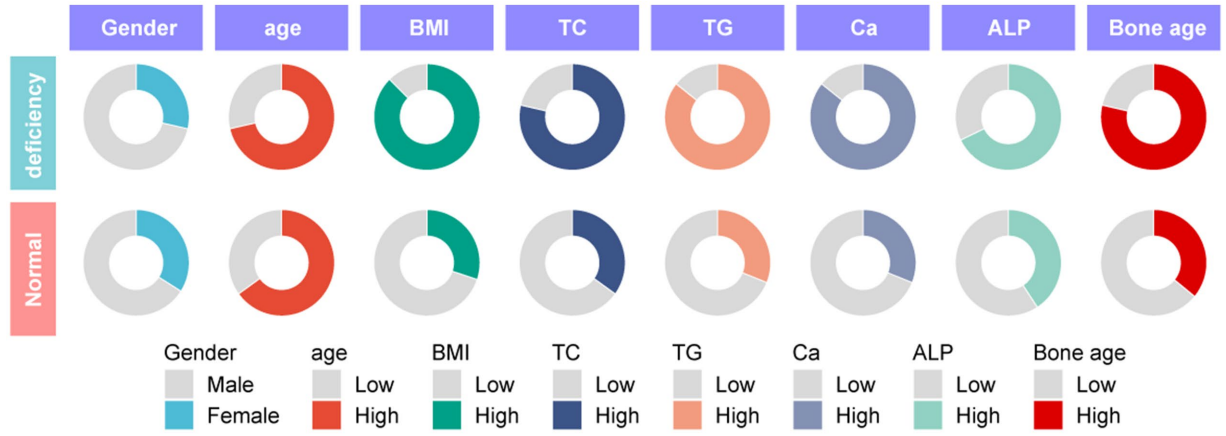


FIGURE 1
Patient baseline characteristics diagram.

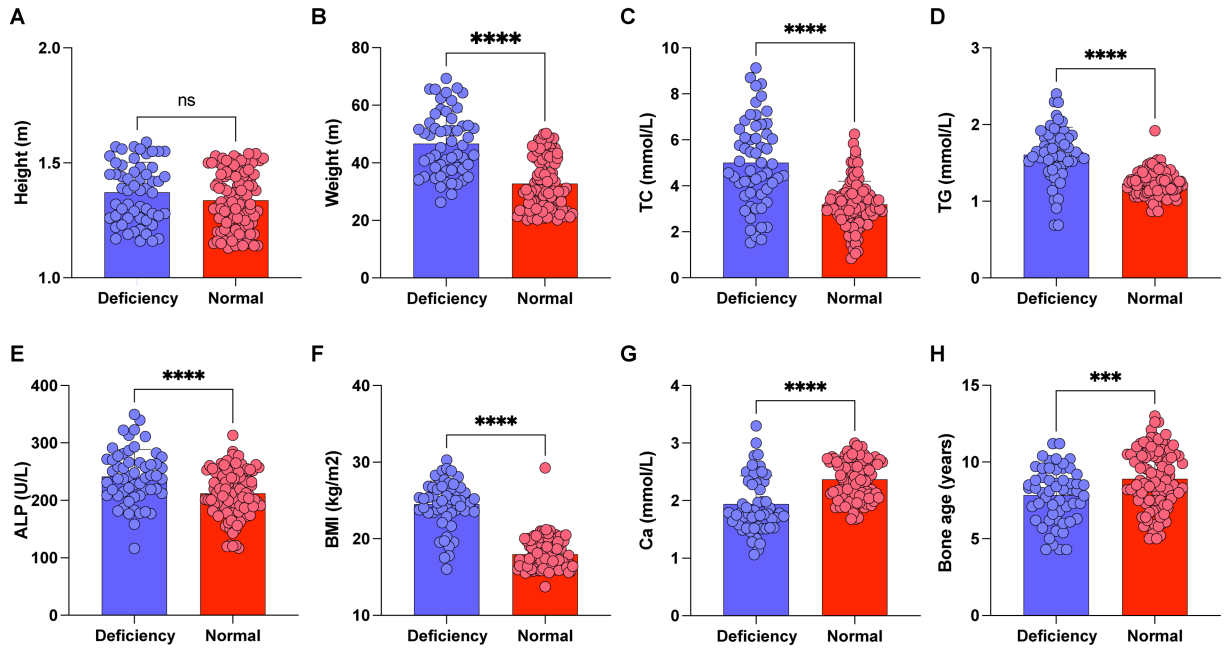


FIGURE 2
Comparison of height, weight, BMI, TC, TG, Ca, ALP and bone age between 25-(OH)$D_3$ deficiency group and non-25-(OH)$D_3$ deficiency group. (A) Height. (B) Weight. (C) TC. (D) TG. (E) Ca. (F) BMI. (G) ALP. (H) Bone age. ns $p > 0.05$, ***$p < 0.001$, ***$p < 0.0001$.

In summary, our research findings indicate that a deficiency in 25(OH)$D_3$ during the school-age period is a significant risk factor for delayed growth and development.

## 3.3 The value of BMI, TC, TG, Ca, ALP, and bone age in predicting 25(OH)$D_3$ deficiency in school-aged children

We further constructed the receiver operating characteristic (ROC) curve to assess whether BMI, TC, TG, Ca, ALP, and bone age could be utilized for forecasting 25(OH)$D_3$ deficiency in school-aged children. The AUC for each parameter was BMI (AUC: 0.879), TC (AUC: 0.785), TG (AUC: 0.872), Ca (AUC: 0.839), ALP (AUC: 0.688), and bone age (AUC: 0.809), respectively, all of which presented a significance level of $p < 0.05$ (Table 2). The results confirmed that a vast majority of clinical Indicators have a significant diagnostic value (Figure 4).

## 3.4 Analysis of the relationship between 25(OH)$D_3$ levels and BMI, TC, TG, Ca, ALP, and bone age

To further analyze whether there is a direct correlation between 25(OH)$D_3$ levels and BMI, BMI, TC, TG, Ca, ALP, and bone age.

TABLE 1 Baseline characterization of participation.

| Item | 25-(OH)$D_3$ deficiency group ($n$ = 56) | Non-25-(OH)$D_3$ deficiency group ($n$ = 103) | $x^2/t$ | $P$ |
|---|---|---|---|---|
| Gender ($n$) | | | 0.01 | 0.88 |
| Male [$n$ (%)] | 38 | 71 | | |
| Female [$n$ (%)] | 18 | 32 | | |
| Age (years) | 9.24 ± 2.06 | 9.30 ± 2.11 | 0.17 | 0.86 |
| Height (m) | 1.36 ± 0.11 | 1.31 ± 0.11 | 5.23 | 0.1 |
| Weight (kg) | 48.60 ± 9.37 | 32.09 ± 7.23 | 8.83 | <0.001 |
| BMI (kg/m$^2$) | 24.10 ± 3.12 | 17.96 ± 1.28 | 9.62 | <0.001 |
| TC (mmol/L) | 4.92 ± 1.88 | 3.18 ± 1.07 | 7.44 | <0.001 |
| TG (mmol/L) | 1.62 ± 0.39 | 1.23 ± 0.14 | 9.14 | <0.001 |
| FBG (mmol/L) | 4.23 ± 1.01 | 4.24 ± 1.06 | 0.05 | 0.95 |
| HbA1c (%) | 4.90 ± 0.67 | 4.88 ± 0.63 | 0.18 | 0.85 |
| Ca (mmol/L) | 1.94 ± 0.15 | 2.64 ± 0.21 | 22.05 | <0.001 |
| ALP (U/L) | 241.50 ± 61.27 | 212.72 ± 46.85 | 3.31 | <0.001 |
| Bone age (years) | 6.18 ± 1.36 | 7.58 ± 1.51 | 5.77 | <0.001 |

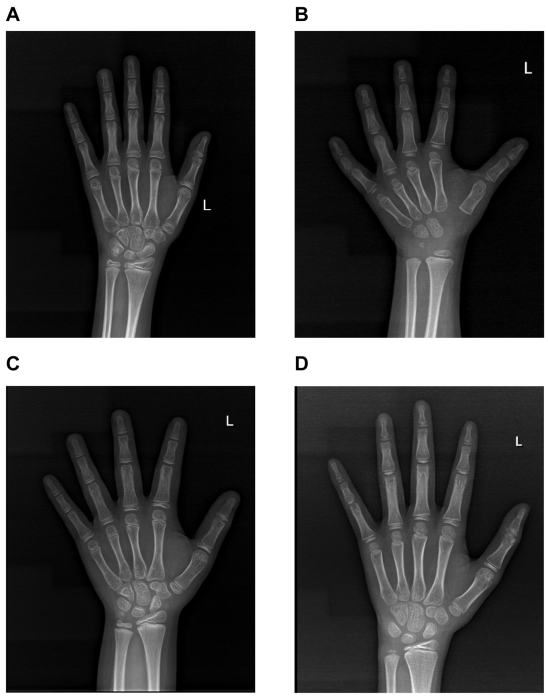


FIGURE 3
Images of normal-position X-rays of the left wrist in the two cohorts. (A) The normal-position X-ray image of the left wrist in a 9-year-old female from the 25(OH)$D_3$ normal group. (B) The normal-position X-ray image of the left wrist in a 9-year-old male from the 25(OH)$D_3$ normal group. (C) The normal-position X-ray image of the left wrist in a 9-year-old male from the 25(OH)$D_3$ insufficiency group. (D) The normal-position X-ray image of the left wrist in a 9-year-old male from the 25(OH)$D_3$ deficiency group.

We selected 56 children from the 25(OH)$D_3$ deficiency cohort and used Spearman's correlation analysis to assess whether there is an association between their serum 25(OH)$D_3$ levels and BMI, TC, TG, Ca, ALP, and bone age. The outcomes illustrated that there was a negative correlation between 25(OH)$D_3$ levels in the children's serum and BMI ($R^2 = -0.6234$, $p < 0.0001$), TC ($R^2 = -0.5998$, $p < 0.0001$), TG ($R^2 = -0.6125$, $p < 0.0001$), and ALP ($R^2 = -0.6019$, $p < 0.0001$) (Figures 5A–D), whereas a positive correlation was observed with Ca ($R^2 = 0.5920$, $p < 0.0001$) and bone age ($R^2 = 0.6729$, $p < 0.0001$) (Figures 5E–F). These correlations were statistically significant with $p < 0.05$, as presented in Table 3.

To further explore the relationship between 25(OH)$D_3$ levels and BMI, TC, TG, Ca, ALP, and bone age, we performed a logistic regression analysis. The dependent variable was the presence of 25(OH)$D_3$ deficiency, while BMI, TC, TG, Ca, ALP, and bone age were included as independent variables in the model. The logistic regression analysis revealed that Ca, ALP levels and bone age were significant independent predictors of 25(OH)$D_3$ deficiency, with odds ratios (ORs) greater than 1 ($p < 0.05$), indicating an increased risk of deficiency (Figure 6A). To further substantiate our findings, we developed a ROC curve using multiple indicators (BMI, TC, TG, Ca, ALP, and bone age), which demonstrated the strong predictive value of these factors for identifying 25(OH)$D_3$ deficiency (Figure 6B). These findings further support the significant correlations observed in the Spearman analysis, demonstrating the strength of association between these metabolic and bone-related markers and 25(OH)$D_3$ deficiency.

## 3.5 Subgroup analysis based on BMI in 25(OH)$D_3$ deficient children

Based on our findings, vitamin D deficiency is closely linked to obesity in school-age children. We further conducted a subgroup analysis of children with 25(OH)$D_3$ deficiency stratified by their BMI levels. Our analysis revealed that 25(OH)$D_3$ deficient children with higher BMI had significantly elevated levels of TC, ALP, and advanced bone age, while Ca levels were relatively lower (Figures 7A–F). These findings highlight a stronger

TABLE 2 The value of BMI, TC, TG, Ca, ALP, and bone age in predicting 25-(OH)$D_3$ deficiency in school-aged children.

| Index | AUC | SE | *p* | 95% CI | Optimum cutoff value | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|
| BMI | 0.879 | 0.815–0.943 | 0.682 | 24.50 kg/m$^2$ | 0.932 | 0.750 | 0.879 |
| TC | 0.785 | 0.700–0.868 | 0.530 | 4.08 mmol/L | 0.816 | 0.714 | 0.785 |
| TG | 0.872 | 0.797–0.948 | 0.698 | 1.39 mmol/L | 0.913 | 0.785 | 0.872 |
| Ca | 0.839 | 0.762–0.915 | 0.704 | 2.18 mmol/L | 0.884 | 0.821 | 0.839 |
| ALP | 0.688 | 0.598–0.778 | 0.297 | 306.26 U/L | 0.922 | 0.375 | 0.688 |
| Bone age | 0.809 | 0.736–0.881 | 0.545 | 7.25 years | 0.777 | 0.768 | 0.809 |

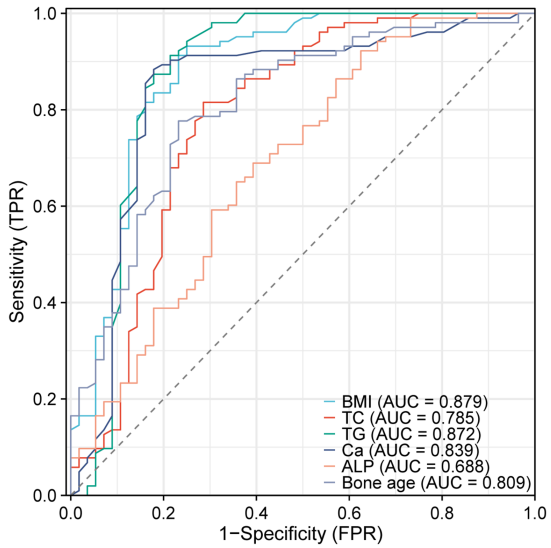


FIGURE 4
ROC curves of BMI, TC, TG, Ca, ALP, and bone age predicting 25(OH)$D_3$ deficiency in school-aged children.

association between obesity and specific metabolic and bone-related markers in children with 25(OH)$D_3$ deficiency, providing further insight into the complex interplay between 25(OH)$D_3$ status and childhood obesity.

## 4 Discussion

Over the last several years, with the improvement in people's quality of life, childhood obesity has become increasingly prominent. As opposed to healthy children, this group shows a dramatic elevation in BMI, and the risk of cardiovascular and metabolic diseases is also vigorously heightened (12–14). 25(OH)$D_3$, as a common indicator for evaluating vitamin D, plays a crucial role in regulating Ca levels and influencing cell proliferation and differentiation, which are of great significance in the body's growth and development. Therefore, this research seeks to probe the relationship between 25(OH)$D_3$ and BMI, TC, and TG in school-aged children, observing the impact of alterations in 25(OH)$D_3$ levels on childhood obesity. In addition, Ca, ALP, and bone age are important indicators of bone metabolism. Actively investigating the influence of 25(OH)$D_3$ changes on Ca, ALP, and bone age may provide a theoretical basis for understanding the abnormalities in Ca, ALP, and bone age caused by vitamin D deficiency in school-aged children.

The findings of this study suggested that the 25(OH)$D_3$ deficiency cohort had substantially heightened BMI, TC, and TG levels compared to the non-deficiency cohort, which meant that 25(OH)$D_3$ deficiency could culminate in childhood obesity. In a preceding study, researchers have ascertained that 25(OH)$D_3$ in obese children is vigorously lowered vis-à-vis normal-weight children. In this scenario, the BMI of obese children abnormally increases. They have also pointed out that with the increasing age of obese children, the 25(OH)$D_3$ deficiency worsens, which can mutually support the findings of this study (15). TC and TG are both commonly utilized clinical indicators for assessing the lipid content within the blood. The former reflects the total cholesterol contained in lipoproteins in the blood, while the latter reflects the total triglycerides contained in lipoproteins. An uplift in their levels denotes fat accumulation within the body (16, 17). 25(OH)$D_3$ assumes a function in augmenting calcium ion levels within fat cells and fatty acid synthetase activity, making itself an indispensable inhibitor during the process of fat cell differentiation. When there is a deficiency of 25(OH)$D_3$ in school-aged children, the inhibitory effect of 25(OH)$D_3$ is affected, resulting in fat accumulation within the body and abnormally elevated BMI, TC, and TG levels (18, 19). It is worth noting that in the current research, FBG and HbA1c serum levels in both cohorts did not exhibit remarkable disparities, revealing that 25(OH)$D_3$ deficiency in school-aged children might not have a huge impact on glucometabolic. Nonetheless, in prior research, Safarpour et al. (20) have unraveled that vitamin D supplementation can achieve FBG and HbA1c modulation. Corica et al. (21) have also confirmed that vitamin D deficiency in obese children can bring about impaired glucose metabolism and elevated blood glucose levels. The divergences between the above-mentioned reports and the findings of this study may be attributed to factors such as differences in the age and geographical location of the study subjects.

Our research also unveiled that the 25(OH)$D_3$ deficiency cohort had significantly lower levels of Ca, ALP, and bone age vis-a-vis the non-deficiency cohort, suggesting that 25(OH)$D_3$ insufficiency impinged on the bone growth and development of school-aged children. Vitamin D is an essential humoral factor that modulates bone metabolism and sustains normal development in the body. It can be obtained through sunlight exposure, UV radiation, and dietary intake. On one hand, vitamin D stimulates the production of intestinal calcium-binding proteins, augments blood Ca levels, and boosts bone mineralization. On the other hand, vitamin D induces the maturation and differentiation of osteoblasts, facilitating the formation and maturation of bone matrix (22–24). In cases of vitamin D deficiency, only 10–15% of dietary calcium can be absorbed due to the lack of calcium within the serum, giving rise to an imbalance in the

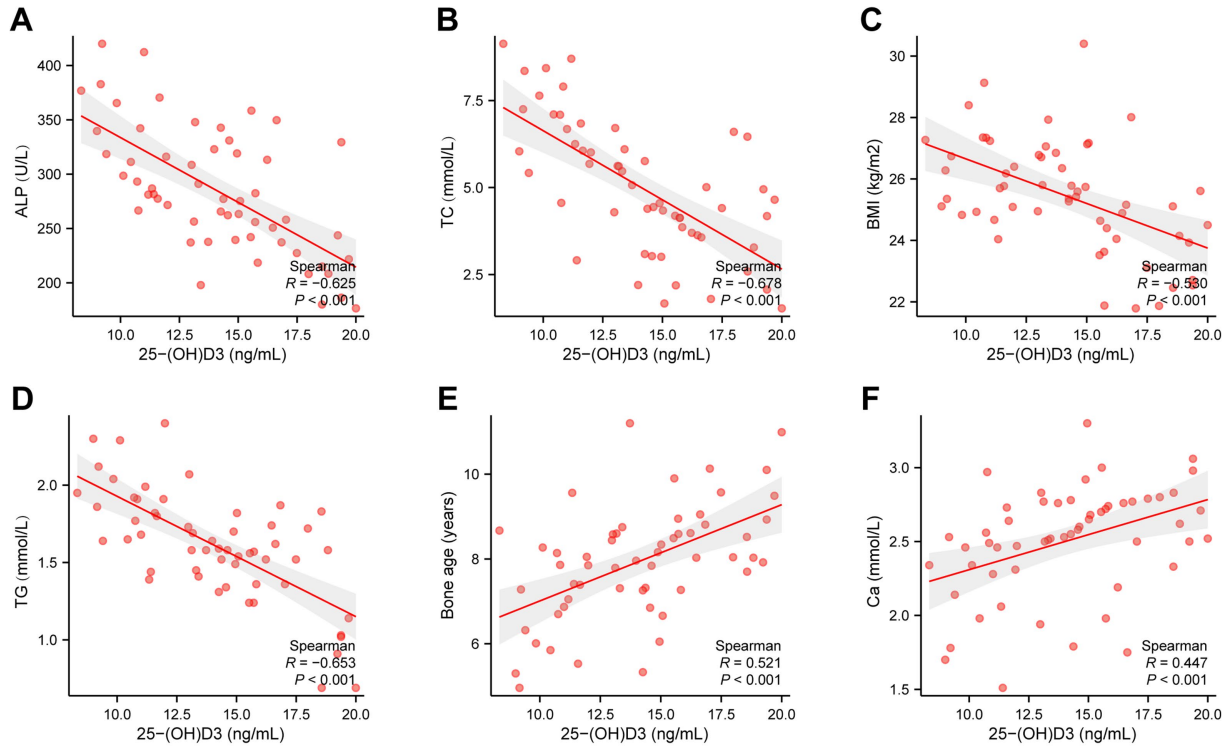


FIGURE 5
Spearman's correlation analysis of the relationship between 25(OH)$D_3$ levels and BMI, TC, TG, Ca, ALP, and bone age. (A) ALP ($R^2 = -0.6019$, $p < 0.0001$). (B) TC ($R^2 = -0.5998$, $p < 0.0001$). (C) BMI ($R^2 = -0.6234$, $p < 0.0001$). (D) TG ($R^2 = -0.6125$, $p < 0.0001$). (E) Bone age ($R^2 = 0.6729$, $p < 0.0001$). (F) Ca ($R^2 = 0.5920$, $p < 0.0001$).

TABLE 3 Analysis of the relationship between 25-(OH)$D_3$ levels and outcomes.

| Index | $R^2$ | $p$ |
|---|---|---|
| BMI | −0.530 | <0.001 |
| TC | −0.678 | <0.001 |
| TG | −0.653 | <0.001 |
| Ca | 0.447 | <0.001 |
| ALP | −0.625 | 0.009 |
| Bone age | 0.521 | <0.001 |

calcium-phosphorus ratio, which disrupts normal epiphyseal cartilage growth and mineralization, leading to growth retardation and bone deformities. Thus, in situations of vitamin D deficiency, the supplementation of calcium alone has minimal effect on growth and development and may even cause bone deformities such as epiphyseal protrusion and rib beading (25). ALP is an enzyme present in multiple tissues throughout the body, originating from the liver, bones, intestines, or kidneys. However, bone ALP and liver ALP account for approximately 95% of the total ALP activity in human serum. Research has unveiled that the most common cause of heightened ALP levels in the blood is related to liver or bone diseases (26). ALP exerts a critical function in modulating calcium absorption and utilization through its involvement in mineral transformation in the bones and the activation of vitamin D. In bones, ALP steps up the release of phosphate ions and forms minerals in combination with calcium ions, maintaining bone structure and strength. Furthermore, the activity level of ALP can reflect alterations in calcium and phosphorus metabolism. When there is an imbalance in calcium and phosphorus metabolism, such as inadequate calcium absorption or excessive excretion, the activity of ALP often undergoes changes. Therefore, by monitoring ALP activity, the status of calcium and phosphorus metabolism can be assessed, providing further insights into bone health. This study further demonstrated that the 25(OH)$D_3$ deficiency cohort displayed a dramatic elevation in ALP, and the reason for this is associated with the high bone turnover state resulting from vitamin D insufficiency. Due to the impact of vitamin D deficiency, there is an imbalance in the calcium-phosphorus proportion, culminating in impaired bone growth and development. In this state, osteoblasts become more active, which can cause a rise in the ALP level. Bellastella et al. (27) have also pinpointed in their research that serum ALP profile is modulated by vitamin D, denoting a close correlation between the two.

In our research, the value of BMI, TC, TG, Ca, ALP, and bone age in forecasting 25(OH)$D_3$ insufficiency in school-aged children was observed through ROC analysis. It was discovered that BMI ≥24.50 kg/$m^2$, TC ≥4.08 mmol/L, TG ≥1.39 mmol/L, Ca ≤2.18 mmol/L, ALP ≤306.26 U/L, and bone age ≤7.25 years are indicators with high sensitivity for predicting 25(OH)$D_3$ deficiency. Actively monitoring these indicators may provide assistance in early identification of 25(OH)$D_3$ deficiency in school-aged children. Additionally, this research investigated the correlation between 25(OH)$D_3$ levels and BMI, TC, TG, Ca, ALP, and bone age in school-aged children through the assistance of Spearman coefficients. It was confirmed that 25(OH)$D_3$ levels in school-aged children were

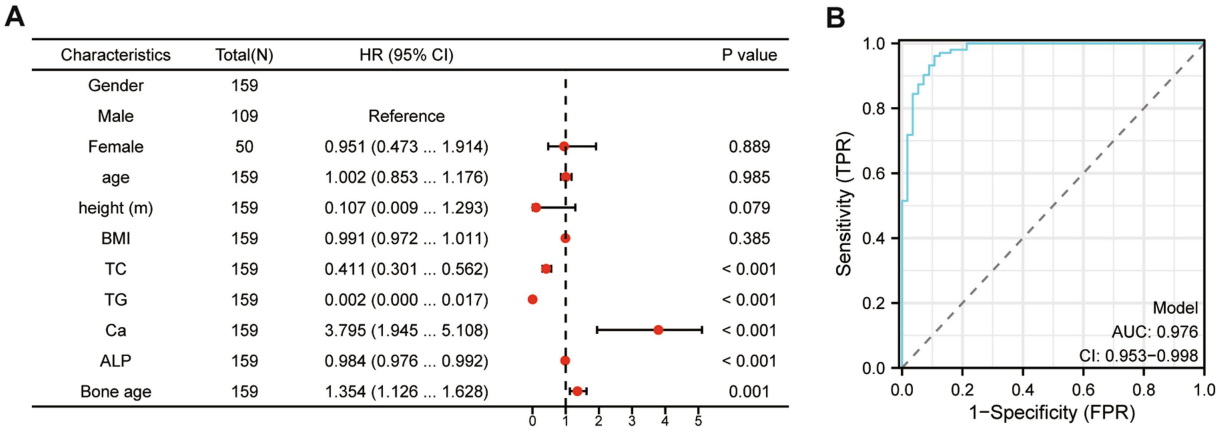


FIGURE 6
The logistic regression and multivariate ROC curve comprehensive analysis of the relationship between 25(OH)$D_3$ levels and BMI, TC, TG, Ca, ALP, and bone age. (A) The logistic regression analysis. (B) Multivariate ROC curve comprehensive analysis (BMI, TC, TG, Ca, ALP, and bone age).

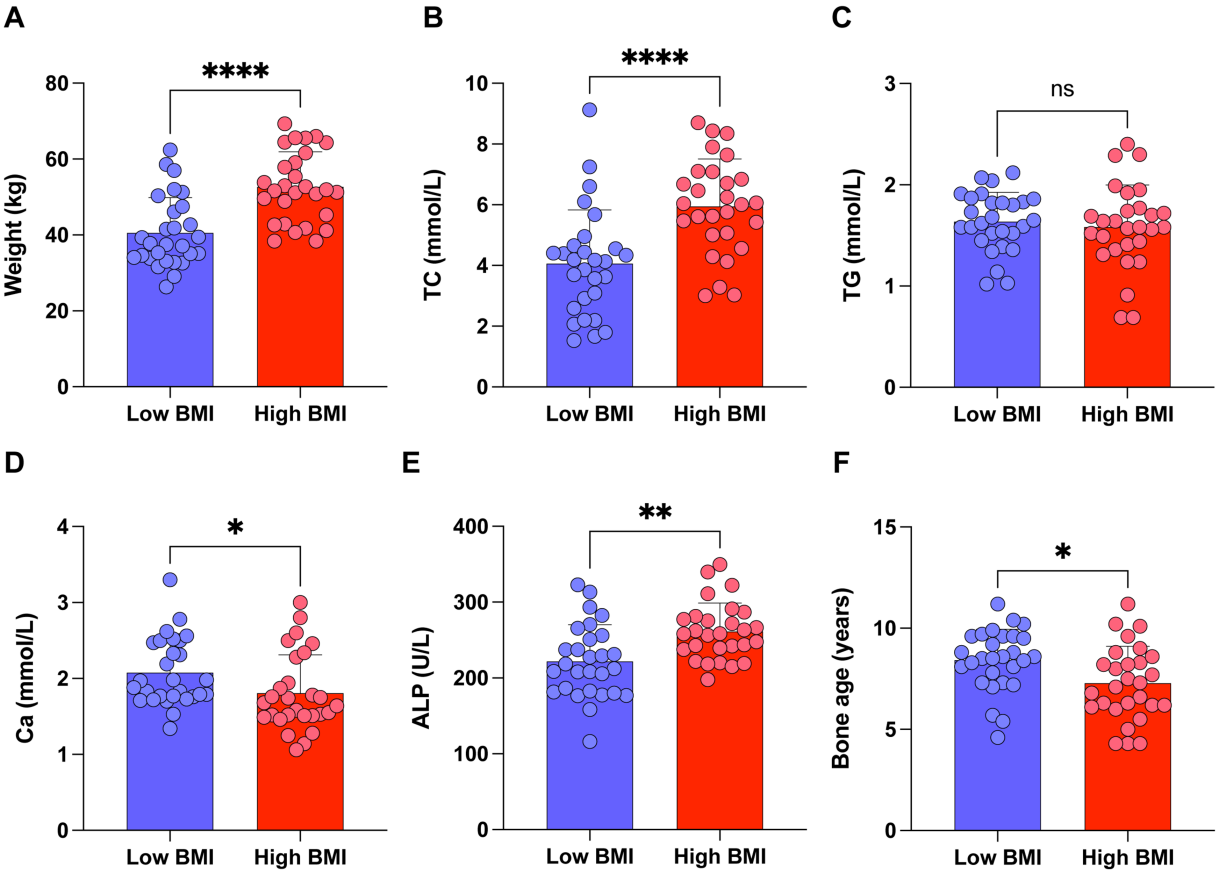


FIGURE 7
Subgroup analysis of children with 25(OH)$D_3$ deficiency stratified by BMI levels. (A) Weight. (B) TC. (C) TG. (D) Ca. (E) ALP. (F) Bone age. ns $p > 0.05$, *$p < 0.05$, **$p < 0.01$, and ****$p < 0.0001$.

negatively associated with BMI, TC, TG, and ALP but positively correlated with Ca and bone age. This unveiled a close relationship between 25(OH)$D_3$ deficiency and childhood obesity as well as bone growth and development. In clinical practice, particular attention should be devoted to monitoring the fluctuations in 25(OH)$D_3$ levels among school-aged children, ensuring their optimal growth and development during this critical period.

Nonetheless, our study is subject to certain limitations. Firstly, while the two hospitals participating in this research are situated within the same geographical region—thereby reducing potential bias

from geographic disparities—the relatively small sample size may still introduce a degree of bias into the final statistical results. Secondly, the obesity-related indicators analyzed were somewhat limited; due to incomplete data, specific metrics such as waist circumference could not be further examined. In future investigations, we intend to conduct multicenter collaborative analyses that encompass a wider array of relevant indicators and delve deeper into the mechanisms by which 25(OH)$D_3$ affects obesity and growth retardation in school-aged children. These initiatives will significantly contribute to enhancing health management strategies for this demographic.

## 5 Conclusion

In conclusion, it can be inferred that insufficiency of 25(OH)$D_3$ may contribute to school-age children's obesity. Furthermore, this deficiency exerts an impact on bone growth and development in these children, leading to reduced levels of calcium, delayed bone maturation, and ALP levels. When conducting clinical work, prioritizing the screening for vitamin D deficiency in school-age children is particularly crucial.

## 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 Hainan Hospital of PLA General Hospital. 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

YX: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. LS: Writing – original draft, Visualization, Resources, Project administration, Supervision. LZ: Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Data curation.

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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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# Complementary food hygiene practice and associated factors among mothers with children aged 6–23 months in Dessie Zuria, South Wollo Zone, Amhara, Ethiopia, 2023

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**Background:** Implementing appropriate complementary food hygiene practices is essential to lower the incidence of food-borne disease and malnutrition in children. However, this aspect is often overlooked in resource-limited settings, and information regarding these practices is not fully available and is not assessed enough. Therefore, this study aimed to assess complementary food hygiene practices and their associated factors in Dessie Zuria, South Wollo Zone, Amhara, Ethiopia, in 2023.

**Methods:** An institutional-based cross-sectional study design was conducted from 17 April to 18 May 2023, among 366 mothers with children aged 6–23 months. Dessie Zuria was purposively selected, and a systematic random sampling technique was used to recruit study participants. Data were collected using pretested and structured questionnaires. Finally, the data were entered using EPI-info and then exported to SPSS version 26. Bivariable and multivariable logistic regression analyses were used to identify factors associated with complementary feeding hygiene practices. Both crude odds ratios (COR) and adjusted odds ratios (AOR) with a 95% confidence level (CI) were computed, and a $p$-value of <0.05, in the final model, was considered statistically significant.

**Results:** The proportion of households practicing complementary food hygiene was 22.22%. Factors associated with these practices included access to media such as television or radio (AOR = 10.51, 95% CI: 2.8, 39.28), starting complementary feeding before 6 months (AOR = 2.01, 95% CI: 1.05, 3.84), and the child's age being 6 to 11 months (AOR = 0.25, 95% CI: 0.08, 0.7).

**Conclusion:** The prevalence of complementary food hygiene practices was poor. Healthcare professionals should promote starting breastfeeding at the age of 6 months. In addition, media companies ought to make an effort to create a positive social and cultural environment that encourages complementary feeding practices for young children.

KEYWORDS

**complementary feeding, hygiene practice, associated factors, children aged, 6–23 months**

# Introduction

Complementary feeding begins when breast milk alone is no longer enough to meet a baby's nutritional needs, and additional foods are required. In environments with limited resources, complementary foods can produce microbiologically hazardous diets that increase the risk of contracting food-borne infections (1). Food hygiene practices aim to prevent diseases associated with consuming contaminated food and water during the complementary feeding period (1).

Complementary feeding practices that are incorrect and unhygienic worldwide have been associated with malnutrition outcomes (wasting, stunting, and underweight) and under-five mortality. Previous studies have indicated that the timely introduction of complementary foods (CFs) to infants and young children (IYC) reduces the likelihood of malnutrition, infectious diseases, and mortality (2). According to the WHO and UNICEF, breastfeeding should continue until infants are at least 2 years old, after which they should begin eating a healthy diet (3). In addition, the WHO warns against starting CFs too soon or too late. IYC are more prone to diarrheal illnesses and subsequent malnourishment due to their early exposure to microbiological pathogens and the consumption of potentially hazardous or contaminated complementary foods and drinks (4, 5).

Contamination of food during the complementary phase is a major cause of diarrheal diseases in both the developed and developing world (6). If the hygienic conditions of complementary feeding are not correctly controlled, it can result in diarrhea and months of developmental retardation, which can lead to kwashiorkor, marasmus, and immunodeficiency characterized by recurring and chronic illnesses that can be fatal (7).

An average of 65% of deaths caused by diarrheal diseases could be reduced if good hygiene practices were accompanied by the provision of clean water and proper sanitation (8). Children's growth and development greatly depend on eating a healthy diet, especially during their first 2 years of life. Every year, approximately 10 million children die, with 41% of these deaths occurring in sub-Saharan Africa and 34% in South Asia (9). The practice of complementary feeding (CF) is linked to detrimental, multifaceted effects on one's health and development. It is the primary cause of over two-thirds of child mortality under five in Sub-Saharan Africa (10). Furthermore, poor food hygiene practices are linked to child undernutrition, and any harm resulting from nutritional deficiencies in early childhood is linked to impaired cognitive development, low educational attainment, and low economic output (11).

Since the majority of African nations have many socioeconomic and cultural characteristics in common, it is critical to pinpoint the causes of poor complementary feeding practices that are prevalent in these nations. Targeting individuals, families, and communities susceptible to inadequate hygiene practices related to complementary feeding (CF) is crucial for designing successful nutritional interventions. This approach focuses on identifying modifiable characteristics that are consistent across many developing nations (12).

According to population-based studies in West Africa, due to inadequate breastfeeding and other feeding hygiene practices, children between the ages of 3 and 15 months are most at risk for nutritional deficiencies and developmental retardation (13).

Poor feeding habits were caused by a lack of information about proper food handling, poor sanitation, and inadequate social amenities such as kitchens, sewage systems, and toilets (8). The causes of diarrheal illnesses extend beyond medical factors; social, economic, environmental, and behavioral facets of the family unit play a significant role. Studies conducted in Ethiopia, including those in Amhara (1), Harare (9), and Jigjiga, highlight these facets (7).

Significant effort has been dedicated to emphasizing the importance of maintaining proper hygiene when preparing complementary foods, ensuring enough food for the entire household, and having an appropriate understanding of nutrition (14). However, the application of these requirements during complementary feeding has not been adequately addressed. In addition, there is a problem with real hygiene practices of complementary feeding, resulting in serious consequences of poor child health outcomes. Therefore, this study aimed to explore complementary food hygiene practices and their associated factors among mothers with children aged 6–23 months in Dessie Zuria Woreda, South Wollo Zone, Amhara region, Ethiopia, 2023.

# Materials and methods

## Study design, area, and period

An institutional-based cross-sectional study design was conducted from 28 April 28 to 7 June 2023, in the Dessie Zuria district, which is located in the South Wollo Zone of Amhara Regional State. It is bordered by Albuko and Wereilu to the south; Tenta to the northwest; Kutaber to the north; Tehuledere to the northeast; and Kalu to the east. There are 32 kebele in the area, housing a total of 201,000 people. There are 8 governmental health centers, and 32 health posts exist in the study area. Health centers were provided Stabilization Centers (SC), and health posts provided Outpatient Therapeutic Programme (OTP) complementary feeding.

### Source population

All lactating mothers with children aged 6–23 months who attended the health institutions of the Dessie Zuria district were the source population.

### Study population

The study population included all lactating mothers who visited the selected health institutions and who had children aged 6–23 months during the study period.

### Eligibility criteria

#### Inclusion criteria

- Mothers whose children were between the ages of 6 and 23 months were included.

#### Exclusion criteria

- Mothers who were seriously ill and unable to hear were not included in the study.

## Sample size determination

The sample size was calculated using the single population proportion formula, based on the following assumptions: a 95% confidence level (CI), a margin of error (D = 0.05), and a percentage of hygienic practices among mothers of infants aged 6 to 23 months

during complementary feeding, which was found to be 38.9% in a previous study conducted in Bahir Dar, Amhara (1).

$$n = \frac{Z^2 a / 2 \times P(1-P)}{d^2}$$

where $n$ = the required sample size,

$Z$ = a standard score corresponding to a 95% confidence level;

$P$ = proportion of hygienic practice among mothers with children aged 6–23 months during complementary feeding found = 38.9%.

$d$ = margin of error = 0.05.

$$n = \frac{(1.96)^2 \times 0.389(0.611)}{(0.05)^2} = 366$$

then, the total required sample size was 366.

## Sampling procedure

From a total of 40 (32 health posts and 8 health centers) facilities providing health services in the Dessie Zuria district, 15 (11 health posts and 4 health centers) facilities were selected using simple random sampling. Sample sizes were proportionally allocated to each health facility, including health centers and health posts, and a systematic random sampling technique was used to recruit the study participants. Considering N (the total number of women who came for their complementary feeding in the previous 2 months at the health facility = 472), n (the calculated sample size = 366), and the k-interval (where $K = N/n = 472/366 = 2$), the first participant was selected using a lottery method among the first two complementary feeding users at each health center and health post.

## Variables

### Dependent variable

Complementary food hygiene practices (categorized as poor or good).

### Independent variables

- Socio-economic and demographic characteristics: Age, marital status, family size, educational status, husband's educational status, occupational status, and family wealth.
- Maternal health service and related characteristics: Parity, ANC visit, place of delivery, PNC visit, knowledge, and access to mass media.
- Components of hygienic practice: a latrine, mother hand washing with soap after using the toilet, hand washing with soap before feeding and food preparation, access to a private latrine, feeding of leftovers, washing of utensils, serving cooked food immediately for children, food cooking type, place of food preparation and its modernity, water supply, and source/access to information media such as television.
- Child-related characteristics: child age, sex, birth order, and breastfeeding.

## Operational definitions

- Food hygienic practice is defined as the feeding practice(s) of mothers when feeding their children based on the latest WHO recommendations among the WHO feeding practice indicators (15).
- Complementary feeding is the period (between 6 months and 2 years) during which foods or liquids are provided along with continued breastfeeding (16).
- Complementary food hygiene practices are a collection of fundamental guidelines used to systematically regulate the environmental conditions during manufacture, storage, and use when providing children between the ages of 6 and 23 months with complementary feeding. Six questions regarding hand washing with soap and water and three scales were used to quantify it: 1—always, 2—sometimes, and 3—wash only with water; 10 questions with a "yes" or "no" response on safety precautions to take when preparing food. The responses forwarded by the study participants to the 6 questions related to hand washing with water and soap were dichotomized as 1 "for always" and 0 "for sometimes and washing only with water." The responses forwarded by the study participants to 10 questions related to safety measures during food preparation were dichotomized as 1 "for yes" and 0 "for no responses." Study participants were classified as having good hygiene practices during complementary feeding if they correctly answered 75% of the questions; if not, they were classified as having poor hygiene practices during complementary food feeding (14).

## Data collection procedure

A structured questionnaire that included questions that assessed the study variables was prepared and adapted from different literature. The questionnaire consisted of demographic data and complementary feeding practice tools. The data were collected by four healthcare workers and were supervised by the principal investigator.

## Data quality control measure

The relevant literature was reviewed, and a structured validated questionnaire was created in English, translated into Amharic, the local language, and then back into English to guarantee consistency. A pretest was conducted for 5% of the sample size both in health centers and health posts where actual data were not collected. After that, appropriate modifications were made before the actual data collection. Training data collectors, tight monitoring, timely feedback, and daily assessment of all completed questionnaires were used to ensure the quality of the data. Before beginning the data collection, data collectors received a 1-day training covering the administration of each question and ethical guidelines. The supervisor monitored the data every day to ensure its accuracy and completeness.

## Data analysis and management

The data were coded and entered using Epi-Data version 4.6 software. The data were exported to SPSS version 26 for further

statistical analyses. Descriptive and analytical analyses were also performed. For continuous data, descriptive features were expressed as mean (standard deviation), median (interquartile range), and frequency distribution for categorical data. Frequency tables, graphs, and cross-tabulations were used to present the findings of the study. Both bivariable and multivariable logistic regression models were used to identify factors associated with complementary feeding hygiene practices, and those variables with a *p*-value of ≤0.25 during bivariable analysis were entered into the multivariable analysis. Adjusted odds ratios with 95% confidence level were computed to assess the association between independent predictors and outcome variables. Then, the significance association was declared at a *p*-value of <0.05.

# Results

## Socio-demographic characteristics

A total of 351 mothers with children aged 6–23 months participated in this study, with a response rate of 96%. The mean age of the mothers was 28.54, with a standard deviation of ±0.25 years and (95% CI of 28.04, 29.03). A total of 80 (22.79%) and 92 (26.21%) of mothers were government employees and merchants, respectively. For fathers, 142 (22.79%) and 84 (26.21%) were merchants and daily laborers, respectively (Table 1).

TABLE 1 Socio-demographic characteristics of the CFHP participants in the Dessie Zuria health institutions, Amhara, Ethiopia, 2023 (*n* = 366).

| Variables | Groups | Frequency | Percent |
|---|---|---|---|
| Resident | Urban | 41 | 11.7 |
| | Rural | 310 | 88.3 |
| Educational status | Unable to read and write | 21 | 5.98 |
| | Able to read and write | 198 | 56.4 |
| | Grades 9–12 complete | 31 | 8.83 |
| | Diploma | 18 | 5.13 |
| | First-degree and above | 83 | 23.7 |
| Occupational status of mothers | Government employee | 80 | 22.8 |
| | Merchant | 92 | 26.2 |
| | Daily labor | 68 | 19.4 |
| | Urban agriculture | 14 | 3.99 |
| | Housewife | 59 | 16.8 |
| | Other | 38 | 10.8 |
| Occupational status of fathers | Government employee | 51 | 14.5 |
| | Merchant | 142 | 40.5 |
| | Daily labor | 84 | 23.9 |
| | Urban agriculture | 46 | 13.1 |
| | Other | 28 | 7.98 |
| Access to media | Yes | 102 | 29.1 |
| | No | 249 | 70.9 |
| Child age | 6–11 | 228 | 65 |
| | 12–23 | 123 | 35 |
| Child sex | M | 180 | 51.3 |
| | F | 171 | 48.7 |
| Household private latrine | Yes | 73 | 20.8 |
| | No | 278 | 79.2 |

## Maternal, child, and service-related characteristics of respondents

Among the participating children, 236 (67.24%) started their complementary feeding at the age of 6 months; during this data collection, 244 (69.52%) of children were not currently breastfeeding. Among the total respondents, only 69 individuals (19.66) were cleaning food utensils with hot water. Similarly, 82 (23.36%) participants were using soap or ash for washing food utensils. Of the total study participants, 209 (59.54%) reported that their household's source of drinking water was piped water (Table 2).

## Food hygienic practice

The current complementary food hygienic practice was 78 (22.22%) among mothers with children aged 6–23 months according to this research finding (Figure 1).

Complementary food hygienic practices among mothers with children aged 6–23 months were evaluated based on 6 handwashing indicators and 10 questions related to safety measures during food preparation, according to the following responses (Table 3).

## Factors associated with complementary food hygienic practices

The bivariable analysis showed that resident, occupational status of mothers, occupational status of fathers, access to media, child age, household private latrine, currently breastfeeding, age of starting complementary feeding, use of hot water for cleaning food utensils, source of drinking water, and water treatment options were selected candidate variables for the multivariable analysis.

In the final multivariable logistic regression analysis, this study found that the presence of a private latrine (AOR = 0.13, 95% CI: 0.021, 0.87), starting complementary feeding before 6 months (AOR = 8.30, 95% CI: 1.15, 59.81), and starting complementary feeding at 6 months (AOR = 9.10, 95% CI: 1.16, 71.21) were found to be associated factors of complementary food hygienic practices at the p-value of less than 0.05 (Table 4).

# Discussion

In this study, the proportion of hygienic practice of complementary food among mothers with children aged 6–23 months who lived in Dessie Zuria was 22.22, 95% CI: (17.85–26.59). The prevalence of hygienic complementary food feeding practices in this study was lower than that reported in previous studies conducted in Bahir Dar (38.9%) (1), Harare (39.6%) (9), Jigjiga (7), Debark (14), and Bangladesh (15). This difference could be due to the study setting; previous studies were conducted in both rural and urban communities,

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TABLE 2 Services for complementary food hygienic practices demonstrated among children aged 6–23 months in the Dessie Zuria health institutions, Amhara, Ethiopia.

| Variables | Groups | Frequency | Percent |
|---|---|---|---|
| Age of starting complementary feeding | Before 6 months | 61 | 17.4 |
| | At 6 months | 236 | 67.2 |
| | Later after 6 months | 54 | 15.4 |
| Currently breastfeeding | Yes | 107 | 30.5 |
| | No | 244 | 69.5 |
| Use of hot water for cleaning food utensils | Yes | 69 | 19.7 |
| | No | 282 | 80.3 |
| Use soap or ash for washing food utensils | Yes | 82 | 23.4 |
| | No | 269 | 76.6 |
| Source of drinking water | Piped water | 209 | 59.5 |
| | Well water | 54 | 15.4 |
| | River water | 68 | 19.4 |
| | Spring water | 20 | 5.7 |
| Water treatment options | Chlorine | 148 | 42.2 |
| | Water treatment solution | 96 | 27.4 |
| | Boiling | 69 | 19.7 |
| | No usage of water treatment | 38 | 1.83 |
| Food groups in the last 24 h | Dairy products | 152 | 43.3 |
| | Eggs | 43 | 12.2 |
| | Grains, roots, and tubers | 27 | 7.69 |
| | A-rich fruits and vegetables | 24 | 6.84 |
| | Other fruits and vegetables | 47 | 13.4 |
| | Meat, poultry, fish, and shellfish | 18 | 5.13 |
| | Legumes and nuts | 24 | 6.84 |
| | Foods cooked with fats | 16 | 4.56 |
| Consumed food groups | Consumed 0–2 food groups | 213 | 60.7 |
| | Consumed 3–4 food groups | 138 | 39.3 |

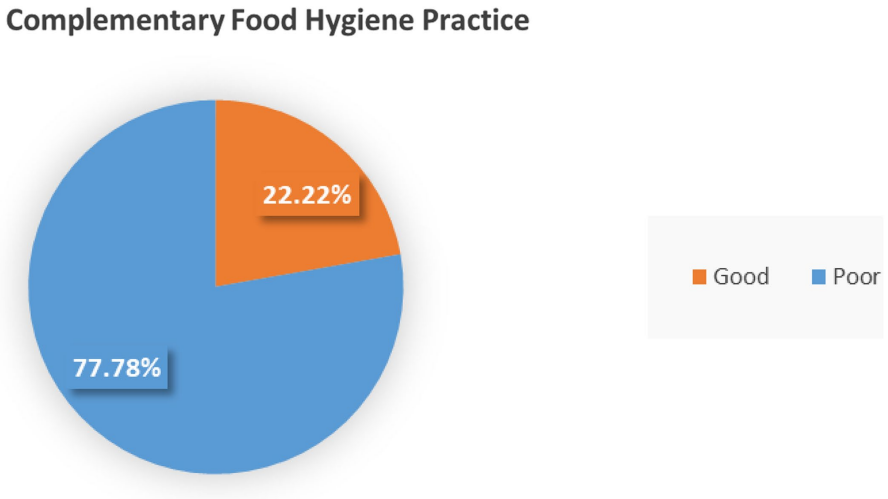


FIGURE 1
Complementary food hygienic practice among mothers who had children aged 6—23 months in the Dessie Zuria health institutions, Amhara, Ethiopia.

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TABLE 3 Complementary food hygienic practice questionnaire among mothers with children aged 6–23 months in the Dessie Zuria health institutions, Amhara, Ethiopia, 2023.

| Variables | Groups | Frequency | Percent |
|---|---|---|---|
| Mothers hand washing with soap after using the toilet | Always water with soap | 213 | 60.7 |
| | Not always water with soap | 80 | 22.8 |
| | Wash only with water | 36 | 10.3 |
| | Do not wash | 22 | 6.27 |
| Mothers hand washing with soap before feeding the child | Always water with soap | 236 | 67.2 |
| | Not always water with soap | 81 | 23.1 |
| | Wash only with water | 34 | 9.69 |
| Hand washing with soap before food preparation | Always water with soap | 230 | 65.5 |
| | Not always water with soap | 71 | 20.2 |
| | Wash only with water | 50 | 14.3 |
| Washing of utensils | Always water with soap | 219 | 62.4 |
| | Not always water with soap | 82 | 26.2 |
| | Wash with ash | 40 | 11.4 |
| Mother's fingernails cut short | Yes | 76 | 21.7 |
| | No | 275 | 78.4 |
| Children hand washing after using the toilet | Always water with soap | 213 | 60.7 |
| | Not always water with soap | 94 | 26.8 |
| | Do not wash | 44 | 12.5 |
| Children hand washing before eating | Always water with soap | 227 | 64.7 |
| | Not always water with soap | 57 | 16.2 |
| | Did not wash | 67 | 19.1 |
| Serving cooked food immediately | Yes (if served within two 2 h) | 226 | 64.4 |
| | No (if not served within two 2 h) | 126 | 35.6 |
| Serving leftover food for children. | Always serving leftover food | 147 | 41.9 |
| | Sometimes serving leftover food | 104 | 29.6 |
| | Never serving leftover food | 100 | 28.5 |
| Presence of children's private feeding utensils | Yes | 67 | 19.1 |
| | No | 284 | 80.9 |
| Children's clean feeding utensils | Yes | 269 | 76.6 |
| | No | 823 | 23.4 |
| Separating utensils for raw and cooked food | Yes | 100 | 28.5 |
| | No | 251 | 71.5 |
| Place of food cooking preparation | Cultural stove | 225 | 64.1 |
| | Modern stove | 126 | 35.9 |
| Keeping ready-to-eat food | Always | 235 | 67 |
| | Not always | 116 | 33.1 |
| HH has a hand washing facility after a toilet visit | Yes | 80 | 22.8 |
| | No | 271 | 77.2 |
| Hand washing facility has soap or ash with water | Yes | 67 | 19.7 |
| | No | 206 | 80.3 |

while this study was conducted solely in a rural area. Consequently, women in this rural setting may have less access to information about hygienic practices, which could be the reason for a lower prevalence of hygienic complementary food practices than the previous findings. In addition, complementary food hygienic practices are affected by a range of climatic conditions and socio-political statuses.

Concerning the factors, household access to media, such as TV or radio, was a significant predictor of hygienic complementary food

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TABLE 4 Factors associated with complementary food hygienic practices among women with children aged 6–23 months in the Dessie Zuria health institutions, Amhara, Ethiopia, 2023.

| Variables/categories | Complementary food hygienic practice | | COR (95% CI) | AOR (95% CI) |
|---|---|---|---|---|
| | Good | Poor | | |
| **Resident** | | | | |
| Urban | 14 | 27 | 3.11(1.68–5.77) | 0.61(0.25–1.45) |
| Rural | 64 | 246 | 1 | 1 |
| **Occupational status of mothers** | | | | |
| Government employee | 9 | 72 | 3.13(1.37–7.13) | 2.48(0.68–8.94) |
| Merchant | 12 | 69 | 5.52(2.38–12.78) | 1.72(0.45–6.56) |
| Daily labor | 15 | 42 | 0.88(0.10–7.85) | 2.25(0.68–7.39) |
| Urban agriculture | 11 | 9 | 1.83(0.70–4.75) | 0.98(0.28–3.50) |
| House wife | 13 | 48 | 0.24(0.02–1.99) | 1.13(0.19–6.61) |
| Other | 18 | 33 | 1 | 1 |
| **Occupational status of fathers** | | | | |
| Government employee | 17 | 57 | 1.97(0.76–5.01) | 0.37(0.07–1.81) |
| Merchant | 27 | 51 | 4.32(1.64–11.37) | 0.69(0.15–3.17) |
| Daily labor | 28 | 116 | 2.43(0.89–6.66) | 0.99(0.22–4.51) |
| Urban agriculture | 6 | 49 | 1 | 1 |
| **Access to media** | | | | |
| Yes | 6 | 96 | 6.51(2.73–15.52) | 10.51(2.8–39.28)* |
| No | 72 | 177 | 1 | 1 |
| **Child age** | | | | |
| 6–11 | 63 | 165 | 0.36(0.19–0.67) | 0.25(0.08–0.7) * |
| 12–23 | 15 | 108 | 1 | 1 |
| **Household private latrine** | | | | |
| Yes | 12 | 61 | 1.58(0.80–3.11) | 1.62(0 0.69–3.81) |
| No | 66 | 212 | 1 | 1 |
| **Currently breastfeeding** | | | | |
| Yes | 88 | 19 | 1.47(0.83–2.62) | 0.61(0.25–1.47) |
| No | 185 | 59 | 1 | 1 |
| **Age of starting complementary feeding** | | | | |
| less than 6 months | 35 | 88 | 1.71(1.02-2.85) | 2.01(1.05-3.84) * |
| 6 months and above | 43 | 185 | 1 | 1 |
| **Use of hot water for cleaning food utensils** | | | | |
| Yes | 10 | 59 | 1.87(0.90–3.86) | 0.25(0.04–1.45) |
| No | 68 | 214 | 1 | 1 |
| **Source of drinking water** | | | | |
| Piped water | 56 | 152 | 0.219(0.07–0.62) | 0.44(0.08–2.44) |
| Well water | 5 | 50 | 0.52(0.25–1.07) | 3.35(0.78–14.38) |
| River water | 10 | 57 | 1.359(0.52–3.53) | 2.93(0.86–9.87) |
| Spring water | 7 | 14 | 1 | 1 |
| **Water treatment options** | | | | |
| Chlorine | 43 | 108 | 0.46(0.24–0.88) | 0.62(0.25–1.51) |
| Water treatment solution | 16 | 80 | 0.54(0.27–1.09) | 0.51(0.14–1.87) |
| Boiling | 13 | 56 | 0.24(0.07–0.03) | 0.52(0.13–2.02) |
| No usage of treatment | 6 | 29 | 1 | 1 |

COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval. *$p$-value < 0.05.

feeding practices among mothers with children aged 6–23 months. The odds of hygienic complementary food feeding practices were higher in mothers who had access to media, such as TV or radio, than in mothers who did not have access to media (AOR = 10.51, 95% CI: 2.8, 39.28). A similar finding was reported in a study conducted in Antsokia Gemza district, Wolaita Sodo town, and Bangladesh (17–19). This may be due to the fact that the media is vital in providing knowledge regarding complementary feeding techniques, which is necessary for their adoption. In addition, mothers and other caregivers who have access to the media are probably more knowledgeable and adhere to proper hygienic practices when it comes to complementary feeding. Thus, they adhere to specific habits including maintaining their diet, cutting their fingernails, and washing their hands before cooking complementary foods.

Starting complementary feeding before 6 months was significantly associated with complementary food hygiene practices. The odds of complementary food hygiene practices were 2 times more than starting complementary feeding after 6 months (AOR = 2.01, 95% CI: 1.05, 3.84). This finding is contrary to studies using secondary data analysis from the Ethiopian Mini-Demographic and Health Survey 2019, in which the age of starting complementary feeding was not significantly associated with complementary food hygienic practices (20). The possible explanation for this difference is that mothers may pay more attention to hygiene when starting complementary feeding before 6 months, and later on, they may reduce these hygiene precautions.

In the present study, children aged 6 to 11 months were less likely to be practicing complementary food hygiene as compared to a child aged 12–23 months (AOR = 0.25, 95% CI: 0.08, 0.7). This result is supported by studies conducted in Tigray, Western Ethiopia, and Nigeria (21–23). The reason may be that younger children receive suboptimal complementary feeding since family foods are introduced to them later than they are to older children, who then incorporate them into their meals. In other words, older children's food consumption more readily reflects the nutritional diversity of the home than does the dietary intake of younger children. In addition, younger children are more likely to have fewer eating occasions, which could make it more difficult to achieve the requirements for complementary feeding. Mothers might also believe that their younger children's digestive systems are still developing, leading them to avoid or omit specific foods from their meals, such as fats or meat products.

## Strengths and limitations of the study

A major strength of the present study is the use of the latest WHO recommendations on complementary feeding practices. In addition, the data were collected only from respondents who were on complementary feeding practices. However, the findings of this study were not triangulated with qualitative findings; in addition, the study presented self-reported data, which could be prone to social desirability and recall bias.

## Conclusion

The prevalence of good hygienic practices during complementary food feeding among mothers with children aged 6–23 months was low in this study area. This study also revealed that household access to media, such as television or radio, starting complementary feeding before 6 months, and children aged 6 to 11 months had a statistically significant association with complementary food hygienic practices. It is recommended that the Dessie Zuria health office and institutions work on enhancing health posts and training health extension workers to increase the prevalence of complementary food hygienic practices. Additionally, efforts should be made to promote the start of breastfeeding at the age of 6 months. In addition, governments, health professionals, and media outlets should collaborate to create and disseminate evidence-based messages to successfully reach the target population. Healthcare workers need to strengthen counseling mothers during growth monitoring sessions on complementary food handling.

## 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 Institutional Research and Ethics Review Committee (IRB) of Zemen Postgraduate College. 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

AA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft. YD: Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. GY: Formal analysis, Software, Writing – original draft, Writing – review & editing. YA: Software, Writing – original draft, Writing – review & editing.

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## Conflict of interest

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

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# Association between dietary antioxidant intake and overweight/obesity risk among children and adolescents: a cross-sectional analysis from NHANES 2011–2016

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**Objective:** Overweight and obesity among children and adolescents has emerged as a critical global public health issue. Oxidative stress, a key factor in obesity-related inflammation and metabolic dysregulation, underscore the importance of dietary antioxidants. The composite dietary antioxidant index (CDAI), which integrates vitamins A, C, E, carotenoids, selenium, and zinc, provide a comprehensive measure of overall dietary antioxidant intake. However, the relationship between CDAI and overweight/obesity in children and adolescents remains insufficient explored.

**Methods:** This study utilized data from the National Health and Nutrition Examination Survey (NHANES) collected between 2011 and 2016, including 17,919 participants aged 6–19 years. The CDAI were calculated based on dietary intake data from 24-hour dietary recalls. To account for total energy intake, two widely recognized adjustment methods were used: the standard regression model and the nutrient density model. In the nutrient density model, an energy-standardized CDAI (E-CDAI) was computed. Logistic regression models were conducted to examine associations between CDAI, E-CDAI, mCDAI, mE-CDAI, and overweight/obesity risk, adjusting for potential confounders such as age, gender, race, physical activity, and socioeconomic status.

**Results:** The analysis showed a significant negative association between CDAI and overweight/obesity risk among adolescents aged 12–19 years. However, no significant association was observed in children aged 6–11 years. In contrast, E-CDAI showed no significant association with overweight/obesity risk in adolescents (OR = 0.87; 95% CI: 0.71–1.07). Notably, selenium exhibited a negative association with overweight/obesity in the standard regression model but a positive association in the nutrient density model. After excluding the selenium from the original 6 antioxidants included in the CDAI, the modified CDAI (mCDAI) demonstrated a significant negative association with overweight/obesity in both the standard regression model (OR = 0.74; 95% CI: 0.63–0.86) and nutrients density model (OR = 0.78; 95% CI: 0.69–0.89).

**Conclusion:** This study developed a modified CDAI, comprising of vitamins A, C, E, carotenoids, and zinc, and identified a consistent negative association between mCDAI and overweight/obesity risk, irrespective of energy adjustment method.

These findings suggest that a diet rich in antioxidants may play a protective role in preventing obesity in adolescent aged 12–19 years.

KEYWORDS

composite dietary antioxidant index, obesity, children and adolescents, antioxidant intake, NHANES

# 1 Introduction

Overweight and obesity have emerged as critical global public health challenges, particularly among children and adolescents. According to the latest World Health Organization (WHO) report, more than 300 million children and adolescents aged 5–19 years worldwide are classified as overweight or obese (1). The prevalence of overweight has increased nearly fivefold, while obesity rates have risen approximately sevenfold compared to levels four decades ago (2). In the United States, this trend is particularly pronounced, with the obesity rate among children and adolescent escalating from 17.7% in 2011 to 21.5% by 2020 (3). Obesity is now widely recognized as a complex, multifactorial disease that adversely impacts multiple physiological systems and can profoundly affect a child's intellectual, behavioral, psychological, and sexual development, with consequences that often persist throughout the lifespan (4, 5). Moreover, childhood obesity is strongly associated with an increased susceptibility to chronic condition in adulthood, including cardiovascular disease, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD) and certain types of cancer (6, 7). These compelling health implications underscore the urgent need for developing and implementing effective prevention and intervention strategies to mitigate the growing burden of childhood obesity.

Emerging evidence suggests that oxidative stress plays a pivotal role in the development and progression of obesity-related metabolic complications (8, 9). Excessive adipose tissue in obesity is a major source of reactive oxygen species (ROS), which can trigger chronic inflammation, contributing to insulin resistance, endothelial dysfunction, and other metabolic disturbances (10). These findings have sparked increasing interest in the potential protective effect of dietary antioxidants against obesity and its related disorders (11, 12). Some studies indicated that regions with high rates of antioxidant nutrient deficiencies also experience greater obesity prevalence (13). A recent systematic review found that obese individuals tend to have a lower concentration of antioxidants, particularly carotenoids, vitamins E and C, zinc, magnesium and selenium (14). However, contradictory results have been regarding the association between obesity and dietary antioxidants, especially in adolescents. For example, Galan et al. found no significant association between zinc and selenium concentration and obesity in 3,128 participants (15). Similarly, Yang et al. (16) found that selenium was not an independent protective factor against obesity in US adults but rather showed a positive association with obesity risk.

Although the health benefits of individual antioxidants have been extensively investigated, recent research has increasingly focused on the synergistic effects of multiple dietary antioxidants. Several studies have explored the relationship between weight status and various antioxidant indices, including the dietary antioxidant index (DAI) (17), total antioxidant capacity (TAC) (18), and dietary antioxidant quality score (DAQS)(19). Using weighted quantile sum (WQS) regression, Yang et al. (16) demonstrated that a combination of 11 antioxidants was negatively related to prevalence of obesity and abdominal obesity. The composite dietary antioxidant index (CDAI) is a comprehensive metric designed to assess overall dietary antioxidant intake by incorporating various key antioxidants (20), including vitamins A, C, E, carotenoids, selenium, and zinc. Previous studies have demonstrated an association between higher CDAI and reduced markers of oxidative stress and inflammation (21–24). Despite distinct dietary patterns and metabolic profiles in children and adolescents, the potential impact of overall antioxidant intake on obesity risk in this population remains underexplored.

This study aims to address this gap by examine the association between the composite dietary antioxidant index (CDAI) and the prevalence of overweight or obesity among children and adolescents in the United States, using data from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2016. We hypothesize that higher CDAI, indicative of greater antioxidant intake, is associated with a lower risk of overweight and obesity in this population. Total energy intake may represent a key confounder in the relationship between CDAI and overweight/obesity risk (25). To account for this, we employed two distinct models, the standard regression model and the nutrient density model (26). In the nutrient density model, we developed an energy-standardized CDAI (E-CDAI) score. Additionally, the dietary antioxidant quality score (DAQS) was calculated by comparing antioxidants intakes to their respective age-specified daily recommended intake values. Logistic regression models were conducted to examine associations between CDAI, E-CDAI, DAQS, and overweight/obesity risk, adjusting for potential confounders such as age, gender, race, physical activity, and socioeconomic status.

# 2 Methods

## 2.1 Study design and population

This study used data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2016. NHANES employs a complex, stratified, multistage probability sampling method to collect health and nutritional information from a representative sample of the civilian, non-institutionalized U.S. population. The survey protocol was approved by the NCHS Research Ethics Review Committee, and written informed consent was obtained from all participants.

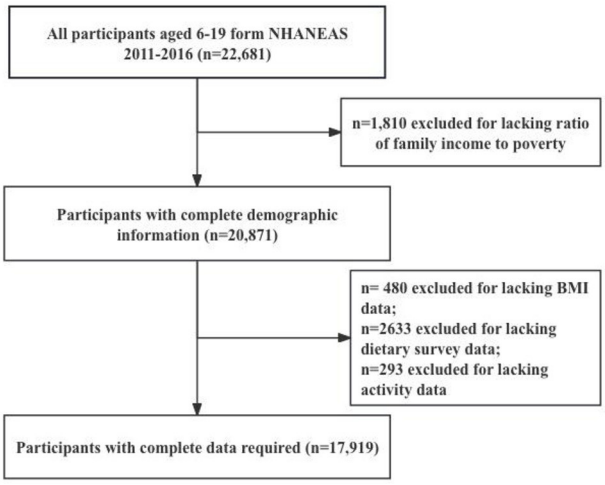


FIGURE 1
Flow chart of inclusion and exclusion criteria for the study sample. NHANES, National Health and Nutrition Survey; BMI, Body Mass Index.

Detailed information on the NHANES design and procedures can be found in previous studies.

Inclusion criteria required participants to have completed at least two 24-h dietary recalls. Exclusion criteria included missing data on key variables such as BMI, energy intake, or household income. The NHANES database provides information on various parameters such as age, gender, race, socioeconomic status, physical activity, energy intake, dietary components, and anthropometric measurements for study participants. This process resulted in a final sample of 17,919 participants. A detailed study flowchart is depicted in Figure 1.

## 2.2 Overweight and obesity data

Overweight and obesity data, including height and weight, were collected using standardized procedures. BMI was calculated as weight in kilograms divided by height in meters squared. Based on the CDC growth charts, participants were classified into the following categories (24): underweight (BMI below the 15th percentile), normal weight (BMI between the 15th and 85th percentiles), overweight (BMI between the 85th and 95th percentiles), and obesity (BMI at or above the 95th percentile).

## 2.3 Composite dietary antioxidant index

The composite dietary antioxidant index (CDAI) was computed using dietary data from the NHANES 24-h recall interviews. The index encompasses 6 key antioxidants: vitamins A, C, E, carotenoids, selenium, and zinc. To calculate the CDAI, we used the method proposed by Wright et al. (20), which involves standardizing each antioxidant by subtracting the global mean and dividing by the global standard deviation, which is calculated as follows:

$$CDAI = \sum_{i=1}^{6} \frac{x_i - mean\,(x_i)}{std\,(x_i)},$$

where $x_i$ represents the daily antioxidant intake, $mean(x_i)$ indicates the mean amount of these antioxidants within the study cohort, and $std(x_i)$ denotes the standard deviation. By leveraging these 24-h dietary recall data, CDAI scores can provide a comprehensive evaluation of the antioxidant intake at the individual level.

To adjust for total energy intake in the analysis, we employed two widely recognized adjustment approach, the standard regression model and the nutrient density model (26). Within the nutrient density model, we calculated the density of each antioxidant nutrient by dividing the absolute antioxidant intake by the total energy intake, expressed as $y_i = x_i/energy$. Subsequently, we derived an energy-standardized CDAI (E-CDAI) using the following formula:

$$E - CDAI = \sum_{i=1}^{6} \frac{y_i - mean\,(y_i)}{std\,(y_i)}.$$

## 2.4 Covariates

NHANES adjusted for individual characteristics using several covariates, including age, sex, race, ethnicity, BMI, physical activity, poverty-income ratio and vitamin D. Detailed information on measurement procedures is available on the CDC website. Physical activity data were collected following World Health Organization guidelines. For adolescents, physical activity was categorized according to the 2018 Physical Activity Guidelines Advisory Committee report (27), participants who reported <10 min of moderate-to-vigorous physical activity per week were labeled as inactive. For children, physical activity was categorized into two groups: active (≥4 days) or inactive (<4 days) according to the question: "Days physically active at least 60 min."

## 2.5 Statistical analysis

The study conducted descriptive analyses on the entire sample, with data further stratified by age group (children aged 6–11 years vs. adolescents aged 12–19 years). Results were presented as weighted median with interquartile range [median (interquartile range)] or percentage (%) for baseline characteristics. Continuous variables were analyzed using the Wilcoxon test or Kruskal–Wallis test. The association between categorical variables was examined using the Chi-square test. Multiple logistic regression was employed to assess the association between CDAI or E-CDAI and weighted-related measures (overweight/obesity, obesity). We construct 3 models to comprehensively evaluate the relationship between them: Model 1 includes age, gender,

race, and household income-to-poverty ratio (PIR); Model 2 includes adjustments for physical activity. In model 3, we further adjusted for total energy intake. After dividing CDAI or E-CDAI into quartiles, trends tests were utilized to analyze their linear association trend. The results were presented as odds ratios (ORs) with 95% confidence intervals (CIs) across quartiles of CDAI and E-CDAI. All analyses were conducted using R software (version 4.4.2), with significance set at a *p*-value of <0.05.

# 3 Results

## 3.1 Baseline characteristics

The study included 17,919 participants from the NHANES 2011–2016 dataset, consisting of 9,052 males (51.5%) and 8,867 females (48.5%). Participants were stratified into two age groups: children (6–11 years 43.1%) and adolescents (12–19 years, 56.9%). There were no statistically significant differences in gender,

TABLE 1 Baseline characteristics of US children and adolescents aged 6–19 years, NHANES 2011–2016.[a]

| Characteristic | Overall | Children aged 6–11 | Adolescents aged 12–19 | *P* |
|---|---|---|---|---|
| Overall, *n* (%) | 17,919 (100%) | 8,638 (43.1%) | 9,281 (56.9%) | |
| Age (years) | 12.00 (9.00, 16.00) | 8.00 (7.00, 10.00) | 16.00 (14.00, 17.00) | <0.001 |
| Gender (%) | | | | |
| Male | 9,052.0 (51.5%) | 4,372.0 (52.2%) | 4,680.0 (51.0%) | 0.6 |
| Female | 8,867.0 (48.5%) | 4,266.0 (47.8%) | 4,601.0 (49.0%) | |
| Race (%) | | | | |
| Mexican American | 3,722.0 (15.1%) | 1,781.0 (15.4%) | 1,941.0 (14.8%) | 0.7 |
| Other Hispanic | 1,969.0 (7.5%) | 980.0 (8.0%) | 989.0 (7.2%) | |
| Non-Hispanic White | 4,830.0 (54.0%) | 2,387.0 (52.9%) | 2,443.0 (54.8%) | |
| Non-Hispanic Black | 4,629.0 (14.2%) | 2,256.0 (14.1%) | 2,373.0 (14.3%) | |
| Other race | 2,769.0 (9.2%) | 1,837.53 (9.5%) | 1,535.0 (8.9%) | |
| Energy (kcal) | 1,881.00 (1,534.00, 2,282.00) | 1,859.39 (1,566.96, 2,208.00) | 1,905.45 (1,489.00, 2,369.00) | 0.077 |
| Physical activity (%) | | | | |
| Inactive | 4,000.0 (22.0%) | 1,282.0 (15.4%) | 2,718.0 (27.0%) | <0.001 |
| Active | 13,919.0 (78.0%) | 7,356.0 (84.6%) | 6,563.0 (73.0%) | |
| PIR, (%) | | | | |
| <130% | 7,947.0 (34.3%) | 3,970.0 (34.8%) | 3,977.0 (33.8%) | 0.7 |
| >130% | 9,972.0 (65.7%) | 4,668.0 (65.2%) | 5,304.0 (66.2%) | |
| BMI status (%) | | | | |
| Underweight | 578.0 (3.7%) | 275.0 (4.6%) | 303.0 (3.0%) | 0.069 |
| Normal weight | 10,612.0 (60.2%) | 5,216.0 (60.1%) | 5,396.0 (60.2%) | |
| Overweight | 3,038.0 (16.4%) | 1,437.0 (17.1%) | 1,601.0 (15.9%) | |
| Obesity | 3,691.0 (19.7%) | 1,710.0 (18.2%) | 1,981.0 (20.8%) | |
| Vitamin D (mcg) | 4.99 (2.92, 7.08) | 5.66 (3.70, 7.55) | 4.40 (2.40, 6.57) | <0.001 |
| Vitamin A (mcg) | 561.92 (379.00, 749.00) | 617.00 (445.00, 780.08) | 519.91 (332.00, 714.86) | <0.001 |
| Vitamin C (mg) | 60.30 (29.80, 95.12) | 70.10 (39.32, 102.39) | 53.10 (24.20, 88.89) | <0.001 |
| Vitamin E (mg) | 6.70 (4.91, 8.62) | 6.79 (5.13, 8.47) | 6.60 (4.73, 8.76) | 0.2 |
| Carotene (mcg) | 828.00 (301.00, 1,443.00) | 896.00 (321.00, 1,595.67) | 780.84 (286.00, 1,355.05) | <0.001 |
| Selenium (mcg) | 96.90 (75.44, 121.42) | 94.04 (75.08, 114.00) | 100.07 (75.60, 129.40) | <0.001 |
| Zinc (mg) | 9.74 (7.39, 12.44) | 9.75 (7.57, 11.91) | 9.73 (7.24, 12.95) | 0.4 |
| CDAI | −0.54 (−2.14, 1.13) | −0.45 (−1.84, 1.02) | −0.67 (−2.35, 1.22) | 0.025 |
| E-CDAI | −0.71 (−1.78, 0.42) | −0.56 (−1.59, 0.48) | −0.82 (−1.94, 0.35) | 0.001 |

BMI, Body Mass Index; PIR, income-to-poverty ratio; CDAI, Composite Dietary Antioxidant Index; E-CDAI, energy-standardized composite Dietary Antioxidant Index.
Data are presented as median [interquartile range], or n (%).
[a]All estimates are weighted except sample sizes (n).

race/ethnicity, BMI status, energy intake, or poverty-income ratio between children and adolescents. However, adolescents had significantly lower average intakes of certain micronutrient, including vitamin D, vitamin A, vitamin C, and carotenoids, than children ($p < 0.001$). Conversely, selenium intake was higher in adolescents ($p < 0.001$). Overall, adolescents exhibited lower scores for both the composite dietary antioxidant index (CDAI) and the energy-standardized CDAI (E-CDAI) compared to children (CDAI: $p = 0.025$; E-CDAI: $p < 0.001$). These differences may reflect age-related changes in dietary habits, with adolescents possibly consuming more processed foods with lower antioxidant content. Table 1 details these baseline characteristics.

## 3.2 Univariate analysis of overweight/obesity

As presented in Table 2, univariate analyses were conducted to evaluated factors associated with the risk of overweight/obesity. Ethnicity emerged as a significant factor, with Non-Hispanic White participants demonstrating the highest rates of overweight/obesity ($p < 0.001$). Lower income-to-poverty ratios were significant associated with a higher prevalence of overweight/obesity in both children ($p = 0.023$) and adolescents ($p = 0.035$). Among adolescents, overweight/obese individuals had significantly lower CDAI scores compared to their normal-weight counterparts ($p < 0.001$), whereas no significant differences were observed for the E-CDAI. In children, neither CDAI nor E-CDAI showed significant differences between BMI categories. Notably, overweight/obese adolescents had significant lower average intake of all assessed micronutrients, including vitamin D, vitamin A, vitamins C, vitamin E, carotene, selenium, and zinc (all $p < 0.05$). In contrast, no such difference were observed in children. These findings suggest that the role of dietary antioxidants in overweight/obesity may vary by age group, reflecting difference in metabolic profile and dietary patterns between children and adolescent.

## 3.3 Association between CDAI and overweight/obesity

Logistic regression models were conducted to explore the relationship between the composite dietary antioxidant index (CDAI), energy-standardized CDAI (E-CDAI), and overweight/obesity risk across different age groups, as presented in Table 3.

In children aged 6–11 years, no statistically significant associations were observed between either CDAI or E-CDAI and overweight/obesity in children across all adjusted models. The odds ratios (ORs) for overweight/obesity show no significant variation across quartiles of CDAI ($p$ for trend $> 0.05$). Similarly, E-CDAI also demonstrated no significant association with overweight/obesity in this age group ($p$ for trend $> 0.05$).

Among adolescents aged 12–19 years, a significant negative association was observed between CDAI and the risk of overweight/obesity among adolescents. Participants in the highest quartile of CDAI had a significantly lower odds of being overweight/obese compared to those in the lowest quartile (Model 3 OR = 0.73; 95% CI: 0.61–0.86; $p$ for trend $< 0.001$). However, in the nutrient density model, E-CDAI showed no significant association with overweight/obesity risk ($p$ for trend = 0.061). This discrepancy suggest that the method of energy adjustment may significantly influence the observed association between antioxidants indices and overweight/obesity.

## 3.4 Association of antioxidants with overweight/obesity

We explored the relationship between overweight/obesity and both the absolute intake and nutrient density of individual antioxidants included in the CDAI, such as carotenoids, vitamins E and C, zinc, magnesium, and selenium. Comparative analyses of these measures are presented in Tables 4, 5. Nutrient density for each antioxidant nutrient was calculated as the ratio of absolute antioxidant intake to total energy intake.

In children aged 6–11 years, no significant associations were found between the intake of individual antioxidants (vitamins A, C, E, carotenoids, selenium, and zinc) and the risk of overweight/obesity in children after adjustment for potential confounding factors.

Among adolescents aged 12–19 years, higher intakes of vitamins A, C, and E were significantly associated with a reduced risk of overweight/obesity in adolescents. Specifically, individual in the highest quartile of vitamin A intake had a 27% lower risk of overweight/obese compared to those in the lowest quartile (Model 3 OR = 0.73; 95% CI: 0.63–0.83). A similar protective effect was observed for vitamin C intake (Model 3 OR = 0.80; 95% CI: 0.70–0.90). Notably, these reverse association remained statistically significant in the nutrient density model (Table 6). Interestingly, while selenium density showed a positive association with overweight/obese (Model 2 OR = 1.23; 95% CI: 1.09–1.39; Table 5), absolute selenium showed negative association (Model 2 OR = 0.71, 95% CI: 0.62–0.80) (Table 4), suggesting a complex relationship between selenium and weight status.

## 3.5 Association between modified CDAI and overweight/obesity

The above analysis demonstrated that the method of energy adjustment can reverse the direction of the association between selenium and weight status, potentially explaining the lack of a significant association between E-CDAI and overweight/obesity was observed in the multivariate nutrient density model. To address this, we developed a modified CDAI (mCDAI) score by excluding selenium from the original 6 antioxidants included in the CDAI. Following the same analytical apporach, we applied both the standard regression model and nutrient density model to adjust the confounding effect of total energy intake. Logistic regression models were conducted to explore the relationship

TABLE 2 Univariate analysis of overweight/obesity in US children and adolescents aged 6–19 years, NHANES 2011–2016.[a]

| Characteristic | Children aged 6–11 years | | | Adolescents aged 12–19 years | | |
|---|---|---|---|---|---|---|
| | Underweight/ normal *N* = 5,491 | Overweight/ obesity *N* = 3,147 | *P* | Underweight/ normal *N* = 5,6991 | Overweight/ obesity *N* = 3,5821 | *P* |
| **Gender (%)** | | | | | | |
| Male | 2,779 (50.3%) | 1,593 (55.7%) | 0.10 | 2,934 (52.1%) | 1,746 (49.2%) | 0.3 |
| Female | 2,712 (49.7%) | 1,554 (44.3%) | | 2,765 (47.9%) | 1,836 (50.8%) | |
| **Race (%)** | | | | | | |
| Mexican American | 930 (12.3%) | 851.0 (21.2%) | <0.001 | 1,049 (12.6%) | 892 (18.7%) | <0.001 |
| Other Hispanic | 550 (6.8%) | 430 (10.1%) | | 611 (7.0%) | 378 (7.4%) | |
| Non-Hispanic White | 1,671 (57.0%) | 716 (45.5%) | | 1,586 (59.1%) | 857 (47.5%) | |
| Non-Hispanic Black | 1,443 (14.0%) | 813 (14.5%) | | 1,384 (12.9%) | 989 (16.6%) | |
| Other race | 897.0 (9.9%) | 337 (8.8%) | | 1,069 (8.4%) | 466 (9.8%) | |
| Energy (kcal) | 1,852.15 (1,563.00, 2,197.61) | 1,874.68 (1,571.79, 2,232.00) | 0.5 | 1,957.47 (1,550.00, 2,427.67) | 1,812.60 (1,414.00, 2,256.00) | <0.001 |
| **Physical activity (%)** | | | | | | |
| Inactive | 683 (11.6%) | 599 (22.4%) | <0.001 | 1,599 (25.5%) | 1,119 (29.6%) | 0.15 |
| Active | 4,808 (88.4%) | 2,548 (77.6%) | | 4,100 (74.5%) | 2,463 (70.4%) | |
| **PIR (%)** | | | | | | |
| <130% | 2,400 (32.4%) | 1,570 (39.3%) | 0.023 | 2,300 (31.8%) | 1,677 (37.4%) | 0.035 |
| >130% | 3,091 (67.6%) | 1,577 (60.7%) | | 3,399 (68.2%) | 1,905 (62.6%) | |
| CDAI | −0.48 (−1.87, 0.95) | −0.38 (−1.81, 1.16) | 0.4 | −0.46 (−2.12, 1.52) | −1.05 (−2.74, 0.67) | <0.001 |
| E-CDAI | −0.56 (−1.61, 0.49) | −0.56 (−1.54, 0.48) | 0.8 | −0.79 (−1.91, 0.40) | −0.90 (−2.04, 0.29) | 0.3 |
| Vitamin D (mcg) | 5.60 (3.54, 7.56) | 5.70 (3.81, 7.50) | 0.5 | 4.50 (2.54, 6.80) | 4.14 (2.20, 6.07) | <0.001 |
| Vitamin A (mcg) | 618.84 (444.00, 781.72) | 614.25 (447.00, 777.00) | 0.7 | 541.50 (359.00, 745.86) | 483.32 (304.00, 663.18) | <0.001 |
| Vitamin C (mg) | 69.03 (38.51, 100.64) | 72.30 (40.80, 105.20) | 0.13 | 55.59 (26.70, 92.81) | 48.66 (20.90, 82.50) | <0.001 |
| Vitamin E (mg) | 6.81 (5.14, 8.50) | 6.74 (5.09, 8.44) | 0.8 | 6.79 (4.92, 9.05) | 6.34 (4.41, 8.30) | <0.001 |
| Carotene (mcg) | 905.40 (324.00, 1,654.00) | 883.00 (316.00, 1,488.00) | 0.3 | 801.00 (296.00, 1,389.97) | 726.85 (269.00, 1,310.75) | 0.027 |
| Selenium (mcg) | 92.72 (74.30, 112.40) | 96.40 (77.00, 117.64) | 0.015 | 102.64 (78.10, 133.30) | 95.81 (72.10, 122.13) | <0.001 |
| Zinc (mg) | 9.67 (7.53, 11.89) | 9.86 (7.59, 11.93) | 0.5 | 10.04 (7.55, 13.38) | 9.25 (6.78, 12.05) | <0.001 |

BMI, Body Mass Index; PIR, income-to-poverty ratio; CDAI, Composite Dietary Antioxidant Index; E-CDAI, energy-standardized composite Dietary Antioxidant Index.
Data are presented as median [interquartile range], or n (%).
[a] All estimates are weighted except sample sizes (n).

between the modified composite dietary antioxidant index (mCDAI), modified energy-standardized CDAI (mE-CDAI), and overweight/obesity risk across different age groups, as detailed in Table 6.

In children aged 6–11 years, no statistically significant associations were observed between either mCDAI or mE-CDAI and overweight/obesity in children across all adjusted models. In contrast, among adolescents aged 12–19 years, a significant negative association was observed between mCDAI and the risk of overweight/obesity among adolescents in both standard regression model (Model 3 OR = 0.74; 95% CI: 0.63–0.86; $p$ for trend < 0.001) and multivariate nutrient density model (Model 3 OR = 0.78; 95% CI: 0.69–0.89; $p$ for trend < 0.001). These findings suggest that the exclusion of selenium from the CDAI may enhance the robustness of the association between dietary intake and overweight/obesity. In addition, there was no sex difference in the relationship between mCDAI, mE-CDAI and overweight/obesity (Table 7).

## 3.6 Association of DAQS with overweight/obesity

Recognizing that nutritional requirement vary significantly across different developmental stages, particularly within the broad

TABLE 3 Association between overweight/obesity and CDAI, E-CDAI in children and adolescents in US, NHAENS 2011–2016.

| Subgroups | Q1 | Q2 OR (95% CI) | Q3 OR (95% CI) | Q4 OR (95% CI) | *P* for trends[d] |
|---|---|---|---|---|---|
| 6–11, CDAI | | | | | |
| Model 1[a] | Ref | 1.03 (0.91, 1.17) | 1.08 (0.95, 1.22) | 1.06 (0.93, 1.20) | 0.329 |
| Model 2[b] | Ref | 1.03 (0.90, 1.16) | 1.08 (0.95, 1.22) | 1.06 (0.93, 1.21) | 0.285 |
| Model 3[c] | Ref | 1.01 (0.88, 1.15) | 1.05 (0.91, 1.20) | 1.01 (0.85, 1.19) | 0.847 |
| 6–11, E-CDAI | | | | | |
| Model 1[a] | Ref | 0.98 (0.86, 1.11) | 1.06 (0.94, 1.20) | 1.02 (0.90, 1.16) | 0.577 |
| Model 2[b] | Ref | 0.98 (0.87, 1.12) | 1.06 (0.94, 1.21) | 1.01 (0.89, 1.15) | 0.694 |
| Model 3[c] | Ref | 0.99 (0.87, 1.12) | 1.07 (0.94, 1.21) | 1.03 (0.90, 1.17) | 0.515 |
| 12–19, CDAI | | | | | |
| Model 1[a] | Ref | 0.85 (0.76, 0.96) | 0.74 (0.657, 0.834) | 0.576 (0.508, 0.652) | <0.001 |
| Model 2[b] | Ref | 0.86 (0.76, 0.96) | 0.75 (0.66, 0.84) | 0.58 (0.51, 0.66) | <0.001 |
| Model 3[c] | Ref | 0.93 (0.82, 1.05) | 0.84 (0.74, 0.96) | 0.73 (0.61, 0.86) | <0.001 |
| 12–19, E-CDAI | | | | | |
| Model 1[a] | Ref | 1.00 (0.89, 1.13) | 0.99 (0.88, 1.12) | 0.94 (0.83, 1.06) | 0.295 |
| Model 2[b] | Ref | 1.01 (0.90, 1.14) | 1.00 (0.88, 1.12) | 0.94 (0.84, 1.07) | 0.318 |
| Model 3[c] | Ref | 1.00 (0.89, 1.13) | 0.96 (0.85, 1.08) | 0.86 (0.76, 1.07) | 0.061 |

OR, odds ratio; 95% CI, 95% confidence interval.
[a]Model 1, adjusted for age, gender, race and household income-to-poverty ratio (PIR).
[b]Model 2, adjusted for covariates of model 1 plus physical activity.
[c]Model 3, according to model 2 plus the total energy intake.
[d]*P* for trend based on variable containing median value for each quantile.

age range of 6–19 years, we evaluated individual antioxidant against the daily recommended intake (DRI) established by the National Academies of Science, Engineering, and Medicine (NASEM) (28). Given the absence of an official DRI for carotenoids, this nutrient was excluded from the analysis. For each of five remained nutrients, a binary scoring system was implemented: a score of 0 was assigned if the nutrient intake fell below the age-specific DRI, and a score of 1was assigned if the intake meets or exceeded the age-specific DRI. Subsequently, we calculated the dietary antioxidant quality score (DAQS) by summing the score for the five antioxidants, resulting in a scale ranging from 0 (very poor quality) to 5 (high quality).

We further examined the association between overweight/obesity and both individual antioxidant score and the DAQS, as presented in Table 8. In children aged 6–11 years, no statistically significant associations were observed between overweight/obesity and either DAQS or individual antioxidant across all adjusted models. In contrast, among adolescents aged 12–19 years, a significant negative association was observed between DAQS and the risk of overweight/obesity (OR = 0.91; 95% CI: 0.86–0.96). Additionally, vitamins A (OR = 0.83; 95% CI: 0.73–0.94) and vitamins C (OR = 0.88; 95% CI: 0.86–0.96) demonstrated significant inverse association with overweight/obesity in this age group. However, no significant associations were observed between overweight/obesity and Vitamin E, Selenium or Zinc in adolescents.

## 4 Discussion

In this cross-sectional study, we investigate the relationship between the composite dietary antioxidant index (CDAI) and overweight/obesity among 17,919 participants aged 6–19 years in the United States, utilizing data from NHANES spanning 2011–2016. We employed two distinct models, the standard regression model and the nutrient density model, to adjust for total energy intake. In the standard regression model, a significant negative association was observed between CDAI score and overweight/obesity among adolescents, but not among children. Similarly, the dietary antioxidant quality score (DAQS) was also inversely associated with overweight/obesity in adolescents. However, in the nutrient density model, no significant association was found between the energy standardized CDAI (E-CDAI) score and overweight/obesity in either age group. Interestingly, we find that selenium showed a negative association with overweight/obesity in the standard regression model, but a positive association in the nutrient density model. After excluding the selenium from the original 6 antioxidants included in the CDAI, the modified CDAI (mCDAI) demonstrated a significant negative association with overweight/obesity in both the standard regression model.

Oxidative stress plays a critical role in the pathogenesis of obesity (29), characterized by an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses. Increased adiposity is linked with heightened ROS production, leading to oxidative damage and chronic inflammation

TABLE 4 Association between overweight/obesity and individual antioxidants in children and adolescents.

| Variables | Children aged 6–11 years | | | Adolescents aged 12–19 years | | |
|---|---|---|---|---|---|---|
| | Model 1[a] | Model 2[b] | Model 3[c] | Model 1[a] | Model 2[b] | Model 3[c] |
| Vitamin A | | | | | | |
| Q2 | 1.04 (0.91, 1.18) | 1.04 (0.92, 1.18) | 1.03 (0.9, 1.17) | 0.97 (0.86, 1.09) | 0.97 (0.86, 1.09) | 1.02 (0.91, 1.15) |
| Q3 | 1.09 (0.96, 1.23) | 1.08 (0.95, 1.23) | 1.06 (0.93, 1.21) | 0.75 (0.67, 0.85)* | 0.76 (0.67, 0.85)* | 0.83 (0.74, 0.94)* |
| Q4 | 1.04 (0.91, 1.18) | 1.03 (0.91, 1.17) | 0.99 (0.86, 1.14) | 0.61 (0.54, 0.69)* | 0.62 (0.54, 0.7)* | 0.73 (0.63, 0.83)* |
| Vitamin C | | | | | | |
| Q2 | 0.92 (0.81, 1.04) | 0.92 (0.81, 1.05) | 0.91 (0.8, 1.04) | 0.88 (0.78, 0.99)* | 0.88 (0.78, 0.99)* | 0.93 (0.82, 1.04) |
| Q3 | 0.97 (0.86, 1.1) | 0.98 (0.86, 1.11) | 0.96 (0.85, 1.09) | 0.79 (0.7, 0.89)* | 0.79 (0.7, 0.89)* | 0.85 (0.75, 0.96)* |
| Q4 | 0.91 (0.8, 1.04) | 0.92 (0.81, 1.05) | 0.9 (0.79, 1.03) | 0.7 (0.62, 0.79)* | 0.7 (0.62, 0.79)* | 0.8 (0.7, 0.9)* |
| Vitamin E | | | | | | |
| Q2 | 0.99 (0.87, 1.12) | 0.99 (0.88, 1.13) | 0.96 (0.84, 1.09) | 0.83 (0.73, 0.93)* | 0.83 (0.74, 0.93)* | 0.91 (0.81, 1.03) |
| Q3 | 0.89 (0.78, 1.01) | 0.89 (0.78, 1.01) | 0.84 (0.73, 0.96) | 0.77 (0.68, 0.87)* | 0.77 (0.68, 0.87)* | 0.9 (0.79, 1.03) |
| Q4 | 0.96 (0.85, 1.09) | 0.98 (0.86, 1.11) | 0.88 (0.75, 1.03) | 0.64 (0.57, 0.73)* | 0.65 (0.57, 0.73)* | 0.85 (0.73, 1) |
| Carotene | | | | | | |
| Q2 | 0.93 (0.82, 1.06) | 0.93 (0.82, 1.06) | 0.91 (0.8, 1.04) | 1.01 (0.9, 1.14) | 1.01 (0.9, 1.14) | 1.12 (0.99, 1.26) |
| Q3 | 1.05 (0.92, 1.19) | 1.05 (0.92, 1.19) | 1.03 (0.91, 1.17) | 0.9 (0.8, 1.01) | 0.9 (0.8, 1.01) | 1.01 (0.89, 1.14) |
| Q4 | 0.89 (0.78, 1.01) | 0.9 (0.79, 1.02) | 0.88 (0.77, 1) | 0.81 (0.72, 0.91)* | 0.82 (0.72, 0.92)* | 0.93 (0.82, 1.06) |
| Selenium | | | | | | |
| Q2 | 1.01 (0.89, 1.15) | 1.01 (0.89, 1.15) | 1.02 (0.89, 1.16) | 0.88 (0.78, 0.99)* | 0.88 (0.78, 0.99)* | 0.99 (0.88, 1.12) |
| Q3 | 1.11 (0.98, 1.26) | 1.11 (0.98, 1.26) | 1.12 (0.98, 1.29) | 0.78 (0.69, 0.88)* | 0.79 (0.7, 0.89)* | 0.96 (0.84, 1.09) |
| Q4 | 1.16 (1.02, 1.32) | 1.17 (1.03, 1.33) | 1.19 (1.01, 1.4) | 0.7 (0.62, 0.8)* | 0.71 (0.62, 0.8)* | 1.02 (0.86, 1.2) |
| Zinc | | | | | | |
| Q2 | 0.97 (0.85, 1.1) | 0.97 (0.85, 1.1) | 0.96 (0.84, 1.09) | 0.88 (0.78, 0.99)* | 0.89 (0.79, 1)* | 0.99 (0.87, 1.11) |
| Q3 | 1.08 (0.95, 1.23) | 1.08 (0.95, 1.23) | 1.06 (0.92, 1.22) | 0.84 (0.74, 0.94)* | 0.84 (0.75, 0.95)* | 1 (0.88, 1.14) |
| Q4 | 1.08 (0.95, 1.23) | 1.09 (0.96, 1.23) | 1.06 (0.9, 1.23) | 0.67 (0.59, 0.76)* | 0.67 (0.59, 0.77)* | 0.91 (0.78, 1.06) |

Data are presented as OR (95% CI), OR, odds ratio; 95% CI, 95% Confidence Interval.
[a]Model 1, adjusted for age, gender, race and household income-to-poverty ratio (PIR).
[b]Model 2, adjusted for covariates of model 1 plus physical activity.
[c]Model 3, according to model 2 plus the total energy intake.
*denotes $P < 0.05$.

(30), which can further exacerbate fat accumulation and metabolic dysregulation. Numerous studies have investigated the association between individual antioxidants and obesity, as well as the underlying causal mechanism. For instance, Aeberli et al. (31) found that dietary intake of antioxidant vitamins (vitamin E, A, and C) was significantly associated with leptin level in Swedish children, suggesting that low concentration of these vitamins may alter the leptin genetic expression, contributing to leptin resistance and increases obesity risk. Similarly, Puchau et al. (18) reported that obese children and adolescents consumed lower amounts of vitamin E and C compared to their non-obese counterparts. A case-control study in Thailand further identified a negative association between BMI, waist, and serum concentrations of vitamins E (32). These findings align with our partial results, which indicate that vitamins A, C, and E were inversely associated with overweight/obesity in adolescents, both in the standard regression model and nutrient density model. Previous research has also demonstrated significant associations between dietary carotene intake and blood carotenoid levels, with lower serum carotene concentrations often observed in obese individuals (33). Our analysis similarly revealed a negative association between absolute carotene intake and obesity risk; however, this association became non-significant in the nutrient density model. Interestingly, selenium exhibits a negative association with obesity risk in adolescents in the standard regression model, but this relationship shifted to a positive association in the nutrient density model. Some studies have reported a significant correlation between dietary selenium intake and obesity. For example, Yang et al. (16) found that selenium was not an independent protective factor against obesity in US adults but was positive associated with it. Emerging evidence suggests that selenium toxicity can manifests as oxidative stress, impaired biofilm development, and suppression of enzyme function when present in excessive amounts (34, 35). These findings are consistent with our results.

TABLE 5 Association between overweight/obesity and antioxidants[d] density in children and adolescents.

| Variables | Children aged 6–11 years | | | Adolescents aged 12–19 years | | |
|---|---|---|---|---|---|---|
| | Model 1[a] | Model 2[b] | Model 3[c] | Model 1[a] | Model 2[b] | Model 3[c] |
| Vitamin A | | | | | | |
| Q2 | 1.01 (0.89, 1.14) | 1 (0.88, 1.14) | 1 (0.88, 1.13) | 0.97 (0.86, 1.09) | 0.97 (0.86, 1.09) | 0.99 (0.88, 1.11) |
| Q3 | 1.02 (0.9, 1.16) | 1.01 (0.89, 1.15) | 1.01 (0.89, 1.15) | 0.89 (0.79, 1)* | 0.89 (0.79, 1)* | 0.89 (0.79, 1)* |
| Q4 | 1.01 (0.89, 1.14) | 0.99 (0.87, 1.13) | 1 (0.88, 1.14) | 0.79 (0.7, 0.89)* | 0.79 (0.7, 0.89)* | 0.76 (0.68, 0.86)* |
| Vitamin C | | | | | | |
| Q2 | 0.9 (0.79, 1.02) | 0.9 (0.79, 1.02) | 0.9 (0.79, 1.02) | 0.9 (0.8, 1.01) | 0.9 (0.8, 1.01) | 0.93 (0.82, 1.04) |
| Q3 | 0.92 (0.81, 1.04) | 0.92 (0.81, 1.05) | 0.92 (0.81, 1.04) | 0.82 (0.73, 0.93)* | 0.83 (0.73, 0.93)* | 0.84 (0.74, 0.94)* |
| Q4 | 0.96 (0.85, 1.09) | 0.97 (0.85, 1.1) | 0.98 (0.86, 1.11) | 0.86 (0.76, 0.97)* | 0.86 (0.76, 0.97)* | 0.84 (0.75, 0.95)* |
| Vitamin E | | | | | | |
| Q2 | 1.03 (0.91, 1.17) | 1.03 (0.91, 1.17) | 1.03 (0.91, 1.17) | 0.91 (0.81, 1.02) | 0.91 (0.81, 1.02) | 0.95 (0.84, 1.07) |
| Q3 | 1 (0.88, 1.14) | 1 (0.88, 1.14) | 1 (0.88, 1.13) | 0.85 (0.75, 0.95)* | 0.85 (0.75, 0.95)* | 0.87 (0.77, 0.98)* |
| Q4 | 0.94 (0.83, 1.07) | 0.94 (0.83, 1.07) | 0.94 (0.83, 1.07) | 0.88 (0.78, 0.99)* | 0.88 (0.78, 0.99)* | 0.9 (0.8, 1.01) |
| Carotene | | | | | | |
| Q2 | 0.94 (0.83, 1.07) | 0.94 (0.83, 1.07) | 0.94 (0.83, 1.07) | 1.09 (0.97, 1.23) | 1.1 (0.97, 1.23) | 1.14 (1.01, 1.29) |
| Q3 | 0.96 (0.85, 1.09) | 0.96 (0.84, 1.09) | 0.96 (0.84, 1.09) | 1.05 (0.93, 1.18) | 1.05 (0.93, 1.18) | 1.07 (0.95, 1.21) |
| Q4 | 0.9 (0.79, 1.02) | 0.91 (0.8, 1.03) | 0.91 (0.8, 1.03) | 0.92 (0.82, 1.04) | 0.93 (0.82, 1.05) | 0.93 (0.82, 1.05) |
| Selenium | | | | | | |
| Q2 | 0.99 (0.87, 1.13) | 1 (0.88, 1.14) | 1 (0.88, 1.13) | 1.06 (0.94, 1.19) | 1.06 (0.94, 1.19) | 1.06 (0.94, 1.2) |
| Q3 | 1.14 (1, 1.29) | 1.13 (1, 1.29) | 1.14 (1, 1.29) | 1.1 (0.98, 1.24) | 1.1 (0.97, 1.24) | 1.07 (0.95, 1.21) |
| Q4 | 1.13 (0.99, 1.28) | 1.12 (0.99, 1.28) | 1.13 (1, 1.29) | 1.24 (1.1, 1.39)* | 1.23 (1.09, 1.39)* | 1.15 (1.01, 1.29)* |
| Zinc | | | | | | |
| Q2 | 1.05 (0.93, 1.19) | 1.05 (0.93, 1.2) | 1.05 (0.93, 1.2) | 1 (0.89, 1.13) | 1 (0.89, 1.13) | 1.01 (0.89, 1.13) |
| Q3 | 1.02 (0.9, 1.16) | 1.02 (0.9, 1.16) | 1.03 (0.91, 1.17) | 1.08 (0.96, 1.22) | 1.08 (0.96, 1.22) | 1.06 (0.94, 1.2) |
| Q4 | 1.05 (0.92, 1.19) | 1.04 (0.92, 1.18) | 1.05 (0.93, 1.19) | 0.97 (0.86, 1.1) | 0.98 (0.87, 1.1) | 0.92 (0.82, 1.04) |

Data are presented as OR (95% CI), OR, odds ratio; 95% CI, 95% confidence interval.
[a]Model 1, adjusted for age, gender, race and household income-to-poverty ratio (PIR).
[b]Model 2, adjusted for covariates of model 1 plus physical activity.
[c]Model 3, according to model 2 plus the total energy intake.
[d]Energy-standardized nutrient intake is defined as the ratio between antioxidants and total energy intake.
*denotes $P < 0.05$.

Given that the effect of antioxidants is often dependent on their interaction with one another, their collective effect on weight status may differ from that of individual antioxidant. Therefore, in this study we focus on the association between the composite dietary antioxidant index (CDAI) and overweight/obesity in children and adolescents. To our knowledge, few studies have explored similar relationships using alternative dietary antioxidant indices. Notably, Kokkou et al. conducted a cross-sectional study involving 1,580 students aged 10–12 years, utilizing a dietary antioxidant index (DAI) that incorporated magnesium instead of carotenoids (17). Their findings revealed a significant inverse correlation between DAI scores and body weight status. Similarly, Aminnejad et al. investigated a modified version of DAI (including manganese rather than carotenoids) in a cohort of 593 adolescent boys (12–16 years), demonstrating a beneficial association between elevated antioxidant intake and improved weight status (36). In contrast, a study employing the dietary antioxidant quality score (DAQS) (excluding magnesium) in a larger sample of 4,270 participants aged 6–18 years paradoxically found that overweight and obese children exhibited higher intakes of certain dietary antioxidants compared to their normal-weight counterparts (19). These findings provide valuable insights for further research and underscore the need for standardized assessment of dietary antioxidant capacity in future studies.

Nutrient intake is generally correlated with total energy intake, as individuals who consume more energy tend to ingest larger quantities of most specific nutrients. As depicted in Figure 2A, CDAI shows a strong positive correlation with total energy intake. Total energy intake is a well-established risk factor for overweight/obesity, contributing to increased adiposity regardless of the dietary composition (37). Thus, total energy intake may represent a key confounder in the

TABLE 6 Association between overweight/obesity and mCDAI, mE-CDAI in children and adolescents in US, NHAENS 2011–2016.

| Subgroups | Q1 | Q2 OR (95% CI) | Q3 OR (95% CI) | Q4 OR (95% CI) | *P* for trends[d] |
|---|---|---|---|---|---|
| 6–11, mCDAI | | | | | |
| Model 1[a] | Ref | 1.02 (0.9, 1.16) | 1.04 (0.91, 1.18) | 0.98 (0.87, 1.12) | 0.809 |
| Model 2[b] | Ref | 1.02 (0.9, 1.16) | 1.04 (0.92, 1.18) | 0.99 (0.87, 1.13) | 0.899 |
| Model 3[c] | Ref | 0.99 (0.87, 1.13) | 0.99 (0.86, 1.13) | 0.91 (0.78, 1.06) | 0.235 |
| 6–11, mE-CDAI | | | | | |
| Model 1[a] | Ref | 0.89 (0.78, 1.01) | 0.95 (0.84, 1.08) | 0.96 (0.84, 1.08) | 0.716 |
| Model 2[b] | Ref | 0.89 (0.79, 1.01) | 0.95 (0.84, 1.08) | 0.95 (0.84, 1.08) | 0.629 |
| Model 3[c] | Ref | 0.89 (0.79, 1.01) | 0.96 (0.84, 1.09) | 0.96 (0.85, 1.09) | 0.785 |
| 12–19, mCDAI | | | | | |
| Model 1[a] | Ref | 0.89 (0.79, 1) | 0.74 (0.66, 0.83) | 0.59 (0.52, 0.67) | <0.001 |
| Model 2[b] | Ref | 0.89 (0.79, 1) | 0.74 (0.66, 0.84) | 0.59 (0.53, 0.67) | <0.001 |
| Model 3[c] | Ref | 0.96 (0.85, 1.08) | 0.84 (0.74, 0.96) | 0.74 (0.63, 0.86) | <0.001 |
| 12–19, mE-CDAI | | | | | |
| Model 1[a] | Ref | 0.89 (0.79, 1) | 0.87 (0.77, 0.98) | 0.83 (0.74, 0.94) | 0.003 |
| Model 2[b] | Ref | 0.89 (0.79, 1) | 0.87 (0.77, 0.98) | 0.83 (0.74, 0.94) | 0.004 |
| Model 3[c] | Ref | 0.9 (0.8, 1.01) | 0.85 (0.76, 0.96) | 0.78 (0.69, 0.89) | <0.001 |

OR, odds ratio; 95% CI, 95% confidence interval.
[a]Model 1, adjusted for age, gender, race and household income-to-poverty ratio (PIR).
[b]Model 2, adjusted for covariates of model 1 plus physical activity.
[c]Model 3, according to model 2 plus the total energy intake.
[d]*P* for trend based on variable containing median value for each quantile.

TABLE 7 Association between obesity and mCDAI, mE-CDAI in adolescents aged 12–19 years by sex NHAENS 2011–2016.

| Subgroups | Q1 | Q2 OR (95% CI) | Q3 OR (95% CI) | Q4 OR (95% CI) | *P* for trends[d] |
|---|---|---|---|---|---|
| Male, mCDAI | | | | | |
| Model 1[a] | Ref | 0.8 (0.68, 0.94) | 0.72 (0.61, 0.85) | 0.55 (0.46, 0.65) | <0.001 |
| Model 2[b] | Ref | 0.81 (0.69, 0.96) | 0.74 (0.63, 0.88) | 0.56 (0.47, 0.67) | <0.001 |
| Model 3[c] | Ref | 0.89 (0.75, 1.06) | 0.87 (0.72, 1.05) | 0.73 (0.59, 0.91) | 0.007 |
| Male, mE-CDAI | | | | | |
| Model 1[a] | Ref | 0.87 (0.74, 1.03) | 0.92 (0.78, 1.09) | 0.83 (0.7, 0.98) | 0.05 |
| Model 2[b] | Ref | 0.88 (0.74, 1.04) | 0.93 (0.78, 1.1) | 0.84 (0.71, 1) | 0.078 |
| Model 3[c] | Ref | 0.88 (0.74, 1.04) | 0.91 (0.77, 1.08) | 0.79 (0.66, 0.94) | 0.011 |
| Female, mCDAI | | | | | |
| Model 1[a] | Ref | 0.94 (0.8, 1.11) | 0.81 (0.68, 0.96) | 0.59 (0.49, 0.7) | <0.001 |
| Model 2[b] | Ref | 0.94 (0.8, 1.11) | 0.81 (0.68, 0.95) | 0.58 (0.49, 0.69) | <0.001 |
| Model 3[c] | Ref | 0.99 (0.83, 1.18) | 0.87 (0.72, 1.05) | 0.66 (0.53, 0.82) | <0.001 |
| Female, mE-CDAI | | | | | |
| Model 1[a] | Ref | 0.93 (0.79, 1.1) | 0.87 (0.73, 1.03) | 0.84 (0.71, 1) | 0.036 |
| Model 2[b] | Ref | 0.93 (0.79, 1.1) | 0.86 (0.73, 1.02) | 0.84 (0.71, 1) | 0.033 |
| Model 3[c] | Ref | 0.93 (0.79, 1.11) | 0.84 (0.71, 1) | 0.79 (0.67, 0.94) | 0.004 |

OR, odds ratio; 95% CI, 95% confidence interval.
[a]Model 1, adjusted for age, gender, race and household income-to-poverty ratio (PIR).
[b]Model 2, adjusted for covariates of model 1 plus physical activity.
[c]Model 3, according to model 2 plus the total energy intake.
[d]*P* for trend based on variable containing median value for each quintile.

TABLE 8 Association between overweight/obesity and DAQS and individual antioxidants score in children and adolescents.

| Variables | Children aged 6–11 years | | | Adolescents aged 12–19 years | | |
|---|---|---|---|---|---|---|
| | Model 1[a] | Model 2[b] | Model 3[c] | Model 1[a] | Model 2[b] | Model 3[c] |
| Vitamin A | 0.99 (0.89, 1.11) | 0.99 (0.89, 1.11) | 0.96 (0.85, 1.08) | 0.71 (0.63, 0.8) * | 0.72 (0.64, 0.81) * | 0.83 (0.73, 0.94) * |
| Vitamin C | 1 (0.92, 1.1) | 1.01 (0.92, 1.11) | 1 (0.91, 1.1) | 0.82 (0.75, 0.89) * | 0.82 (0.75, 0.9) * | 0.88 (0.8, 0.96) * |
| Vitamin E | 0.92 (0.83, 1.02) | 0.92 (0.84, 1.02) | 0.89 (0.81, 0.99) * | 0.91 (0.83, 1.01) | 0.92 (0.83, 1.01) | 1.01 (0.91, 1.12) |
| Selenium | 1.02 (0.88, 1.18) | 1.02 (0.88, 1.19) | 0.98 (0.83, 1.15) | 0.79 (0.69, 0.9) * | 0.79 (0.7, 0.9) * | 1 (0.87, 1.15) |
| Zinc | 1.2 (0.95, 1.52) | 1.2 (0.95, 1.52) | 1.15 (0.91, 1.47) | 0.75 (0.62, 0.91) * | 0.75 (0.62, 0.91) * | 0.89 (0.73, 1.09) |
| DAQS | 0.98 (0.93, 1.03) | 0.99 (0.94, 1.04) | 0.96 (0.91, 1.02) | 0.86 (0.82, 0.91) * | 0.87 (0.82, 0.91) * | 0.91 (0.86, 0.96) * |

Data are presented as OR (95% CI), OR, odds ratio; 95% CI, 95% confidence Interval.
[a]Model 1, adjusted for age, gender, race and household income-to-poverty ratio (PIR).
[b]Model 2, adjusted for covariates of model 1 plus physical activity.
[c]Model 3, according to model 2 plus the total energy intake.
*denotes $P < 0.05$.

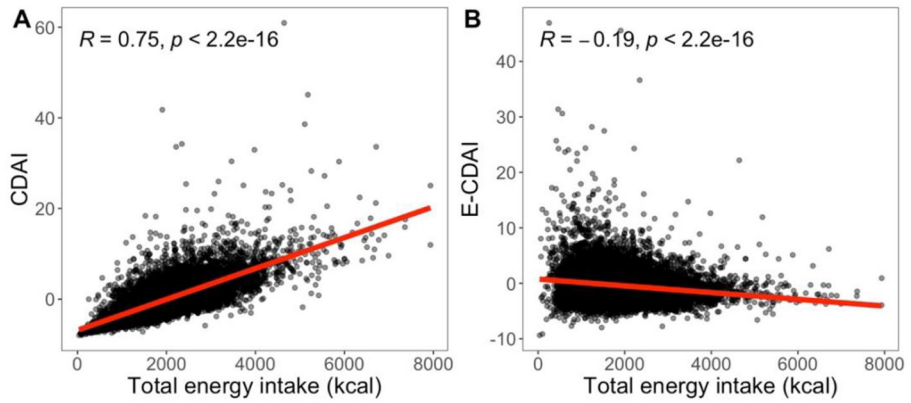


FIGURE 2
**(A)** CDAI has a high positive correlation with total energy intake ($r = 0.75$); **(B)** E-CDAI has a weak negative correlation with total energy intake ($r = -0.19$). Both were evaluated using the Spearman coefficient.

relationship between CDAI and overweight/obesity risk. To adjust for the total energy intake, we employed both the standard regression model and the nutrient density model (E-CDAI). As illustrated in Figure 2B, E-CDAI displayed a weak negative correlation with total energy intake. Our findings indicate a significant negative association between CDAI and the risk of overweight/obesity among adolescents, whereas no significant relationship was observed between E-CDAI and overweight/obesity in either age group. Further analysis revealed a negative association between overweight/obesity and absolute selenium intake, but a positive association between overweight/obesity and selenium density, potentially explaining the lack of a significant association between E-CDAI and overweight/obesity was observed in the nutrient density model. To address this, we developed a modified CDAI (mCDAI) score by excluding selenium from the original 6 antioxidants included in the CDAI. Further analysis demonstrated the modified CDAI (mCDAI) showed a significant negative association with overweight/obesity in both the standard regression model. Since Willet and Stampfer's 1986 publication (38), most nutritional epidemiology studies have routinely incorporated some form of energy adjustment. However, debate persist regarding the most appropriate approach (39, 40). The two models differ in their interpretation: in the standard regression model, the regression coefficient represents the apparent effect of increasing the antioxidant by 1 unit while maintaining a constant total energy intake; in the multivariate nutrient density model, the regression coefficients reflect the apparent effect of nutrient density in units of the percentage of energy from the nutrient. Given of the longstanding use of nutrient densities by nutritionists and the application of nutrient densities in public health recommendations (41, 42), the nutrient density model is widely adopted for estimating dietary effects.

There are several limitations to this study that warrant consideration. The cross-sectional design prevents us from inferring causality between CDAI and obesity. Longitudinal studies are needed to explore whether increasing energy-standardized antioxidant intake can help prevent obesity over time. Additionally, the reliance on self-reported dietary recalls may introduce bias and inaccuracies in estimating

antioxidant intake and energy consumption. Using objective biomarkers of antioxidant status and energy expenditure in future studies could provide more reliable data. Furthermore, this study did not account for other factors that could influence the relationship between antioxidants and obesity, such as individual genetics, hormonal status and gut microbiota. Future research should explore these factors to better understand the complex interactions between diet, oxidative stress, and obesity risk.

## 5 Conclusion

In conclusion, this study found that higher absolute dietary antioxidant intake, as measured by the composite dietary antioxidant index (CDAI), was significantly associated with a reduced risk of overweight and obesity among adolescents aged 12–19 years. However, the energy-standardized CDAI (E-CDAI) did not show a significant relationship with overweight/obesity. When selenium was excluded from the original CDAI, the modified CDAI (mCDAI) demonstrated a robust negative association with overweight/obesity in adolescents, irrespective of energy adjustment method. These findings suggest that a diet rich in antioxidants may play a protective role in preventing obesity in adolescent aged 12–19 years. Further longitudinal studies are needed to validate these findings and to elucidate the underlying mechanisms.

## Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: http://www.cdc.gov/nchs/nhanes.htm.

## Ethics statement

The studies involving humans were approved by NCHS Research Ethics Review Committee. 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

JC: Writing – original draft, Writing – review & editing. CS: Writing – original draft, Writing – review & editing.

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## Conflict of interest

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

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# Hepatic fat and dietary intake as determinants of metabolic health in obese adolescents: a cross-sectional MRI study

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**Background:** Obesity in youth is highly associated with metabolic risk. However, a subset of individuals maintains metabolic health despite the presence of obesity. This study aims to identify key factors associated with a metabolically healthy obese (MHO) in adolescents.

**Methods:** This cross-sectional study included 31 adolescents with obesity [median age: 14 y, median body mass index (BMI) Z-score: 2.58] categorized as MHO or metabolically unhealthy obese (MUO) based on the presence of one or more metabolic syndrome criteria. A comprehensive evaluation included MRI assessments of abdominal adipose tissue distribution and hepatic fat content (HFC), physiological and metabolic assessment, serum biomarkers, prenatal and sociodemographic characteristics, and dietary habits.

**Results:** Compared to the MUO, MHO individuals exhibited significantly lower HFC ($p$ = 0.01), liver enzymes ($p$ = 0.004), and experienced a lower risk of complications during birth ($p$ = 0.03). Additionally, MHO participants had significantly lower intake of total calories ($p$ = 0.04), animal protein ($p$ = 0.005), red meat ($p$ = 0.02), sodium ($p$ = 0.027), palmitic acid ($p$ = 0.04), stearic acid ($p$ = 0.029), arachidonic acid ($p$ = 0.005) and calories from ultra-processed grains ($p$ = 0.049) compared to their MUO counterparts.

**Conclusion:** Adolescents with MHO show lower hepatic fat, improved liver markers, and healthier dietary patterns than MUO peers. These findings underscore the potential influence of prenatal and lifestyle factors in distinguishing metabolic health profiles in adolescents with obesity.

**Clinical trial registration:** https://clinicaltrails.gov/study/NCT06032312; NCT06032312.

KEYWORDS

**metabolic health, obesity, adolescents, hepatic fat content, diet**

# Introduction

The global epidemic of childhood obesity is characterized by a rising prevalence of endocrine, metabolic, and cardiovascular comorbidities and represents one of the major public health challenges of our time (1–4). Recent data underscore alarming trends in childhood obesity and its associated metabolic syndrome (MS) features (2, 4–6). MS refers to a cluster of cardio-metabolic risk factors, including high blood pressure, high blood sugar, excess abdominal adiposity, and abnormal lipid profiles (7). The presence of multiple risk factors extends the likelihood of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases (8). The increasing prevalence of childhood obesity has raised concerns about reduced life expectancy, as early-onset obesity significantly elevates the risk of chronic conditions such as cardiovascular disease and type 2 diabetes, which can lead to premature mortality (9, 10).

A unique subgroup of adolescents with obesity, termed 'metabolically healthy obese' (MHO), has drawn attention due to its atypical profile, lacking the metabolic risk factors typically associated with obesity (11–14). Despite their obesity status, youngsters with MHO exhibit a favorable metabolic profile, characterized by preserved insulin sensitivity, and normal blood pressure, glucose regulation, lipid and liver enzyme levels, as well as balanced hormonal, inflammatory, and immune profiles (7, 15–18). Several prospective studies in both adolescents and adults have demonstrated that MHO is not consistently linked to increased cardiovascular risk or all-cause mortality (19–21). Therefore, identifying and understanding this MHO subgroup among adolescents with obesity is crucial for uncovering mechanisms that may prevent the development of clustered cardiometabolic risk factors and related diseases, enabling more informed clinical, preventive, and therapeutic decisions (4, 11, 18, 22, 23).

Several studies have examined the predictors and risk factors associated with MUO individuals (22, 23). However, these studies focused primarily on adult population and have yielded mixed results, due to variations in the definitions of MHO and criteria used for its classification.

Moreover, previous studies have not comprehensively investigated the interaction among perinatal history, sociodemographic factors, body composition, physical activity, and dietary composition in the pediatric population with obesity, nor have they attempted to establish relationships between these variables. Therefore, the primary objective of this study was to assess factors associated with MHO within a framework encompassing sociodemographic, clinical, body composition, nutritional, and physical performance aspects among adolescents with obesity. Given the emerging relevance of Hepatic fat content (HFC) in metabolic health, we hypothesize that variations in hepatic fat levels will contribute to the process of distinguishing between metabolically healthy and unhealthy states in the context of childhood obesity.

# Methods

## Study design

This prospective observational study was performed in the Nutrition and Obesity Clinic of the Pediatric Gastroenterology Institute, "Dana Dwek" Children's Hospital of the Tel Aviv Soursky Medical Center, which is a tertiary care pediatric hospital. Participants under routine care at the Clinic were invited to participate in the study after obtaining parental consent. The study protocol included a clinic visit to obtain physical examination, anthropometric measurements and record prenatal and sociodemographic information. Participants then completed a full day of assessments, which included magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) scans, along with various physiological performance tests, such as isometric mid-thigh pull and handgrip dynamometer strength tests and resting metabolic rate (RMR) measurements (see below for details). Additionally, self-reported data on physical activity levels and dietary habits were collected. The study was approved by the Institutional Review Board of Tel Aviv Medical Center (TLV-0799-20). All parents provided written informed consent prior to the participant's enrollment (clinical trial registration number: NCT06032312).

## Study population

Eligible participants for the study were adolescents with obesity, treated at the Obesity Clinic between January 2021 and August 2023. Exclusion criteria included any underlying disease or treatments potentially affecting body composition or metabolic risk (e.g., anti-inflammatory medications, Metformin), or inability to complete an MRI scan.

Initially, 52 adolescents were eligible for the study. Of these, nine were excluded due to underlying conditions or medication use (chronic kidney disease, celiac disease, neurologic disability, or regular use of metformin or risperidone), and twelve declined to participate. The final sample included 31 adolescents: 15 in the MUO group and 16 in the MHO group.

## Demographic and clinical variables

Information retrieved from the medical files of the study participants included:

1. Sociodemographic characteristics: age, sex, home address.
2. Medical history: complication during pregnancy, perinatal characteristics (birth weight, gestational age, mode of delivery), medications, and family history of cardiometabolic diseases (diabetes, hypertension, dyslipidemia, cardiovascular disease, and cerebrovascular episodes) among first- and second-degree relatives.
3. Physical examination: systolic and diastolic blood pressure and anthropometric measurements (height and weight conducted following standardized protocols). BMI, height and birth weight Z-scores were calculated by means of sex and age-specific BMI reference values from the Center for Disease Control and Prevention growth charts (24).
4. Documented blood markers at study entry included: total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c), triglycerides (TG), alanine transaminase (ALT), fasting plasma glucose (FPG), and insulin.

5. Socioeconomic position (SEP) was determined by the patient's home address according to the Israel Central Bureau of Statistics' Characterization and Classification of Statistical Areas within Municipalities and Local Councils by the Socio-Economic Level of the Population 2015 (25).
6. The quality of life (QoL) of the study participants was assessed with the Pediatric Quality of Life Inventory (PedsQL), version 3.0 (26). PedsQL is a 23-item assessment of physical, emotional, social, and school functioning.

## RMR assessment

RMR was measured in a metabolic unit using an indirect calorimeter device (Quark RMR; Cosmed, Rome, Italy). Indirect calorimetry was based upon the ratio of gas exchange, specifically, carbon dioxide production ($VCO_2$) versus oxygen consumption ($VO_2$), which reflects energy metabolism according to the Weir equation (27). The 20-min RMR measurement was performed in a supine position after 8 h of fasting and a minimum of 24 h of abstaining from alcohol, caffeine, smoking, and exercise. Gas and turbine calibrations were performed before each test. The first 4 min, also known as the adaptation phase, were excluded from the mean RMR, resulting in the utilization of only the final 16 min to determine RMR values.

## Nutritional assessment

A registered dietitian administered a self-reported semi-quantitative food frequency questionnaire (FFQ) to assess the participant's nutritional intake. The 126-item questionnaire aimed to estimate the participant's dietary habits over the previous year (28). In addition to the measurement of energy intake, the FFQ data underwent a further analysis to generate values for food group consumption, including a macro- and micronutrient breakdown. Ultra-processed foods were classified as falling under NOVA group 4 according to the NOVA food classification system (29). Group 4 includes industrial formulations typically containing five or more ingredients, such as sugars, oils, fats, salt, preservatives, colorings, flavorings, and other additives designed to enhance shelf life, taste, and texture. Examples of ultra-processed foods include sugary breakfast cereals, packaged snacks, and soft drinks, which undergo extensive processing and contain minimal whole food components. This standardized classification was applied to all dietary data to ensure reproducibility and consistency in defining ultra-processed food intake.

The Mediterranean diet score, developed by Panagiotakos et al., evaluates adherence to the Mediterranean diet, with scores ranging from 0 to 55 (30). It assesses the frequency of consumption of various food groups. Including non-refined cereals, fruits, vegetables, legumes, potatoes, fish, meat, poultry, full-fat dairy products, olive oil, and alcohol. Each item within these groups receives a score from 0 to 5 based upon monthly consumption frequency (from never to >18 servings per month). These analyses utilized the Israeli national nutrient database from the Israeli Ministry of Health ('Tzameret'), as per the Food and Nutrition Services and Public Health Services guidelines [2008] in the Israeli Nutrient Database (31).

## Body composition and fat distribution assessment

1. Fat mass, fat-free mass, and skeletal muscle mass were determined by means of a multi-frequency SECA body composition analyzer (mBCA 514 Medical, Hamburg, Germany), utilizing bioelectrical impedance analysis. The calculated bioelectrical impedance analysis variables included appendicular skeletal muscle mass (i.e., skeletal muscle mass of all four limbs) and muscle-to-fat ratio (i.e., appendicular skeletal muscle mass [kg]/total fat mass [kg]). Participants wore light clothing during these assessments and removed all jewelry, socks, and shoes. These measurements were conducted in the morning following an overnight fast.
2. Fatty liver was determined by clinical radiologists via abdominal ultrasonography by a Logic Q700 MR machine (GE, Milwaukee, WI, USA) and a 3.5 MHz probe. The ultrasound images included: (i) sagittal view of the right lobe of the liver and right kidney, (ii) transverse view of the left lateral segment of the liver and spleen, and (iii) transverse view of the liver to assess for altered echo texture. Fatty liver infiltration was identified by an increase in liver echogenicity compared to the echogenicity of the renal cortex, with the diaphragm and intrahepatic vessels appearing normal.
3. Abdominal adipose tissue distribution and HFC were evaluated with MRI and MRS, respectively, by means of the Siemens MAGNETOM Prisma 3-Tesla MRI scanner at the Alfredo Federico Strauss Center at Tel Aviv University. MRI scans were conducted at three axial levels (L5-L4, L4-L3, and L3-L2) to precisely determine visceral fat distribution. The mean values for visceral adipose tissue, deep subcutaneous adipose tissue, and superficial subcutaneous adipose tissue were calculated based upon the three axial slices.

HFC was determined by means of MRS, a well-validated analytical technique that detects radiofrequency electromagnetic signals emitted by atomic nuclei within molecules (32, 33). The total hepatic fat fraction within the image was determined as the ratio of the sum of the area under all fat peaks to the sum of the area under all fat and water peaks.

## Strength performance and physical activity assessment

Muscle strength and function were assessed with an isometric mid-thigh pull and handgrip dynamometer (34). A handgrip strength test was employed to measure upper limb strength by means of a handgrip dynamometer (Baseline® 200 lb. Capacity, New Jersey, USA) (35). Finally, the participants were instructed to wear an accelerometer (GT9X©; ActiGraph, Pensacola, FL, USA) for seven consecutive days to track their sedentary and vigorous activity periods. Data extraction from the device included calibrating the raw data and identifying wear/non-wear episodes to gather validated information on the physical activity levels. Physical activity intensity was classified using established count thresholds: sedentary time as <100 counts per minute (≤1.5 METs) and vigorous activity as ≥5,999 counts per

minute (≥6 METs). This standardized approach for quantifying sedentary and vigorous activity follows Troiano et al. (35).

## Classification of metabolically unhealthy obese and definition of metabolic conditions

The diagnose of MUO was based on the consensus-based definition and includes all children and adolescence with a BMI over the 95th percentile, along with one or more of the following criteria: HDL-c < 40 mg/dL (or <1.03 mmol/L), TG ≥ 150 mg/dL (or ≥1.7 mmol/L), systolic and diastolic blood pressure ≥90th percentile, and FPG ≥ 100 mg/dL (or ≥5.5 mmoL/L) (7).

Insulin resistance was determined with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 (36).

A diagnosis of MASLD was established according to the recent multisociety statement as any case of hepatic steatosis in the setting of cardiometabolic risk factors (37).

## Outcomes

### Primary outcome

The primary outcome of this study was HFC, measured using magnetic resonance spectroscopy (MRS), as a key differentiator between MHO and MUO adolescents.

### Secondary outcomes

1. Assessment of lifestyle factors, such as physical activity levels and dietary quality as predictors of metabolic health in adolescents with obesity.
2. Examination of sociodemographic and perinatal factors, including birth history and socioeconomic position, that may influence metabolic health.
3. Evaluation of muscle strength and RMR to explore their associations with metabolic health among adolescents with obesity.

## Statistical analysis

A convenient sample of 30 participants was chosen after determining the sample size for assessing trends for metabolic health among adolescents with obesity. The power analysis was conducted based on HFC content, our primary outcome, based on a previous study (38) that assessed the metabolic function of HFC among 31 adults. HFC was 5-fold (3.6% ± 0.5 vs., 15.3% ± 3.5) in the MUO group, yielding an effect size of 7.62 (Cohen's d). With $\alpha = 0.05$, this sample size provides over 99% power, confirming adequacy for detecting significant differences in HFC between groups.

Adolescents were matched for age and BMI Z score to minimize confounding variables and enhance result comparability. Epidemiological data and participant descriptors measured on continuous scales were reported as means and standard deviations, while categorical variables were presented as percentages of the number of participants. Parametric tests, including the Student's t-test for continuous variables, were employed for normally distributed data, while non-parametric tests, such as the Mann–Whitney U test, were utilized for non-normally distributed continuous variables. Levene's test assessed the equality of group variances for continuous variables. The Chi-squared test was applied for categorical variable analysis. Logistic regression analysis was employed to assess the impact of HFC on metabolic health, adjusting for BMI, sex, age, and total calories. Additionally, linear regression using the enter method was applied to evaluate the independent effect of HFC on FPG, a primary metabolic health criterion, while adjusting for saturated fatty acid (SFA) and animal protein. Statistical significance was set at $p < 0.05$ following Bonferroni correction for multiple comparisons. Due to the relatively small sample size and the number of outcomes examined, this conservative method was selected to limit type I error and avoid misleading inferences. Data values were excluded if they deviated more than three times the standard deviation from the mean in order to ensure that extreme values do not unjustifiably influence the statistical results. The statistical analyses were carried out using SPSS V. 25 (SPSS Inc., Chicago, IL, USA) software, and Prism V. 8 (GraphPad, La Jolla, CA, USA).

# Results

## Clinical factors and sociodemographic data

The sociodemographic and clinical data of all participants are detailed in Table 1. There were 10 females and 6 males in the MHO group and 7 females and 8 males in the MUO group. The mean age and the BMI were similar for both groups. As anticipated, the MHO group had significantly higher levels of HDL-c and TG concentration as well as higher percentage of hypertension and insulin resistance (Table 1). Moreover, the MUO group also had a significantly higher elevation in ALT compared to the MHO group (45.0 ± 23.6 U/L vs. 21.3 ± 8.1 U/L. $p = 0.004$). This latter finding was consistent with the substantially higher incidence of fatty liver observed on the ultrasound scans in the MUO group (MHO: 15.3% vs. MUO: 76.9%; $p = 0.002$).

Significantly more high-risk pregnancies (defined as any pregnancy that required special care, such as intrauterine growth restriction, maternal hypertension, etc.) were reported for the adolescents with MUO (46.7%) compared to the adolescents with MHO (12.5%) ($p = 0.03$), However, no differences were noted in terms of birth weight, weeks' gestation, or mode of delivery. In addition, MUO adolescents had significantly higher score in school functioning and overall QoL compared to their MHO counterpart ($p < 0.05$).

## Body composition, fat distribution, strength performance and physical activity associated with metabolic health

Physiological and body composition parameters for the two study groups are listed in Table 2. HFC, measured by MRS, was significantly elevated in the MUO group compared to the MHO group (14.0 ± 9.8% vs. 6.1 ± 3.2%, respectively, $p = 0.01$) (Figure 1). However, the levels of fat mass, fat-free mass and muscle-to-fat ratio were comparable for the MHO and MUO groups. The total abdominal fat, visceral adipose tissue, deep subcutaneous adipose tissue and superficial subcutaneous

TABLE 1 Clinical and sociodemographic characteristics of the study population.

| Variables | Metabolically healthy obese (*n* = 16) | Metabolically unhealthy obese (*n* = 15) | *p*-value |
|---|---|---|---|
| Age (y) | 14.5 ± 1.9 | 14.2 ± 2.0 | 0.64 |
| Female, *n* (%) | 10 (62.5) | 7 (46.7) | 0.37 |
| Weight (kg) | 100.0 ± 17.1 | 108.4 ± 12.1 | 0.28 |
| Height (m) | 1.64 ± 0.1 | 1.67 ± 0.1 | 0.41 |
| Height Z-score | 0.35 ± 0.93 | 0.69 ± 0.98 | 0.33 |
| BMI (kg/m$^2$) | 37.1 ± 6.0 | 38.7 ± 8.3 | 0.54 |
| BMI Z-score | 2.47 ± 0.51 | 2.77 ± 0.67 | 0.18 |
| Ultrasonography fatty liver, *n* (%) | 2 (15.3) | 10 (76.9) | **0.002** |
| Hypertension, *n* (%) | 0 (0.0) | 4 (26.6) | **0.02** |
| **Blood tests** | | | |
| Total Cholesterol (mg/dL) | 150.9 ± 20.2 | 165.4 ± 28.3 | 0.13 |
| LDL-c (mg/dL) | 83.0 ± 18.3 | 96.4 ± 25.7 | 0.13 |
| HDL-c (mg/dL) | 44.7 ± 5.7 | 37.0 ± 5.5 | **0.001** |
| TG (mg/dL) | 96.5 ± 27.0 | 152.2 ± 66.7 | **0.01** |
| ALT (u/L) | 21.3 ± 8.1 | 45.0 ± 23.6 | **0.004** |
| FPG (mg/dL) | 89.8 ± 6.5 | 99.0 ± 20.6 | 0.11 |
| Insulin (μU/mL) | 22.0 ± 10.7 | 48.9 ± 23.4 | **0.009** |
| Homa-IR (units) | 4.1 ± 2.8 | 13.2 ± 10.2 | **0.02** |
| **Prenatal characteristics** | | | |
| Birth weight (kg) | 3.2 ± 0.6 | 3.0 ± 0.7 | 0.54 |
| Birth week (weeks) | 38.0 ± 1.5 | 38.5 ± 1.4 | 0.43 |
| Birth weight-for-birth week Z-score | 0.12 ± 1.35 | -0.53 ± 1.70 | 0.24 |
| High-risk pregnancy, *n* (%) | 2 (12.5) | 7 (46.7) | **0.03** |
| Cesarean section, *n* (%) | 5 (26.3) | 3 (21.4) | 0.54 |
| Breastfeeding, *n* (%) | 9 (56.2) | 6 (42.8) | 0.46 |
| **Sociodemographic characteristics** | | | |
| SPS status index | 0.74 ± 0.54 | 0.66 ± 0.59 | 0.71 |
| Physical functioning score | 69.0 ± 14.7 | 68.7 ± 22.5 | 0.97 |
| Emotional functioning score | 60.0 ± 15.8 | 75.8 ± 21.6 | 0.06 |
| Social functioning score | 68.6 ± 20.8 | 78.7 ± 15.9 | 0.19 |
| School functioning score | 46.8 ± 8.7 | 62.5 ± 13.0 | **0.003** |
| Total QoL score | 59.8 ± 11.2 | 71.4 ± 12.1 | **0.03** |
| Cardiometabolic risk, *n* (%) | 9 (56.2) | 12 (80.0) | 0.15 |
| Family history of bariatric surgery, *n* (%) | 3 (18.7) | 7 (50.0) | 0.07 |

Values are means ± SD. BMI, body mass index; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; TG, triglycerides; ALT, alanine transaminase; FPG, fasting plasma glucose; Homa-IR, homeostatic model assessment for insulin resistance; SPS, socioeconomic position; QoL, quality of life. Bold text indicates significant findings $p < 0.05$ (*t*-tests for continuous variables; Chi-square for categorical variables).

adipose tissue distribution was also similar for the MHO and MUO groups (Table 2). Interestingly, there were no significant differences between the MHO and MUO groups in RMR (1962 ± 427 vs. 2,259 ± 379; $p = 0.07$), nor for the physical activity and strength measures of sedentary time per day (58.2 ± 8.4% vs. 59.1 ± 7.6%; $p = 0.81$), handgrip max strength (23.1 ± 7.7 kg vs. 25.2 ± 7.3 kg, $p = 0.43$), and isometric mid-thigh pull max (169.4 ± 38.9 kg vs. 165.9 ± 32.1 kg, $p = 0.80$) (Table 2).

## Differences in dietary patterns between metabolically healthy and unhealthy obese adolescents

Table 3 depicts the self-reported dietary consumption patterns of the MHO and the MUO groups.

TABLE 2 Metabolic and physiological parameters in MHO and MUO.

| Variables | Metabolically healthy obese (*n* = 16) | Metabolically unhealthy obese (*n* = 15) | *p*-value |
|---|---|---|---|
| **Metabolic** | | | |
| Resting metabolic rate (kcal/day) | 1962 ± 427 | 2259 ± 379 | 0.07 |
| Respiratory quotient | 0.85 ± 0.21 | 0.75 ± 0.12 | 0.15 |
| **Body composition and fat pools** | | | |
| Body fat (%) | 46.2 ± 5.9 | 43.9 ± 7.2 | 0.35 |
| Fat mass (kg) | 45.6 ± 10.2 | 48.7 ± 18.2 | 0.58 |
| Fat-free mass (kg) | 53.1 ± 11.6 | 59.6 ± 9.8 | 0.11 |
| Skeletal muscle mass (kg) | 25.0 ± 6.3 | 29.3 ± 5.7 | 0.06 |
| Appendicular skeletal muscle mass (kg) | 18.75 ± 4.75 | 21.99 ± 4.3 | 0.06 |
| Muscle-to-fat ratio (kg) | 0.42 ± 0.1 | 0.48 ± 0.1 | 0.23 |
| HFC (%) | 6.1 ± 3.2 | 14.0 ± 9.8 | **0.01** |
| Total abdominal fat (mm$^3$) | 179.5 ± 42.3 | 209.8 ± 72.1 | 0.20 |
| Visceral adipose tissue (mm$^3$) | 48.6 ± 9.2 | 53.4 ± 12.7 | 0.29 |
| Deep subcutaneous adipose tissue (mm$^3$) | 50.4 ± 20.0 | 51.2 ± 12.8 | 0.91 |
| Superficial subcutaneous adipose tissue (mm$^3$) | 80.4 ± 28.6 | 86.5 ± 37.3 | 0.64 |
| **Physical activity and performance** | | | |
| Days of accelerometer wearing (days) | 7.4 ± 0.8 | 8.0 ± 1.8 | 0.36 |
| Sedentary time (%/day) | 58.2 ± 8.4 | 59.1 ± 7.6 | 0.81 |
| Vigorous time (%/day) | 0 | 0 | |
| Hand grip strength max (kg) | 23.1 ± 7.7 | 25.2 ± 7.3 | 0.43 |
| Isometric mid-thigh pull max (kg) | 169.4 ± 38.9 | 165.9 ± 32.1 | 0.80 |

Values are means ± SD. Bold text indicates significant findings $p < 0.05$ (*t*-tests for continuous variables; Chi-square for categorical variables). HFC, hepatic fat content.

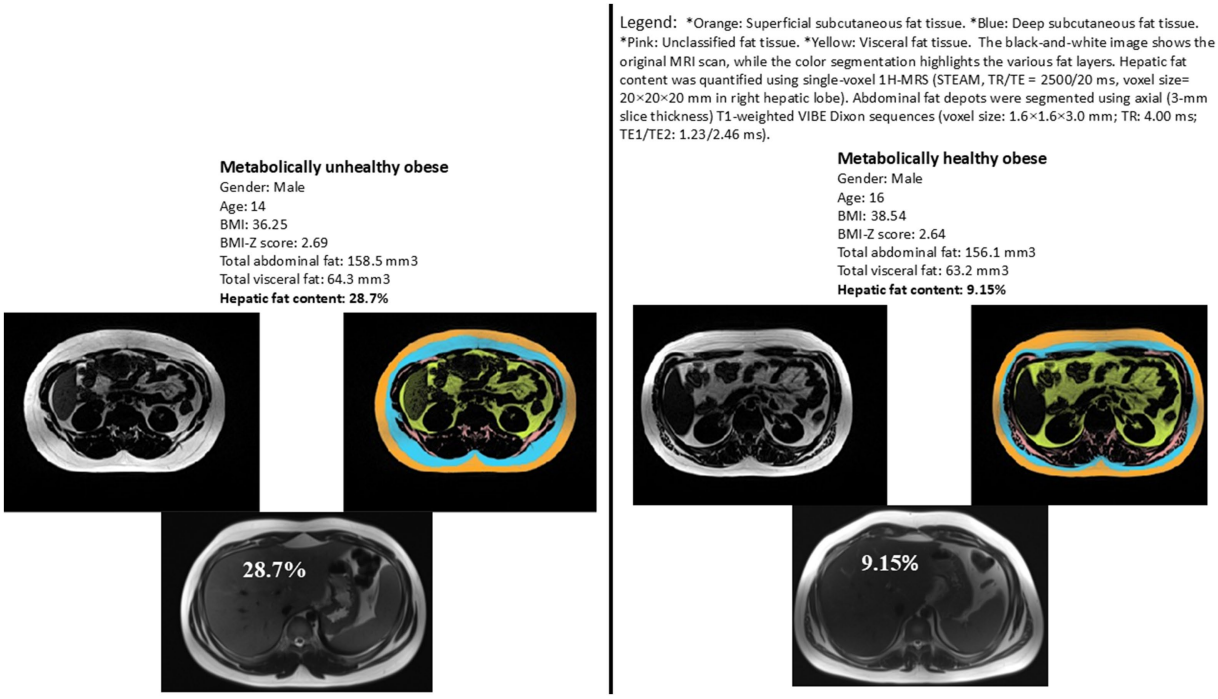


FIGURE 1
Representative images illustrating hepatic fat content for two matched subjects from each study group. Matching criteria include sex, BMI z-score, total abdominal fat, and visceral fat. Variations in hepatic fat content are evident between the two subjects, highlighting the difference between metabolically healthy and unhealthy obese adolescents.

MUO individuals had a significantly higher total daily calorie consumption (MHO: 1655 ± 475 kcal/day vs. MUO: 2071 ± 517 kcal/day; $p = 0.04$). Furthermore, there was a substantial increase in daily protein consumption by MUO individuals (MHO: 75 ± 18 g/day vs. MUO: 110 ± 32 g/day; $p = 0.003$), along with animal protein (MHO: 49 ± 17 g/day vs. MUO: 76 ± 27 g/day; $p = 0.005$), red meat calories (MHO: 40 ± 50 kcal/day vs. MUO: 93 ± 59 kcal/day; $p = 0.02$), and iron intake (MHO: 10.2 ± 4.2 mg/day vs. MUO: 15.0 ± 5.1 mg/day; $p = 0.01$). Likewise, MUO individuals exhibited significantly higher daily intakes of palmitic acid, stearic acid and arachidonic acid ($p < 0.05$). In addition, adolescents with MUO consumed significantly higher calories from ultra-processed grains (MHO: 67 ± 37 kcal/day vs. MUO: 116 ± 78 kcal/day; $p = 0.05$) and significantly higher sodium (MHO: 3050 ± 1,090 mg/day vs. MUO: 4084 ± 1,056 mg/day; $p = 0.02$).

## The independent effect of HFC on metabolic health

Table 4 displays the odds ratios (OR) for MUO status based upon the HFC while adjusting for various covariates. Model 1 represents the unadjusted OR of 1.21 (95% confidence interval [CI]: 1.02–1.41; $p = 0.02$). Model 2 adjusted for BMI, age and sex revealed an OR of 1.19 (95% CI: 1.00–1.41; $p = 0.04$). Model 3 included all the covariates and incorporated total calorie intake demonstrated borderline statistical significance [OR of 1.20 (95% CI: 0.99–1.46; $p = 0.06$)].

Figure 2 presents the key findings from the MHO and MUO group comparison. It highlights the elevated hepatic fat content (HFC) in the MUO group, alongside their higher intake of total calories, sodium, animal protein, red meat, long-chain saturated fatty acids, and ultra-processed grains. Additionally, the figure shows a greater prevalence of high-risk pregnancies in the MUO group. Notably, both groups exhibit similar levels of fat-free mass, fat distribution, and physical strength.

# Discussion

In this study, we observed marked differences in fatty liver presence and extent between adolescents with MHO and those with MUO. Additional distinctions emerged in the history of high-risk pregnancies and dietary habits between the groups. Specifically, adolescents with MUO reported greater consumption of calories, animal protein, sodium, arachidonic acid, long-chain saturated fatty acids, and ultra-processed grains compared to their MHO counterparts.

Our findings reveal that a higher proportion of adolescents in the MUO group were born following high-risk pregnancies, suggesting a potential prenatal origin for their elevated metabolic risk. This observation aligns with Barker's hypothesis, which posits that adverse conditions during gestation, such as those seen in complicated pregnancies, may increase susceptibility to chronic disease later in life (39, 40). These results underscore the possible impact of prenatal factors on the development of metabolic health in adolescence.

As noted above, HFC further distinguished the MUO group, with significantly elevated levels quantified by MRS, a reference standard for the noninvasive measurement of liver steatosis (32, 33), and corroborated by raised liver enzymes and ultrasound indicators of hepatic steatosis. Although the cross-sectional design of the present study precludes causal inference, this finding suggests that liver fat play a pivotal role in distinguishing metabolic phenotypes within the

TABLE 3 Differences in self-reported nutrient intake between healthy and metabolically unhealthy obese adolescents.

| Variables | Metabolically healthy obese ($n$ = 16) | Metabolically unhealthy obese ($n$ = 15) | $p$-value |
|---|---|---|---|
| Total calories (kcal/day) | 1655 ± 475 | 2071 ± 517 | **0.04** |
| Carbohydrate (g/day) | 177 ± 67 | 208 ± 65 | 0.23 |
| Fat (g/day) | 66 ± 19 | 83 ± 24 | 0.06 |
| Protein (g/day) | 75 ± 18 | 110 ± 32 | **0.003** |
| Added sugars (g/day) | 18 ± 13 | 21 ± 14 | 0.66 |
| Fructose (g/day) | 18 ± 10 | 23 ± 10 | 0.26 |
| Dietary fiber (g/day) | 26 ± 15 | 32.5 ± 11 | 0.28 |
| Saturated fat (g/day) | 20 ± 5 | 25 ± 9 | 0.09 |
| Palmitic acid (g/day) | 10.5 ± 2.8 | 13.7 ± 4.9 | **0.04** |
| Stearic acid (g/day) | 4.1 ± 1.1 | 5.5 ± 2.1 | **0.029** |
| Arachidonic acid (g/day) | 0.14 ± 0.1 | 0.30 ± 0.1 | **0.002** |
| Animal protein (g/day) | 49 ± 17 | 76 ± 27 | **0.005** |
| Red meat calories (kcal/day) | 40 ± 50 | 93 ± 59 | **0.02** |
| Calcium (mg/day) | 847 ± 352 | 962 ± 368 | 0.41 |
| Iron (mg/day) | 10.2 ± 4.2 | 15.0 ± 5.1 | **0.01** |
| Sodium (mg/day) | 3050 ± 1090 | 4084 ± 1056 | **0.02** |
| Ultra-processed food calories (kcal/day) | 364 ± 210 | 467 ± 247 | 0.26 |
| Ultra-processed grains calories (kcal/day) | 67 ± 37 | 116 ± 78 | **0.049** |
| Mediterranean diet score (units) | 29 ± 6 | 27 ± 5 | 0.22 |

Values are means ± SD. Bold text indicates significant findings $p < 0.05$ ($t$-tests for continuous variables; Chi-square for categorical variables).

TABLE 4 Odds ratios for unhealthy metabolic obesity according to hepatic fat content percentage, with adjustments for covariates.

| Models | OR (95% CI) | $p$-value |
|---|---|---|
| Unadjusted | 1.21 (1.02–1.41) | **0.02** |
| Adjusted for BMI, age, and sex | 1.19 (1.00–1.41) | **0.04** |
| Adjusted for BMI, age, sex, and total calories | 1.20 (0.99–1.46) | 0.06 |

Multivariable logistic regression analysis assessed the association between hepatic fat content and metabolic health. OR, odds ratio; CI, confidence interval; BMI, body mass index. Bold text indicates significant findings $p < 0.05$.

context of obesity, surpassing the influence of visceral fat, which did not significantly differ between the two groups of adolescents. These findings are consistent with previous trials in adults which demonstrated that hepatic and not visceral fat is strongly linked to obesity-related metabolic complications (38, 41). Our regression models reinforce the independent significance of HFC, even after adjusting for various covariates, our results consistently demonstrated a substantial association between elevated HFC and metabolically unhealthy obesity, these findings emphasize the potential clinical significance of assessing liver fat as an independent biomarker for early identification and intervention in obese adolescents at risk of metabolic disease. It is worth noting that the consensus-based MHO definition currently does not incorporate hepatic steatosis. Given our findings and those of previous studies (38, 42, 43), there is a growing rationale for considering the inclusion of hepatic steatosis in the definition of MHO. However, since liver fat content is not currently part of standard MHO criteria, further studies are needed to validate its predictive value and determine optimal threshold levels for clinical classification.

The precise underlying mechanisms that link metabolic health and hepatic steatosis remain incompletely clarified, but the liver is recognized as playing a pivotal role in governing both carbohydrate and lipid metabolism through an intricate network of metabolic pathways. Primarily, ectopic accumulation of lipids in the liver is closely associated with metabolic dysfunction, leading to MASLD, which exerts a profound impact on the metabolic profile (44, 45). MASLD involves the accumulation of ceramides and diacylglycerols due to excessive free fatty acid accumulation, triggering insulin resistance through insulin receptor dysfunction and downstream signaling pathways (46). The capability of insulin to inhibit hepatic glucose production is compromised in the presence of MASLD-associated insulin resistance, leading to worsening glycemic control. Simultaneously, the suppression of adipose tissue lipolysis is inhibited, perpetuating a vicious cycle of insulin resistance and heightening the risk of cardiovascular complications (47, 48). In line with this perspective, another mechanistic explanation contributing to the metabolically unfavorable profile in MASLD involves the secretion of inflammatory cells and cytokines, known as hepatokines (45). Among these hepatokines are fetuin A, follistatin, HFREP1, LECT2, PEDF, and ectodysplasin, collectively exacerbating insulin resistance in skeletal muscle and adipose tissue through the activation of the c-Jun N-terminal kinase signaling pathway. This pathway is characterized by direct inhibitory phosphorylation of insulin receptor substrates, resulting in diminished insulin signaling and exacerbation of hyperglycemia (45).

Our dietary analysis revealed significant differences in nutrient intake between the two study groups. Adolescents with MUO had a significantly higher total calorie intake, suggesting overconsumption as a contributing factor to metabolic syndrome among them. Furthermore, their dietary patterns were characterized by elevated protein intake, particularly from animal sources, alongside increased consumption of red meat. The detrimental association of high meat consumption on health is well-documented in adults, contributing to metabolic alterations such as insulin resistance and associated diseases such as T2DM (49, 50), MS (51), cardiovascular disease (52, 53), and colorectal cancer (54, 55). A recent study revealed an association between the intake of total, red, and/or processed meat and the incidence and persistence of MASLD, along with clinically significant fibrosis in adult populations (56). This heightened risk may be attributed to several factors, including the impairment in insulin signaling induced by palmitic acid (16:0), which is the most abundant SFA found in animal-derived foods (57–60). Additionally, the consumption of SFAs has been linked to elevated circulating levels of total lipoprotein and LDL-c (61, 62). While our analysis did not find a significant difference in total SFA intake between groups ($p = 0.09$), there was a significant increase in the consumption of major long-chain SFAs, specifically, palmitic and stearic acid (18:0), in the MUO group. These long-chain SFAs were observed as being particularly detrimental to metabolic health compared to short-medium SFAs in a recent systematic review (63). Moreover, the detrimental effect of red meat products can be related to specific cooking methods, such as advanced

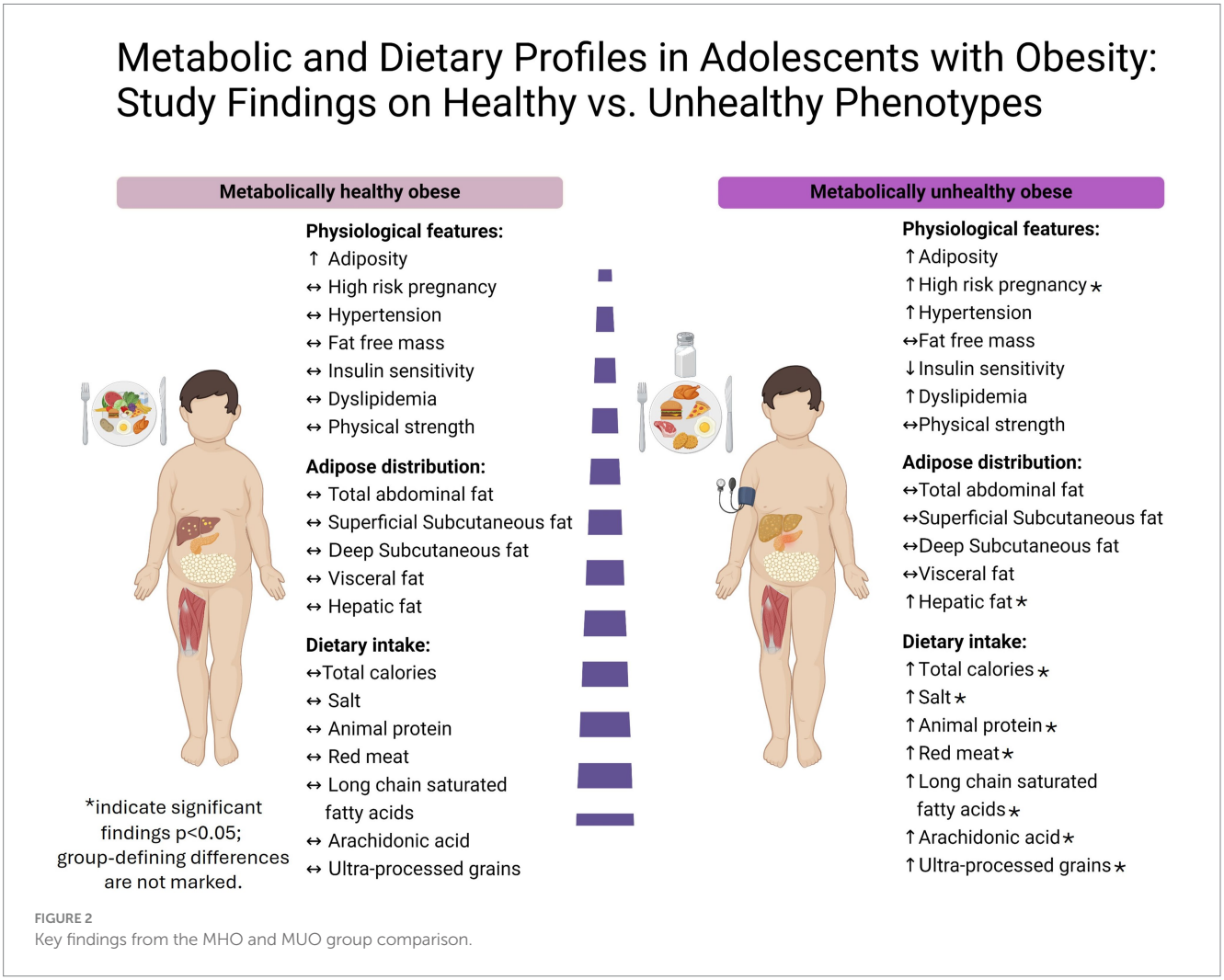


FIGURE 2
Key findings from the MHO and MUO group comparison.

glycation end products, heterocyclic amines, heme iron and other byproducts of muscle protein oxidation, adds to these risks (53, 64–66).

Interestingly, we observed significantly higher consumption of arachidonic acid among adolescents with MUO, which positively correlated with their intake of animal protein and red meat (67). A major role of arachidonic acid is that of a substrate for the synthesis of eicosanoids, which include prostaglandins, thromboxanes, and leukotrienes. These are formed by the metabolism of arachidonic acid by cyclooxygenase, lipoxygenase, and cytochrome P450 pathways (68–70). The resulting metabolites have many roles in inflammation, regulation of the immune response, blood clotting, and smooth muscle contraction (68–70). While the functions of arachidonic acid-derived metabolites are well-established in human health outcomes, recent reviews on the impact of arachidonic acid consumption in adults indicated no adverse effects from their increased intake (71). Also, while there was no significant difference in overall ultra-processed food intake between our two study groups, the MUO group showed a notable increase in the consumption of ultra-processed grains, including white bread and rolls, pastries, sugary breakfast cereals, and more. This observation underscores the negative impact of ultra-processed grains, emphasizing their negative contribution to health outcomes. This effect is evident both independently and when combined with a Western diet that is characterized by high consumption of red and processed meats, sugary snacks and drinks, refined grains, convenience foods, and low intake of fruits, vegetables, and whole grains (72, 73). Sodium intake was significantly higher among our adolescents with MUO compared to those with MHO, and nearly double the recommended daily upper limit of 2,300 milligrams per day (74). Sodium is widely recognized for its substantial role in blood pressure and metabolic health dysregulation, even among adolescent populations (75, 76).

Lastly, our evaluation of physical activity and performance revealed unexpectedly insignificant differences between the MUO and MHO groups. Contrary to prevailing beliefs (77, 78), both groups displayed similar levels of physical activity and sedentary behavior with high levels of sedentary behavior and no regular physical exercise. All participants spent an average of approximately 60% of their day in sedentary pursuits, far exceeding the recognized cutoff that leads to increased cardiovascular disease risk in adults (79). These results highlight the need for further investigation, with larger number of participants, in order to assess the relationship between obesity phenotype and physical activity levels. The inclusion of hand grip strength and isometric mid-thigh pull max test in our study can help to establish a normative range for adolescents with obesity and furnish informative benchmarks for future research and clinical evaluations.

One strength of our study is our employment of advanced imaging techniques, including MRI and MRS, which are considered gold standards and references for assessing body fat distribution

and HFC, respectively. This approach allowed precise and reliable measurements, thereby enhancing the validity of our results. Moreover, the study population of adolescents with obesity provides a unique perspective in understanding the early markers of unhealthy metabolic obesity and valuable insights for developing interventions to prevent metabolic abnormalities during development. Another strength lies in our examination of a wide range of variables, from prenatal factors, such as birth weight and pregnancy conditions, to current markers, such as blood parameters, physiological measures, and dietary patterns assessed by the FFQ.

Several limitations include the cross-sectional design and relatively small sample size. While efforts were made to adjust for confounding factors, it is possible that our model did not fully account for all contributors to metabolic obesity as demonstrated in this study. Therefore, caution is warranted when interpreting the independent influence of HFC, since unmeasured covariates (such as genetic factors and environmental influences) may have influenced the observed associations. Additionally, there may be information bias in dietary self-reporting due to recall bias. We attempted to bridge this gap by using FFQ, which is a reliable and widely accepted tool for assessing dietary patterns in children.

In conclusion, our findings demonstrate a significant association between hepatic fat content (HFC) and metabolic health status in adolescents with obesity, along with distinct differences in dietary patterns and maternal risk factors between metabolically unhealthy and healthy obese subgroups. Although causality cannot be inferred due to the cross-sectional design of the study, the observed associations suggest that HFC may serve as a meaningful marker of metabolic risk in this population.

While no universally accepted HFC threshold currently exists for guiding pediatric intervention, our results support the clinical utility of the >5.5% cutoff—commonly used to define hepatic steatosis—as a pragmatic reference point. We propose that pediatricians consider this threshold as an indicator for initiating early, individualized lifestyle interventions, including dietary counseling, reduction of salt and red or processed meat intake, and increased physical activity. These recommendations may help translate imaging-based hepatic assessments into preventive strategies for at-risk adolescents.

Longitudinal studies in larger, more diverse populations, using more objective dietary methods such food diaries, are essential to validate these findings and to establish evidence-based guidelines for clinical practice.

## Conclusion

- Distinct subgroup of youth with obesity maintains a metabolically healthy profile, though the factors contributing to this status remain incompletely understood.
- Hepatic fat content, but not adipose fat distribution emerged as health marker distinguishing between metabolically healthy and unhealthy obese adolescents.
- Diet that contains ultra processed grains, animal protein and sodium may exert a notable influence on metabolic health during early stages of life.

## Data availability statement

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

## Ethics statement

The studies involving humans were approved by the Institutional Review Board of Tel Aviv Medical Center (TLV-0799-20). 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

HM-L: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. RS: Methodology, Project administration, Software, Writing – original draft. RLa: Data curation, Methodology, Writing – review & editing. RO: Data curation, Methodology, Software, Writing – review & editing. RD: Methodology, Project administration, Validation, Writing – review & editing. AB: Conceptualization, Methodology, Validation, Writing – review & editing. SS: Resources, Writing – review & editing, Validation. SC: Resources, Validation, Visualization, Writing – review & editing. RLu: Investigation, Resources, Writing – review & editing, Visualization. YG: Funding acquisition, Project administration, Resources, Software, 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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# Triponderal mass index can be used as a potential tool to predict the risk of hyperuricemia in children and adolescents with obesity: a population-based study

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**Purpose:** Hyperuricemia (HUA), a common complication in children and adolescents with obesity, has not received sufficient attention. Therefore, the purpose of this study was to compare the predictive ability of different HUA obesity indicators.

**Methods:** The records of 349 children and adolescents with obesity aged 6–17 years (233 boys and 116 girls) who visited the Nutrition Clinic of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine between January 2012 and December 2023 were included in this retrospective study. The relationship between different obesity indices and HUA was analyzed by univariate and multivariate analysis. The predictive value of triponderal mass index (TMI) and waist-to-height ratio (WHtR) for HUA was evaluated by the receiver operating characteristic (ROC) curve, and the optimal cutoff point was calculated.

**Results:** In this study, the prevalence of HUA in the general population was 42.40% (41.20% in boys and 44.82% in girls). Multiple regression analysis revealed that after controlling for age and sex, body mass index (BMI), TMI, waist circumference (WC), hip circumference (HC), WHtR, fat mass (FM), and skeletal muscle mass (SMM) were independent risk factors for HUA ($p < 0.05$). After controlling for age and stratification by gender, BMI, WC, HC, and SMM of boys and girls with obesity were positively correlated with the risk of HUA ($p < 0.05$). However, TMI, WHtR, body fat percentage, and FM were only positively associated with the risk of HUA in obese girls ($p < 0.05$). Moreover, TMI and WHtR were 18.2 kg/m$^3$ and 0.56, respectively, in the ROC curve analysis.

**Conclusion:** The prevalence of HUA was high in children and adolescents with obesity aged 6–17 years. In addition, our results underscored that the combination of TMI and WHtR can be used as a potential early predictor of HUA risk in children and adolescents with obesity, especially in girls.

KEYWORDS

**hyperuricemia, triponderal mass index, waist-to-height ratio, children and adolescents, obesity**

# Introduction

Hyperuricemia (HUA) is an important risk factor for diseases such as metabolic syndrome, cardiovascular disease, hypertension, type 2 diabetes mellitus, and gout (1–4). Unfortunately, HUA has become a common chronic disease among adults. However, its occurrence in children and adolescents has not received sufficient attention from clinicians and parents. It should be noted that with the increasing consumption of purine-rich meats, high fructose beverages, and the rapid rise in obesity rates, HUA has become a disease of high incidence in children and adolescents (5–8). In a study of 54,580 children and adolescents aged 3 to 19, the overall estimated prevalence of HUA was 23.3%, with a prevalence rate of 26.6% among boys, which was higher than 19.8% among girls (9). In addition, the prevalence of HUA was significantly higher in children with overweight (37.6%), obesity (50.6%), and extremely obesity (64.5%) than in normal weight children (9).

Although it has been shown that obesity increases the risk of HUA, current studies focused on which obesity indicators can effectively and rapidly predict HUA during early screening have been inconsistent. An increasing number of studies have found that traditional obesity indicators such as body mass index (BMI), waist circumference (WC), hip circumference (HC), and waist-to-height ratio (WHtR) are significantly positively correlated with HUA (10, 11). In addition, it has been shown that an increase in serum uric acid (SUA) levels leads to gradual and significant increases in BMI, WC, WHtR, percentage body fat (PBF), and muscle mass (10).

Because HUA is a common disease with obvious sex differences, we previously conducted a comparison of various obesity indicators and HUA in children and adolescents of different sex. These previous results showed that after adjusting for age, BMI, WC, HC, skeletal muscle mass(SMM), and PBF were positively associated with the risk of HUA in boys and girls with obesity (12). Although BMI, SMM, and PBF are the most influential indicators of HUA, they have shortcomings such as complex calculations and the need for specific detection equipment, which preclude them from being directly applied to early risk screening for HUA.

Recently, triponderal mass index (TMI) has attracted interest as a new tool for obesity screening in children and adolescents (13, 14). For children and adolescents aged 8–17, the TMI threshold for diagnosing overweight status is 16.0 kg/m$^3$ for boys and 16.8 kg/m$^3$ for girls, and the TMI threshold for diagnosing obesity status is 18.8 kg/m$^3$ for boys and 19.7 kg/m$^3$ for girls (13). Among children and adolescents, BMI has different diagnostic thresholds for overweight and obesity at different age groups. Its advantages include low volatility and convenient detection in different age groups. It can be seen that the advantages of TMI are not only that it changes relatively stably across different age groups, but also that it is more convenient to determine overweight or obesity. Moreover, the correlation between TMI and PBF and fat mass (FM) is much higher than BMI (13, 14).

However, currently, no studies have analyzed the relationship between TMI and HUA in children and adolescents of different sex. In the face of the increasing incidence of HUA in children and adolescents, we explored the predictive role of obesity indicators in boys and girls to provide a more concise, rapid, and reproducible method for the early detection of HUA in children and adolescents.

# Materials and methods

## Study subjects and groups

The data were collected from obese children and adolescents who visited the Nutrition Clinic of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine between January 2012 and December 2023. This study was approved by the Ethics Committee of the Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University (XHEC-C-2024-098-1).

The inclusion criteria for this study were (1) children and adolescents with a BMI at or above the 95th percentile (P95) for children of the same age and sex (based on WHO standards); (2) children and adolescents 6–17 years of age; (3) children and adolescents with complete data. Subjects were excluded from the study if they met one of the following criteria: (1) obesity due to endocrine or inherited metabolic diseases; (2) patients with malignant tumors and severe liver and kidney dysfunction; (3) patients taking drugs that affect uric acid levels; and (4) patients taking psychotropic drugs. The subjects were divided into an HUA group and a non-HUA group based on the SUA level of the population and stratified by male and female sex. In previous studies, HUA in children and adolescents was defined as SUA > 420 μmol/L (7 mg/dL) in boys and SUA > 360 μmol/L (6 mg/dL) in girls (9, 15).

## Anthropometric and clinical measurements

Basic participant information such as age, sex, and physical indicators were measured and recorded by a registered dietitian in the outpatient clinic. Height, WC, and HC were measured according to standard protocols. Participant body weight, PBF, FM, and SMM were measured using whole-body bioelectrical impedance analysis (InBody 720, Biospace Inc., South Korea). BMI, TMI, waist-to-hip ratio (WHR), and WHtR were calculated as follows: BMI (kg/m$^2$) = (weight in kg)/(height in meters)$^2$; TMI (kg/m$^3$) = (weight in kg)/(height in meters)$^3$; WHR = WC (cm)/HC (cm); and WHtR = WC (cm)/height (cm). Venous blood samples were obtained from fasting participants in the morning and sent to the clinical laboratory center for SUA, triglyceride (TG), and total cholesterol (TC) analysis.

## Statistical analysis

Data were analyzed using SPSS V.25.0 statistical software. Kolmogorov–Smirnov test was used to evaluate the normal distribution of parameters. Data for continuous variables are expressed as median (P25, P75), and categorical variables are expressed as frequency and percentage (%). To compare differences in various indicators between HUA and non-HUA based on sex, an independent two-tailed t test was applied for continuous data with a normal distribution, a Wilcoxon signed-rank test was used for continuous variables with a non-normal distribution, and a Chi-squared test was performed for categorical variables. Pearson correlation was used to evaluate the correlation between SUA and various factors. A multiple logistic regression model was used to evaluate the effects of different physical indicators and body composition variables on the risk of HUA. Model 1 used unadjusted regression, and Model 2 used

regression adjusted for age and sex. To explore possible cutoff values for TMI and WHtR, we used receiver operating characteristic (ROC) curves to predict the occurrence of HUA. All *p*-values were calculated using a bilateral test, and the significance level of each test was set at $p < 0.05$.

## Results

A total of 349 subjects with complete data were included in the study (233 boys and 116 girls) with an average age of 10.55 years (8.69, 12.59) (Table 1). The boys were older and had higher WC, HC, WHR, WHtR, BMI, TMI, FM, SMM, and SUA than the girls ($p < 0.05$). The overall estimated prevalence of HUA was 42.4% (148/349), with 41.20% (96/233) in boys and 44.82% (52/116) in girls. WHtR values were ≥ 0.46 in the entire sample.

The age, WC, HC, WHtR, BMI, TMI, FM, SMM, and TG of the HUA group were higher than those of the non-HUA group ($p < 0.05$, Table 2). In boys, age, WC, HC, BMI, TMI, FM, SMM, and TG were higher in the HUA group than in the non-HUA group ($p < 0.05$, Table 2). In girls, age, WC, HC, WHtR, BMI, TMI, PBF, FM, SMM, and TG were higher in the HUA group than in the non-HUA group ($p < 0.05$, Table 2). In the total sample, WHR was not significantly higher in the HUA group than in the non-HUA group ($p > 0.05$, Table 2).

Correlation analysis (Table 3) showed that SUA was significantly positively correlated with age, WC, HC, WHtR, BMI, TMI, FM, SMM, and TG in the whole sample ($p < 0.05$). Further multiple regression analysis (Table 4) revealed that BMI, TMI, WC, HC, WHtR, FM, and SMM were independent risk factors for HUA after controlling for age and sex (Model 2, $p < 0.05$). In the different sex groups, after controlling for age, BMI, WC, HC, and SMM were positively correlated with the risk of HUA in boys with obesity. In addition, BMI, TMI, WC, HC, WHtR, PBF, FM, and SMM were positively associated with the risk of HUA in girls with obesity (Model 2, $p < 0.05$).

To further predict HUA, we performed ROC curve analysis on TMI (systemic obesity index) and WHtR (reflecting abdominal obesity) in the total sample (Figure 1). Results showed that TMI had a cut point value of 18.2 kg/m$^3$ (sensitivity 58.1%; specificity 56.2%) and an area under the curve of 0.579 (95% CI: 0.518–0.639). Additionally, WHtR had a cut point value of 0.56 (sensitivity 83.8%; specificity 35.3%) and an area under the curve of 0.598 (95% CI: 0.538–0.657). Therefore, these values may be used to predict HUA ($p < 0.05$).

## Discussion

In this study, we found that the incidence of HUA in children and adolescents with obesity was as high as 42.4%. By evaluating the possibility of multiple obesity indicators as risk indicators and predictors of HUA in children and adolescents, we found that different obesity indicators had different positive effects on HUA. We also determined that TMI (18.2 kg/m$^3$) and WHtR (0.56) have the potential to predict HUA.

The incidence of HUA in children and adolescents varies by country due to different diagnostic criteria, ethnicities, lifestyles, and obesity incidence. In a Brazilian study of 1,750 overweight and obese

TABLE 1 General characteristics of study participants.

| Characteristics | Total sample | Boys | Girls |
|---|---|---|---|
| *n* | 349 | 233 | 116 |
| Age, y | 10.55 (8.69, 12.59) | 10.97 (9.17, 12.77) | 9.43 (8, 11.88)[b] |
| Height, cm | 149.50 (138.50, 162.05) | 154.40 (141.35, 165.65) | 143.05 (134.17, 157.02)[b] |
| Weight, kg | 60.50 (47.70, 79.65) | 64.80 (50.40, 85.05) | 52.30 (42.88, 69.55)[b] |
| WC, cm | 89 (80.25, 98.05) | 92 (84, 103.85) | 84 (75.90, 90.37)[b] |
| HC, cm | 95 (87.50, 106) | 97.80 (88.95, 108) | 90.50 (83, 99.75)[b] |
| WHR | 0.93 (0.89, 0.97) | 0.95 (0.91,0.98) | 0.90 (0.86, 0.95)[b] |
| WHtR | 0.59 (0.56, 0.63) | 0.60 (0.57, 0.63) | 0.57 (0.54, 0.60)[b] |
| WHtR≥0.46, *n* (%) | 349 (100) | 233 (100) | 116 (100) |
| BMI, kg/㎡ | 27.01 (24.35, 30.22) | 27.83 (25.14, 31.60) | 25.32 (23.15, 28.07)[b] |
| TMI, kg/m$^3$ | 18.18 (16.79, 19.41) | 18.40 (16.97, 19.83) | 17.70 (16.48, 18.99)[b] |
| PBF, % | 39.25 (36.10, 42.50) | 39 (35.95, 42.50) | 39.78 (36.20, 43.09) |
| FM, kg | 23.40 (18.30, 32.15) | 25.30 (19.35, 33) | 21.15 (15.77, 27.47)[b] |
| SMM, kg | 19.10 (15.05, 25.65) | 21.10 (15.90, 28.93) | 16.24 (13.71, 21.67)[b] |
| SUA, umol/L | 372 (311, 457) | 386 (318.5, 483) | 355 (307.25, 409.50)[b] |
| HUA, *n* (%) | 148 (42.40) | 96 (41.20) | 52 (44.82) |
| TC, mmol/L | 4.30 (3.86, 4.77) | 4.23 (3.81, 4.70) | 4.39 (3.96, 4.84) |
| TG, mmol/L | 1.15 (0.79, 1.56) | 1.18 (0.80, 1.60) | 1.13 (0.76, 1.48) |

WC, Waist circumference; HC, Hip circumference; WHR, Waist-to-hip ratio; WHtR, Waist-to-height ratio; BMI, Body mass index; TMI, Triponderal mass index; PBF, Percentage of body fat; FM, Fat mass; SMM, Skeletal muscle mass; SUA, Serum uric acid; HUA, Hyperuricemia; TC, Total cholesterol; TG, Triglyceride.
[b]Significance between boys and girls ($p < 0.01$).

TABLE 2 Comparison of the clinical characteristics between HUA and non-HUA groups.

| Characteristics | Total sample | | Boys | | Girls | |
|---|---|---|---|---|---|---|
| | Non-HUA | HUA | Non-HUA | HUA | Non-HUA | HUA |
| *n* | 201 | 148 | 137 | 96 | 64 | 52 |
| Age, y | 9.81 (8.06, 11.36) | 11.94 (9.53, 14.09)[b] | 10.09 (8.51, 11.45) | 12.73 (10.80, 14.79)[b] | 9 (7.87, 10.58) | 9.73 (8.40, 12.64)[a] |
| Height, cm | 144 (135.50, 156.35) | 159.05 (145.40, 169.07)[b] | 146.30 (136.90, 157.75) | 166.05 (153.55, 174.15)[b] | 139.50 (133.02, 148.10) | 146.30 (140.95, 158.30)[b] |
| Weight, kg | 52.90 (44.45, 66.45) | 72.11 (52.12, 92.90)[b] | 56.40 (46.90, 70.70) | 83.20 (64.85, 102.42)[b] | 48.56 (39.37, 54.49) | 58.50 (50.37, 73.90)[b] |
| WC, cm | 85.50 (77.50, 93) | 94 (88, 106)[b] | 88 (80, 96.75) | 100.50 (91.50, 108.72)[b] | 78.25 (73, 86) | 88.50 (81.12, 93.37)[b] |
| HC, cm | 99.25 (91, 108) | 112.15 (101.25, 120.10)[b] | 92 (86.25, 100) | 105.75 (97.85, 115)[b] | 85.70 (81.40, 93.87) | 95.10 (89.62, 104.87)[b] |
| WHR | 0.93 (0.89, 0.97) | 0.93 (0.89, 0.97) | 0.95 (0.91, 0.97) | 0.94 (0.91, 0.98) | 0.90 (0.86, 0.94) | 0.91 (0.87, 0.96) |
| WHtR | 0.58 (0.55, 0.62) | 0.60 (0.57, 0.63)[b] | 0.60 (0.56, 0.63) | 0.61 (0.58, 0.64) | 0.55 (0.53, 0.58) | 0.58 (0.56, 0.62)[b] |
| WHtR≥0.46, *n* (%) | 201 (100) | 148 (100) | 137 (100) | 96 (100) | 64 (100) | 52 (100) |
| BMI, kg/㎡ | 25.80 (23.55, 28.86) | 28.48 (26.44, 32.79)[b] | 26.56 (24.14, 29.57) | 30.03 (27.24, 34.36)[b] | 24.58 (21.83, 26.41) | 27.07 (24.11, 30.04)[b] |
| TMI, kg/m$^3$ | 17.96 (16.63, 19.25) | 18.41 (17.21, 19.95)[a] | 18.35 (16.89, 19.46) | 18.51 (17.24, 20.43)[a] | 17.07 (16.19, 18.64) | 18.37 (16.98, 19.07)[b] |
| PBF, % | 39.25 (36.25, 42.10) | 39.25 (35.72, 43.17) | 39.30 (36.75, 42.75) | 38.35 (35.42, 41.50) | 38.97 (35.72, 40.85) | 40.70 (37.30, 44.02)[b] |
| FM, kg | 20.86 (17, 27.65) | 27.60 (22.20, 35.97)[b] | 21.90 (17.50, 28.85) | 29.75 (23.32,38.37)[b] | 19.05 (14.08, 22.67) | 24.44 (20.19, 33.12)[b] |
| SMM, kg | 16.80 (14.15, 22) | 23.70 (16.95, 23.70)[b] | 17.60 (14.95, 23) | 29.30 (20.77, 36.15)[b] | 15.07 (12.52, 18.36) | 18.30 (14.95, 23.50)[b] |
| SUA, umol/L | 323 (286, 356) | 473.50 (430.50, 518.75)[b] | 327 (284, 371) | 499.50 (454, 540.25)[b] | 313.50 (293, 335.75) | 417 (385.25, 463.75)[b] |
| TC, mmol/L | 4.26 (3.87, 4.67) | 4.33 (3.81, 5.02) | 4.23 (3.86, 4.66) | 4.24 (3.69, 4.90) | 4.36 (3.92, 4.77) | 4.41 (4.11, 5.18) |
| TG, mmol/L | 1.08 (0.74, 1.46) | 1.31 (0.87, 1.78)[b] | 1.10 (0.75, 1.51) | 1.33 (0.95, 1.87)[b] | 1.05 (0.73, 1.38) | 1.24 (0.78, 1.76) |

HUA Hyperuricemia, WC Waist circumference, HC Hip circumference, WHR Waist-to-hip ratio, WHtR Waist-to-height ratio, BMI Body mass index, TMI Triponderal mass index, PBF Percentage of body fat, FM Fat mass, SMM Skeletal muscle mass, SUA Serum uric acid, TC Total cholesterol, TG Triglyceride.
[a]Significance between HUA and Non-HUA groups in all subjects ($p < 0.05$).
[b]Significance between HUA and Non-HUA groups in all subjects ($p < 0.01$).

TABLE 3 Correlation analysis between clinical characteristics and SUA.

| Characteristics | Total sample | | Boys | | Girls | |
|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* |
| Age | 0.484 | < 0.001 | 0.543 | < 0.001 | 0.263 | 0.004 |
| Height | 0.537 | < 0.001 | 0.579 | < 0.001 | 0.297 | 0.001 |
| Weight | 0.578 | < 0.001 | 0.604 | < 0.001 | 0.389 | < 0.001 |
| WC | 0.544 | < 0.001 | 0.556 | < 0.001 | 0.43 | < 0.001 |
| HC | 0.534 | < 0.001 | 0.570 | < 0.001 | 0.362 | < 0.001 |
| WHR | 0.093 | 0.082 | 0.025 | 0.703 | 0.121 | 0.194 |
| WHtR | 0.278 | < 0.001 | 0.207 | 0.001 | 0.357 | < 0.001 |
| BMI | 0.507 | < 0.001 | 0.508 | < 0.001 | 0.426 | < 0.001 |
| TMI | 0.257 | < 0.001 | 0.199 | 0.002 | 0.356 | < 0.001 |
| PBF | −0.010 | 0.856 | −0.107 | 0.102 | 0.332 | < 0.001 |
| FM | 0.488 | < 0.001 | 0.494 | < 0.001 | 0.402 | < 0.001 |
| SMM | 0.584 | < 0.001 | 0.614 | < 0.001 | 0.340 | < 0.001 |
| TC | 0.072 | 0.181 | 0.069 | 0.291 | 0.142 | 0.128 |
| TG | 0.143 | 0.008 | 0.116 | 0.078 | 0.192 | 0.039 |

SUA, Serum uric acid; WC, Waist circumference; HC, Hip circumference; WHR, Waist-to-hip ratio; WHtR, Waist-to-height ratio; BMI, Body mass index; TMI, Triponderal mass index; PBF, Percentage of body fat; FM, Fat mass; SMM, Skeletal muscle mass; TC, Total cholesterol; TG, Triglyceride.

participants aged 6–17, the overall prevalence of HUA was 10.3%, and the prevalence of HUA in subjects with overweight and obesity was 51.3% (10). This is higher than the 42.4% prevalence of HUA in children and adolescents with obesity in the current study. The difference is mainly because the reference standard for HUA in the above-referenced study was lower (5.5 mg/dL) than the standards used in our study (7 mg/dL in boys and 6 mg/dL in girls) (9, 15). As the prevalence of HUA is high in children and adolescents with overweight and obesity, it is necessary to determine appropriate obesity indicators for the early prediction of HUA.

In children and adolescents, BMI and BMI-Z scores are the most commonly used indicators of obesity. In a study of 1,329 participants (16), BMI and BMI-Z scores in both boys and girls with HUA were higher than those in the non-HUA group, which is consistent with our findings. Moreover, further multiple regression analysis found that BMI and BMI-Z score were independent risk factors for HUA (16, 17). Our study further explored the influence of BMI, HC, and WC on HUA by comparing BMI with HC and WC. Results showed that the BMI odds ratio (OR) value (1.138) was higher than those of HC (1.062) and WC (1.060), and this was consistent in boys and girls.

Although BMI and BMI-Z are widely used as diagnostic indicators of obesity in children and adolescents, they cannot be quickly calculated and evaluated due to the different criteria for different ages and sex. This further limits the use of BMI and BMI-Z as routine screening indicators. Many recent studies have shown that TMI is relatively stable in different age groups, significantly positively correlated with PBF, and more accurately assesses PBF. These are advantages that BMI does not have (13, 14). Therefore, we included TMI in this study of HUA in children and adolescents. Our results suggest that TMI is an independent risk factor for HUA and that TMI OR values are higher than those of WC and HC. Because TMI is a

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TABLE 4 Multifactorial logistic regression analysis of the risk of HUA.

| Characteristics | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| **Total sample** | | | | |
| BMI | 1.203 (1.136, 1.273) | < 0.001 | 1.138 (1.057, 1.225) | 0.001 |
| TMI | 1.172 (1.061, 1.294) | 0.002 | 1.130 (1.010, 1.264) | 0.033 |
| WC | 1.070 (1.049, 1.091) | < 0.001 | 1.060 (1.030, 1.091) | < 0.001 |
| HC | 1.077 (1.055, 1.100) | < 0.001 | 1.062 (1.027, 1.098) | < 0.001 |
| Each increase 0.1 in WHtR | 1.189 (1.224, 2.854) | 0.004 | 1.837 (1.128, 2.991) | 0.015 |
| PBF | 0.997 (0.958, 1.038) | 0.878 | 1.006 (0.963, 1.051) | 0.784 |
| FM | 1.087 (1.059, 1.116) | < 0.001 | 1.049 (1.014, 1.086) | 0.006 |
| SMM | 1.137 (1.099, 1.177) | < 0.001 | 1.175 (1.100, 1.254) | < 0.001 |
| **Boys** | | | | |
| BMI | 1.247 (1.157, 1.344) | < 0.001 | 1.105 (1.010, 1.209) | 0.029 |
| TMI | 1.135 (1.006, 1.281) | 0.039 | 1.072 (0.930, 1.235) | 0.338 |
| WC | 1.088 (1.060, 1.117) | < 0.001 | 1.038 (1.002, 1.075) | 0.039 |
| HC | 1.103 (1.071, 1.135) | < 0.001 | 1.059 (1.017, 1.103) | 0.006 |
| Each increase 0.1 in WHtR | 1.566 (0.920, 2.666) | 0.099 | 1.147 (0.629, 2.092) | 0.654 |
| PBF | 0.948 (0.902, 0.996) | 0.035 | 0.979 (0.925, 1.037) | 0.469 |
| FM | 1.110 (1.064, 1.137) | < 0.001 | 1.036 (0.995, 1.080) | 0.089 |
| SMM | 1.176 (1.125, 1.230) | < 0.001 | 1.161 (1.077, 1.252) | < 0.001 |
| **Girls** | | | | |
| BMI | 1.206 (1.082, 1.345) | 0.001 | 1.204 (1.050, 1.380) | 0.008 |
| TMI | 1.305 (1.077, 1.581) | 0.007 | 1.264 (1.037, 1.542) | 0.021 |
| WC | 1.088 (1.041, 1.138) | < 0.001 | 1.092 (1.034, 1.152) | 0.001 |
| HC | 1.058 (1.022, 1.095) | 0.001 | 1.071 (1.011, 1.136) | 0.021 |
| PBF | 1.118 (1.032, 1.212) | 0.006 | 1.102 (1.014, 1.197) | 0.022 |
| Each increase 0.1 in WHtR | 4.141 (1.705, 10.053) | 0.002 | 4.455 (1.732, 11.461) | 0.002 |
| FM | 1.083 (1.032, 1.137) | 0.001 | 1.088 (1.016, 1.164) | 0.015 |
| SMM | 1.122 (1.041, 1.210) | 0.003 | 1.166 (1.001, 1.359) | 0.048 |

HUA, Hyperuricemia; BMI, Body mass index; TMI, Triponderal mass index; WC, Waist circumference; HC, Hip circumference; WHtR, Waist-to-height ratio; PBF, Percentage of body fat; FM, Fat mass; SMM, Skeletal muscle mass; OR, odds ratios.
Model 1: Crude model.
Model 2: Total sample: adjusted for age and sex; boys and girls: adjusted for age.

simple and relatively stable indicator across age groups, we further used ROC curve analysis to determine the optimal TMI cutoff value based on the ability to determine the presence of HUA. Our ROC curve analysis results suggest that a TMI value of 18.2 kg/m$^3$ can be used to predict the occurrence of HUA to a certain extent. In other words, when the TMI value exceeds 18.2 kg/m$^3$, it should draw the attention of parents. They can consider taking the child to the hospital for a check-up and having the SUA index tested.

BMI and TMI are indicators used to assess obesity, where WC and WHtR have been proposed as simple and effective measures of central obesity (18–20). This study found that HUA was closely and positively correlated with WC and WHtR. In addition, WC was found to be an independent risk factor for HUA, which is consistent with the results of Susann et al. (21) and our previous study (12). Further ROC curve analysis showed that WHtR effectively predicted the occurrence of HUA when the cutoff value of 0.56 was reached. Regarding body composition indicators, the results showed that FM was an independent risk factor for HUA, further explaining why WHtR may play a predictive role; this was more obvious in girls. Moreover, this study found that TG was higher in the HUA group than in the non-HUA group, which may be related to higher FM in the HUA group. However, the mechanism involving the interaction between SUA metabolism, lipid metabolism, and adipogenesis remains unclear and requires further study (22).

Importantly, previous studies have shown that TMI is positively associated with an increase in WHtR in individuals aged 7–20 (23, 24). In addition, TMI has been shown to accurately identify central obesity in children and adolescents, exceeding the accuracy of BMI when WHtR is used as a central obesity reference indicator (25). Therefore, in the prediction of HUA in children and adolescents with obesity, TMI can be used as an indicator of systemic obesity for predicting the risk of HUA. This finding suggests that WHtR, as an indicator of

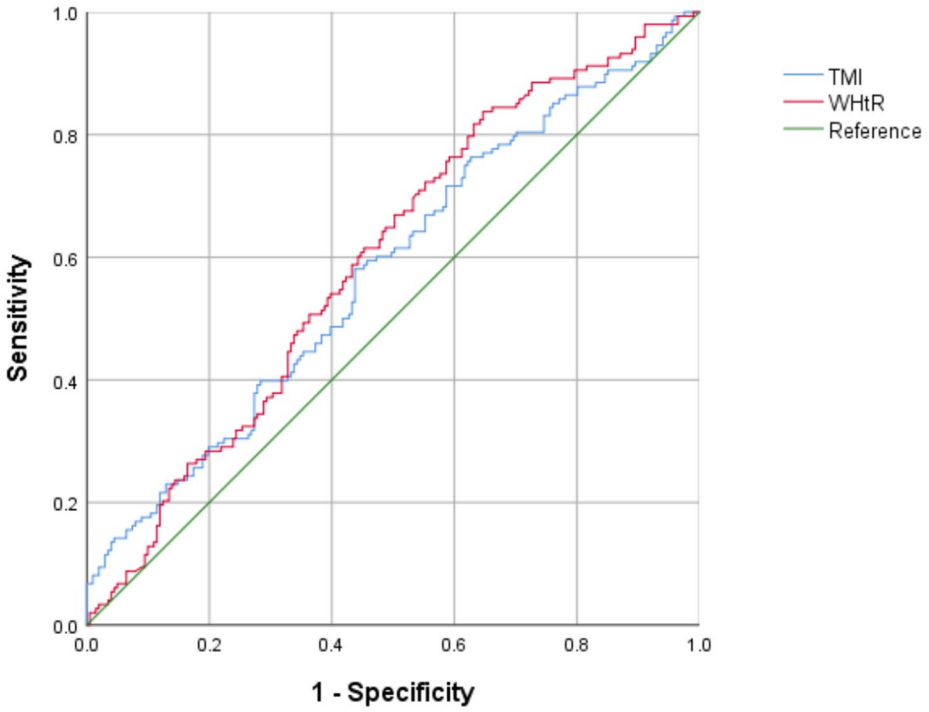


FIGURE 1
Receiver operating characteristic (ROC) curve of TMI and WHtR for identifying HUA in children and adolescents with obesity.

abdominal obesity, can be combined with TMI to predict the risk of HUA.

The occurrence of HUA is not only related to obesity and FM but also to muscle mass. As muscle is a source of purines (26, 27), which plays an important role in promoting the occurrence of HUA. This explains our identification of SMM as an independent risk factor for HUA, both in the general population and in boys and girls. In addition, larger HC generally reflects higher muscle mass (28, 29), which is a potential explanation for the greater effect of HC than WC on HUA. Furthermore, our research shows that the SMM value of boys is higher than that of girls, and the OR value of SMM for boys is higher than that for girls. This result can explain to a certain extent the reason why the OR value of TMI is higher in girls than in boys.

This study has some limitations. First, this was a cross-sectional single-center study, and further multi-center prospective studies are needed to prove the relationship between different obesity indicators and HUA. In addition, indicators such as the dietary habits, physical activities, socioeconomic status and pubertal development of the participants were not included in this study. This may have caused us to overlook some HUA risk factors. Overall, obesity indicators and SUA levels can be considered a profile response to diet, lifestyle and other indicators. Third, unfortunately, blood glucose and insulin were not included in this study. In our future research, we will further conduct studies on the correlation between hyperuricemia and blood glucose and insulin. Fourth, our data were collected at a single center, which are not a representative sample of obese children and adolescents from other regions or ethnicities. In future research, we will conduct multi-center studies and further incorporate indicators such as diet, exercise, economy and genetics (30).

## Conclusion

In conclusion, the prevalence of HUA was higher in children and adolescents with obesity, but there was no difference between the sexes. In this population, BMI, TMI, WC, HC, WHtR, FM, and SMM were identified as the main risk factors for the occurrence of HUA. Furthermore, it is worth noting that considering TMI and WHtR are relatively stable and easy to calculate in all ages, they have the potential to be used as predictive indicators of HUA in children and adolescents with obesity. However, in the future, multi-center prospective studies will still be needed for further research and verification.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to niuyang@xinhuamed.com.cn.

## Ethics statement

The studies involving humans were approved by Ethics Committee of the Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University. 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

YN: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. YZ: Data curation, Methodology, Supervision, Writing – review & editing. JS: Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. YF: Funding acquisition, Methodology, Supervision, Writing – review & editing. QT: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing. XS: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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## Conflict of interest

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

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The authors declare that no Gen AI was used in the creation of this manuscript.

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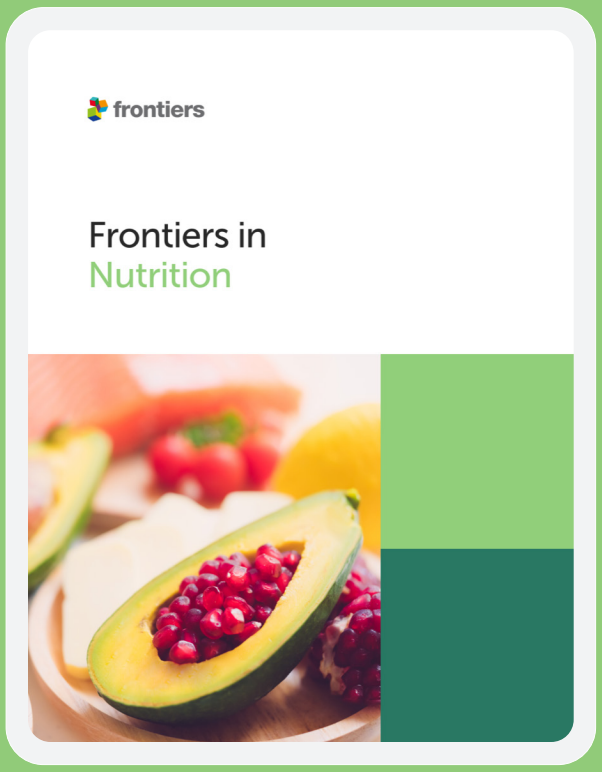


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