Oral Nutrition Supplements Improve Growth and Insulin-like Growth Factor-1 Level in Undernourished Children: A Meta-Analysis

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Abstract

Objectives: Undernutrition in low- and middle-income countries causes nearly half of child mortality under five, with oral nutritional supplementation (ONS) offering a potential strategy to improve growth through enhanced nutritional status. Insulin-like Growth Factor-1 (IGF-1), a critical mediator of growth and a marker of nutritional-hormonal activity, may be upregulated by adequate nutrition, underscoring the need for a meta-analysis to inform clinical guidelines.

Methods: This study followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched PubMed, ScienceDirect, and Scopus for database up to February 2025. R software version 4.4.1 (Pobit PBC, USA) was used for data analysis.

Results: Compared to non-supplementation, ONS in undernourished children significantly improves weight-for-height Z-score (WHZ) (mean difference [MD] 0.17, 95% confidence interval [CI] 0.06 to 0.28; I^2 = 98%; p = 0.003). The effect is more prominent with supplementation plus dietary counseling (MD 0.21, 95% CI 0.06 to 0.35) than with supplementation alone (MD 0.10, 95% CI -0.00 to 0.21), though the subgroup difference is not significant. Supplementation also benefits weight-for-age Z-score (WAZ) (MD 0.15, 95% CI 0.09 to 0.21) and height-for-age Z-score (HAZ) (MD 0.09, 95% CI 0.02 to 0.15). Additionally, it significantly increases weight increment (MD 0.64, 95% CI 0.39 to 0.90) and height increment (MD 0.52, 95% CI 0.33 to 0.71). Four studies reported IGF-1 levels after supplementation. One study showed significant increases at 12 and 18 months ($p < 0.05$) after given ONS.

Conclusions: ONS improves anthropometric outcome in children with undernutrition. Evidence regarding its effect on serum IGF-1 is promising but remains limited because only a small number of heterogenous studies have evaluated this outcome.

Keywords: Child; Undernutrition; Nutritional Support; Growth; Insulin-Like Growth Factor-1

Introduction

The World Health Organization (WHO) identifies child growth as a critical indicator of nutritional status. Although the prevalence of poor growth in children has decreased over the last two decades, the global burden remains substantial.[1] According to the 2025 Joint Child Malnutrition Estimates (JME), approximately 150.2 million children younger than five years were stunted, 42.8 million suffered from wasting, and 35.5 million were overweight globally in 2024.[2] Undernutrition, manifesting as stunting, underweight, or wasting, is strongly linked to increased susceptibility to infections and higher rates of morbidity and mortality.[3] Stunting not only impairs physical growth but also contributes to delayed motor and neurodevelopment, as well as diminished cognitive function.[4] If left unaddressed, the consequences of undernutrition and poor growth can become irreversible.[2]

Undernutrition is a major contributor to growth restriction in children.[5] Growth faltering, particularly stunting, predominantly occurs within the first 1,000 days of life.[3] Inadequate complementary feeding during this critical period has been directly linked to stunting.[6] Significant growth deficits often persist up to five years of age and may extend into adulthood, resulting in shorter stature.[7] While nutritional interventions are most effective in promoting catch-up growth in younger children, evidence indicates that catch-up growth is also possible during later childhood and adolescence when appropriate measures are implemented.[4]

Numerous clinical studies have demonstrated that providing nutritional supplements to undernourished children can enhance nutrient intake, thereby facilitating catch-up growth and improving growth metrics.[8,9]

Nutritional interventions are essential for timely management of growth deficits in children. Early recognition of poor growth allows timely nutritional, intervention based on the WHO Child Growth Standards stratified by age and sex. Key anthropometric indicators include weight-for-age Z-score (WAZ), height-for-age Z-score (HAZ), and weight for-height Z-score (WHZ), typically expressed as Z-scores or percentiles.[10] Undernutrition risk is indicated by Z-score -1 to -2 (mild), -2 to -3 (moderate), and < -3 (severe).[11] Children are classified as underweight, stunted, and wasted when WAZ, HAZ, and WHZ are below -2 SD, respectively.

Addressing poor growth and undernourished children requires effective strategies, as its long-term effects can be severe.[2] The goal is to ensure a balanced diet rich in macronutrients and micronutrients to reduce stunting and underweight risks.[12] Nutritional gaps often result from caregivers' limited knowledge, economic challenges, or cultural factors, compounded by poor sanitation and infections.[13] Dietary supplementation, particularly with micronutrients and proteins from animal-sourced foods, has shown some benefits, though evidence remains limited.[14,15]

Ready-made oral nutritional supplements (ONS) for children, typically providing 1–1.5 kcal/ml in 200 ml bottles, may not meet the needs of those with high energy requirements, poor appetite, or limited feed tolerance. Increasing the energy and nutrient density of ONS can help children with faltering growth, underweight, or volume sensitivity achieve better nutritional intake. When combined with food, these denser formulas have been shown to boost energy intake and appetite without increasing feelings of fullness.[16-18]

Insulin-like Growth Factor-1 (IGF-1) is a hormone that mediates the actions of growth hormone (GH) and plays a crucial role in somatic growth and organ development, particularly during the first two years of life. IGF-1 levels are strongly influenced by weight and dietary intake, especially from amino acid sources like milk and animal proteins. Undernutrition significantly impacts IGF-1 levels, along with thyroid hormones and GH.[7] Due to its sensitivity to both short-term and chronic nutritional changes. IGF-1 is widely used to assess GH–IGF-1 axis disorders in children with short stature. Furthermore, serum IGF-1 is closely associated with nutritional status and has emerged as an important biomarker of nutritional recovery.[19]

Although the effects of ONS on anthropometric growth have been investigated in undernourished children, evidence regarding their influence on serum IGF-1 remains limited. Integrating anthropometric and biochemical outcomes may provide a more comprehensive understanding of the growth response to nutritional intervention. Therefore, this systematic review and meta-analysis was conducted to evaluate the effects of ONS on anthropometric growth outcomes and serum IGF-1 concentrations in undernourished children.

Methods

Conduct of Review

Studies were collected from PubMed, ScienceDirect and Scopus published up to February 2025. The results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.

Search Strategy

Studies were collected from PubMed, ScienceDirect, and Scopus for open articles of randomized controlled trials (RCTs) searching for oral supplementation effect on malnourished children by using the following keywords of (oral nutrition* supplement*) AND (weight OR height OR growth OR IGF-1 OR IGF-1 Level) AND (malnutrition OR malnourish* OR undernutrition OR undernourish*). The bibliographic references of all selected studies and review articles were manually screened for additional eligible studies. The search was completed in 2024 and repeated in February 2025 to ensure that our results were up to date.

Inclusion Criteria

Scientific articles were screened by titles, outlines, and abstracts in regards to the following inclusion criteria: (1) publication in English, (2) RCTs or clinical trials evaluating the effects of oral nutritional supplements (ONS) in children aged up to 9 years; and (3) involving

undernourished children; (4) evaluating ONS; and (5) reporting at least one eligible outcome, including body weight, body length/height, weight-for-age Z-score (WAZ), length-/height-for-age Z-score (LAZ/HAZ), weight-for-length/height Z-score (WLZ/WHZ) and serum insulin-like growth factor-1 (IGF-1). Children were considered undernourished according to the eligibility criteria applied in each original study, which were primarily based on anthropometric indicators (e.g., underweight, stunting, wasting, or growth faltering) assessed using the WHO Child Growth Standards or equivalent growth references. Studies were excluded if they were reviews, meta-analyses, conference abstracts, duplicate publications, unavailable in full text, or did not report extractable data for the predefined outcomes. The results were presented according to the PRISMA 2020 guideline (**Figure 1**). The R software version 4.4.1 (Pobit PBC, USA) was used for data analysis.

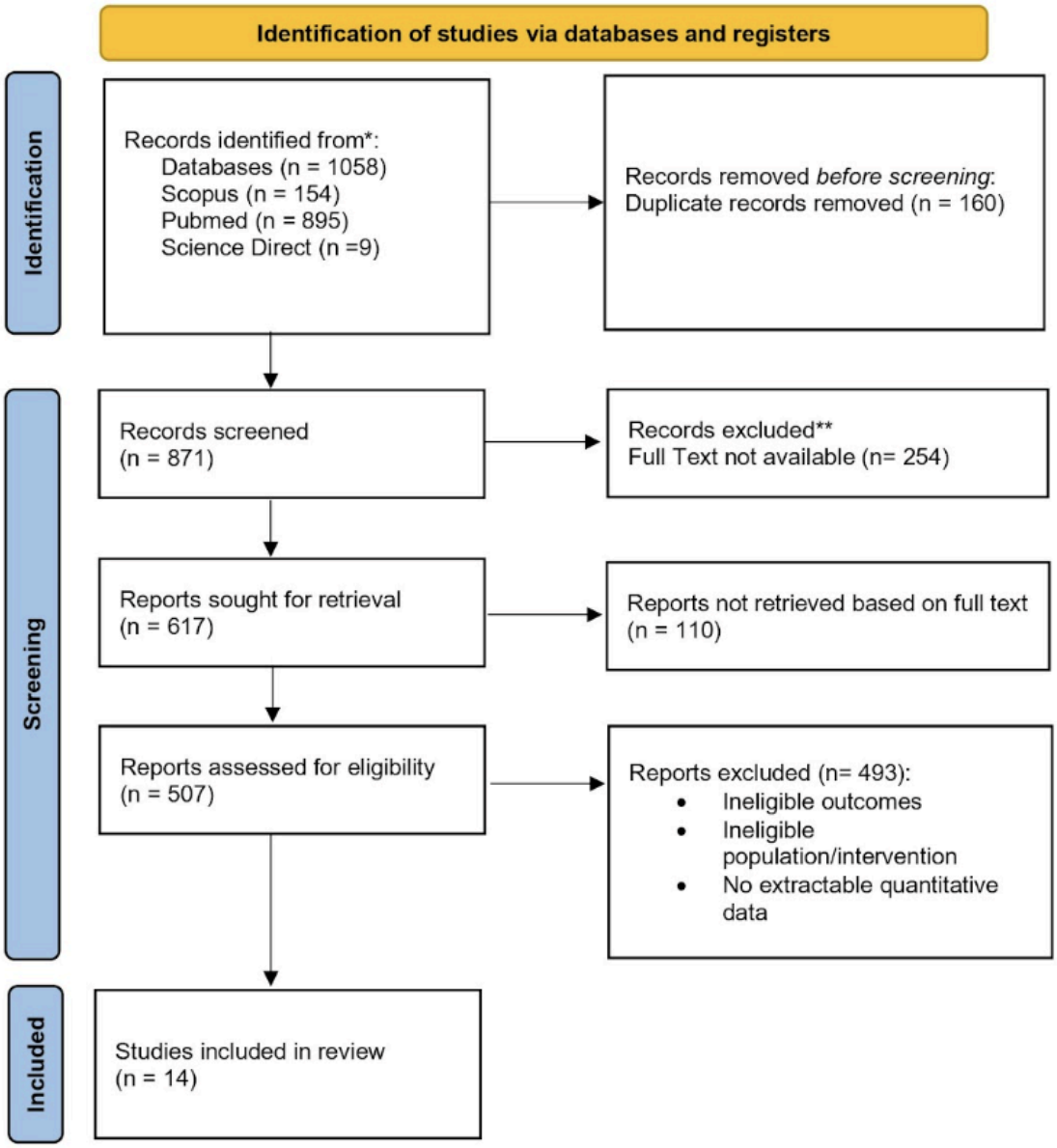

Figure 1: PRISMA flowchart on study screening and selection process.

Oral Nutrition Supplement (ONS)

The effectiveness of ONS programs in reducing undernutrition has resulted in inconsistency at best, sparking debates about their true value and impact. Collectively, ONS is established as a supplementary, ready-made nutritional intake calculating at 1–1.5 kcal/ml per 200 ml bottles used for children with faltered growth status, delayed growth, poor intake and low intake tolerability. The use of ONS however has been known to be of significant impact when calorie is denser and increased, as well as providing improvements when combined with foods.[16-18] In this review and analysis, ONS is identified through keywords as mentioned in literature search, as well as other diets or foods association.

Insulin-like Growth Factor-1 (IGF-1)

IGF-1 is highly responsive to both acute and prolonged changes in nutritional status, serving as a dynamic biomarker that reflects the body's metabolic environment. Accurate interpretation of IGF-1 levels necessitates a comprehensive understanding of the child's nutritional condition, as inconsistencies in dietary intake can significantly influence its synthesis and regulation. This underscores the critical interplay between nutrition and endocrine function in growth and development.[20] Serum IGF-1 was measured according to each designated study by collecting blood samples and further technical laboratory examination of immunoassays, using automated LIAISON analyser; DiaSorin.[21-24]

Anthropometric Status Assessment

WHO provides child growth standards to detect issues early, using indices like WAZ, HAZ, and WHZ, expressed as Z-scores or percentiles. Z-scores from -2 to -1 indicate mild undernutrition, -3 to -2 show moderate undernutrition, and below -3 reflects severe undernutrition. Specific conditions are assessed using these indices: wasting (WHZ), stunting (HAZ), and underweight (WAZ). Classification of the nutritional status were based on gender/sex and age-specific Z-scores using WHO Growth Standards.[10]

Data Extraction

Abstracts from articles and publications retrieved from the database were co-independently screened by four reviewers to collect relevant studies according to the inclusion criteria outlined above, and furthermore assessed the eligibility by independently reviewing available full texts. Differing opinions were resolved through consultation with a fifth reviewer. Data from the articles were then extracted through authors, year of publication, type of study design, country of conducted study, age of subject, subjects by population; children with undernutrition; children at risk of malnutrition; weight and/or length faltering children with or without infection; picky eaters and/or children with feeding problems; children with constitutional delay of growth and maturation (CDGM); children with body weight and/or body length below normal percentile; children given interventional nutritional supplements, type of nutritional supplements in interventional group vs. controlled group (low calorie diet or usual diet), growth status outcomes; body weight; body length; WAZ; LAZ; WLZ, population IGF-1 levels, IGF-1 level outcomes. Reviewers co-efficiently extracted the data and discrepancies were identified and resolved through collective with other reviewers. The selection process is shown in the PRISMA 2020 flow diagram (**Figure 1**).

Study Quality Assessment

The risk of bias was specifically assessed using the Cochrane risk of bias (ROB) tool, based on criteria outlined by Schulz et al., as specified in the Cochrane Handbook for Systematic Reviews of Interventions. Additionally, we use the National Institute of Health Quality Assessment Tool for observational studies. Three reviewers independently assessed the ROB quality of each study. Any disagreements between the reviewers were resolved by the third reviewer.

Statistical Analysis

This search process generated 1,058 articles from 3 databases. After removing duplicates, 871 records were screened. Following the exclusion of records with unavailable full text, 507 articles were assessed for eligibility. Among these, 493 studies were excluded because they did not report one or more of the predefined outcomes of interest (body weight, body length/height, WAZ, LAZ/HAZ, WLZ/WHZ, or serum IGF-1), evaluated ineligible interventions or study populations, or did not provide extractable quantitative data for analysis. Consequently, 14 studies were included in the quantitative synthesis **(Table 1)**. This study selection process is illustrated in the PRISMA 2020 flow diagram **(Figure 1)**. Continuous outcomes measured using comparable units were pooled using the mean difference (MD) with 95% confidence intervals (95% CI). Serum Insulin-like Growth Factor-1 (IGF-1) outcomes were not quantitively synthesized because the included studies reported heterogenous outcome metrics, including absolute serum concentrations, IGF-1 standard deviation scores (SDS), and changes from baseline. Therefore, the IGF-1 findings were summarized narratively.

Results

A total of 14 randomized controlled trials (RCTs) were included in this meta-analysis, focusing on the effects of ONS on children under five years of age experiencing undernutrition. The compiled data, derived from 1207 initially identified articles, provides strong evidence highlighting the efficacy of ONS in improving various growth and nutritional parameters.

The Characteristics of Subjects

The studies included in this analysis represented diverse populations from Jamaica, the Philippines, Taiwan, the USA, Germany, China, Israel, India, and Indonesia. The mean ages of participants ranged from infancy to nine years. Interventions involved ONS formulations of

1 kcal/ml or 1.5 kcal/ml, while control groups received usual diets, low-calorie alternatives, or no supplementation. Follow-up durations ranged from 8 days to one year, enabling the evaluation of both short-and long-term effects, presented in **[Table 1]**. These diverse study settings and populations enhance the generalizability of the findings, providing a comprehensive overview of ONS's potential across varied contexts.

Table 1: The Characteristics of Subjects.

No	Author (year)	Type of Study	Study Location	Mean age month (SD)		Type of Intervention				Follow-up Period (days)
				Case	Control	Case	Sample (n)	Control	Sample (n)	
1.	Walker et al., 1991[25]	RCT	Jamaica	18.8 ± 3.7	18.5 ± 4.5	ONS 1 kcal/ml	32	No ONS	33	180, 365
2.	Alarcon et al., 2003[8]	RCT	Philipines and Taiwan	48.3 ± 6.4	48.7 ± 6.6	ONS 1 kcal/ml-DC	53	DC	51	30, 60, 90
3.	Schrezenmeir et al., 2004[26]	RCT	Germany	50.9 ± 0.22	51.0 ± 0.23	ONS 1 kcal/ml-Probiotics	46	Fruit-flavored drink	44	8
4.	Han et al., 2011[21]	RCT	USA	108.0± 1.6	115.2 ± 1.0	ONS 1 kcal/ml	10	Usual Diet	10	90, 180, 365
5.	Sheng et al., 2014[27]	RCT	China	45.6 ± 0.7	43.2 ± 0.7	ONS 1 kcal/ml-DC	75	DC	67	30, 60, 90, 120
6.	Lebenthal et al., 2014[28]	RCT	Israel	64.8 ± 1.5	67.2 ± 1.5	ONS 1.5 kcal/ml	80	Low-caloric	91	180
7.	Yackobovitch et al., 2016[22]	RCT	Israel	70.8 ± 1.5	74.4 ± 1.5	ONS 1.5 kcal/ml	69	Low-caloric	81	90
8.	O'Reilly et al., 2015[29]	RCT	Ireland	57.6	57.6	ONS 1 kcal/ml-DC	33	DC	34	16, 42
9.	Cervo et al., 2017[30]	RCT	Philipines	48.0 ± 0.13	51.6 ± 0.14	ONS 1 kcal/ml	40	Usual Diet	40	84
10.	Ghosh et al., 2018 (1)[31]	RCT	India	42.8 ± 14.0	45.2 ± 14.4	ONS 1 kcal/ml-DC	127	DC	128	10, 30, 60, 90
11.	Ghosh et al., 2018 (2)[32]	RCT	India	3.8 ± 1.2	3.9 ± 1.1	ONS 1 kcal/ml-DC	64	DC	58	10, 30, 60, 90
12.	Khanna et al., 2021[33]	RCT	India	35.3 ± 3.38	35.0 ± 3.37	ONS 1 kcal/ml-DC	107	DC	107	7, 30, 60, 90
13.	Soliman et al., 2021[23]	RCT	Qatar	10.1 ± 3.82	8.94 ± 4.84	ONS 1,5 kcal/ml	22	ONS 1 kcal/ml	12	90, 180, 360
14.	Widjaja et al., 2024[24]	RCT	Indonesia	17.10 ± 3.87	36.12 ±7.38	ONS 1 kcal/ml	40	ONS 1 kcal/m		15, 30, 60, 90

Abbreviations: RCT = Randomized Controlled Trial, ONS = Oral Nutritional Supplement, DC = Dietary Counseling, SD = Standard Deviation

Outcome Changes on Weight Increment

A total of seven comparisons were pooled to evaluate changes in body weight. The use of ONS showed a significant advantage compared to non-ONS in increasing weight (pooled mean difference [MD] 0.64 kg [95% confidence interval [CI] 0.39 to 0.90], $p < 0.01$), although substantial heterogeneity was observed ($I^2 = 94\%$). While some individual studies showed confidence intervals crossing the line of no effect, the overall pooled estimate remained statistically significant. Subgroup analyses demonstrated significant improvements in both the ONS-only group (pooled MD 0.89 kg [95% CI 0.16-1.61]) and the ONS plus dietary counseling (ONS-DC) group (pooled MD = 0.46 kg [95% CI 0.32 to 0.59. However, the difference between subgroups was not statistically significant ($p = 0.26$) **(Figure 2)**.

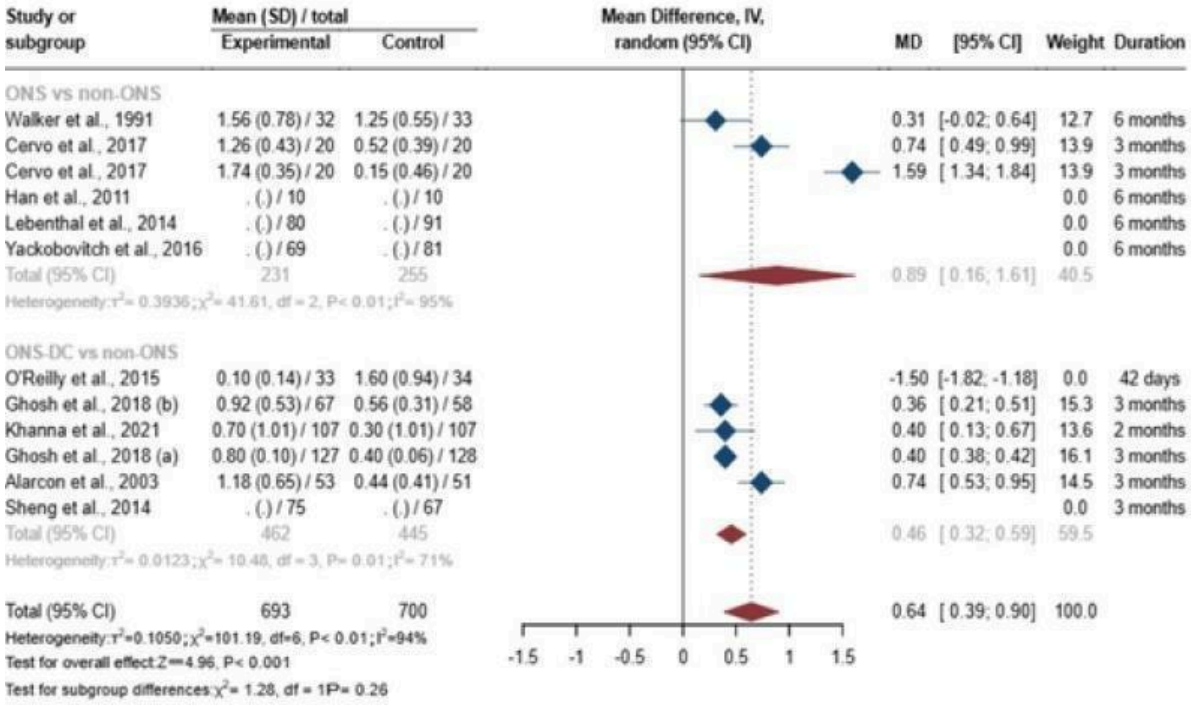

Figure 2: Forest plot comparing the effect of ONS vs control on body weight increment.

Outcome Changes on Length Increment

Six comparisons were pooled to analyze the outcome of length increment. The use of ONS showed a significant advantage compared with the control group in improving body length (pooled MD 0.52 cm [95% CI 0.33 to 0.71], $I^2 = 58\%$, $p < 0.01$), with moderate heterogeneity across studies ($I^2 = 58\%$). Subgroup analyses demonstrated significant improvements in both the ONS-only group (pooled MD 1.01 cm [95% CI 0.49-1.53]) and the ONS-DC group (pooled MD 0.45 cm [95% CI 0.25-0.65]). The difference between subgroups was borderline significant ($p = 0.05$) (**Figure 3**).

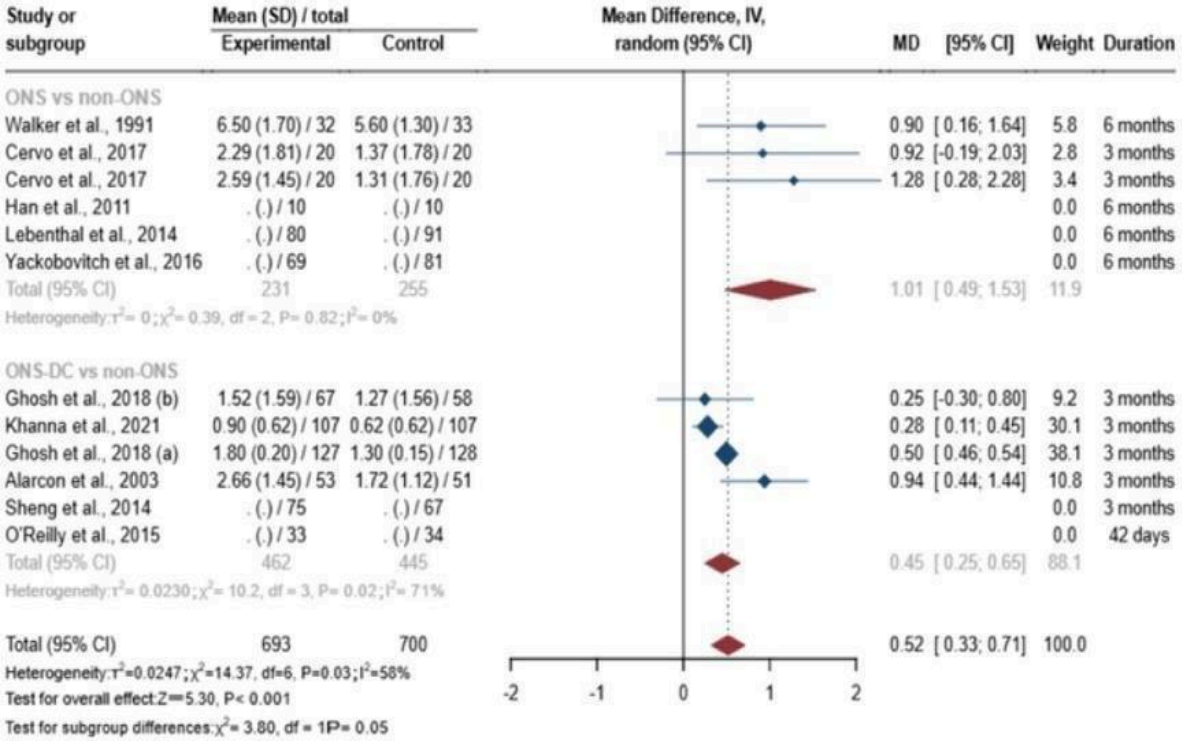

Figure 3: Forest plot comparing the effect of ONS vs control on body length increment.

Outcome Changes on Weight for Ages (WAZ)

Six comparisons were pooled to analyze the outcome of the weight-for-age Z-score (WAZ). ONS significantly improved WAZ compared with the control group (pooled 0.15 [95% CI 0.09-0.21; p <0.01]), although considerable heterogeneity was observed across studies (I^2 = 97%). Subgroup analyses demonstrated significant improvements in both the ONS-only group (pooled MD 0.12 [95% CI 0.02-0.25]) and the ONS-DC group (pooled MD 0.16 [95% CI 0.09-0.24]). However, the difference between subgroups was not statistically significant (p = 0.57) (**Figure 4**).

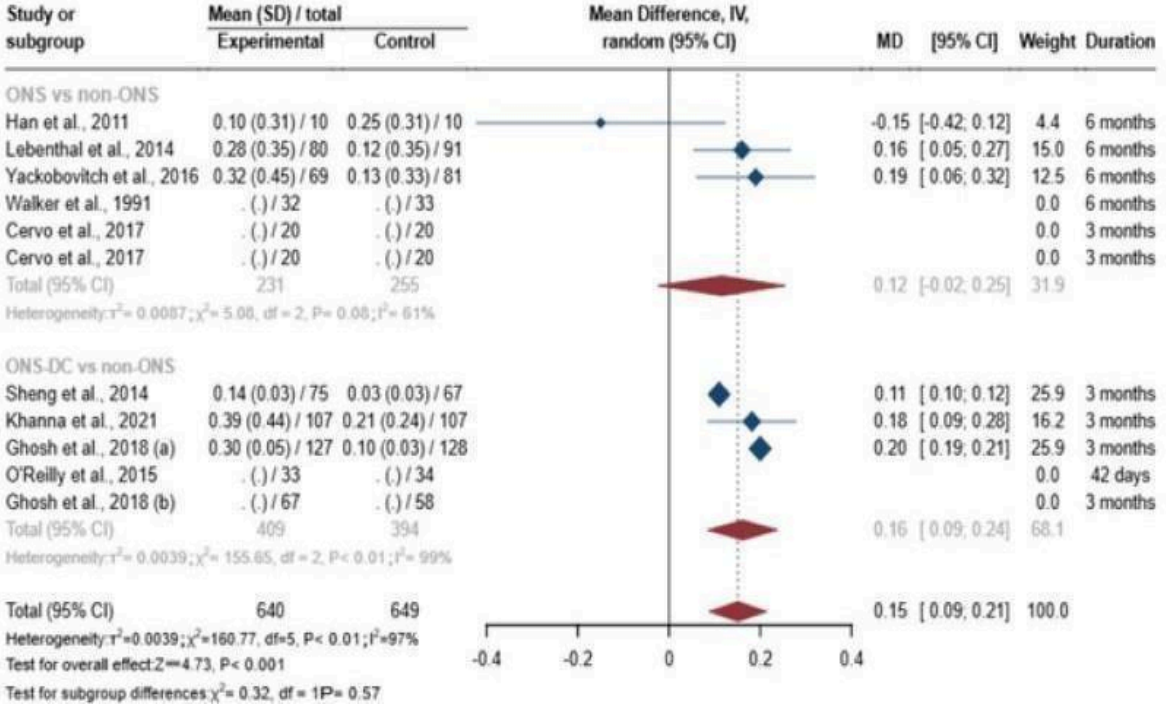

Figure 4: Forest plot comparing the effect of ONS vs control on WAZ.

Outcomes Changes on Length for Ages (LAZ)

Seven comparisons were pooled to evaluate changes in length-for-age Z-score (LAZ). ONS significantly improved LAZ compared with the control group (pooled MD 0.09 [95% CI 0.02 to 0.15], p = 0.008), although substantial heterogeneity was observed across studies (I^2 = 88%). Subgroup analyses demonstrated significant improvements in both the ONS-only group (pooled MD 0.12 [95% CI 0.04-0.20]) and the ONS-DC group (pooled MD 0.02 [95% CI 0.01-0.03]). The difference between subgroups was statistically significant (p = 0.01), indicating a greater improvement in LAZ among studies evaluating ONS alone (**Figure 5**).

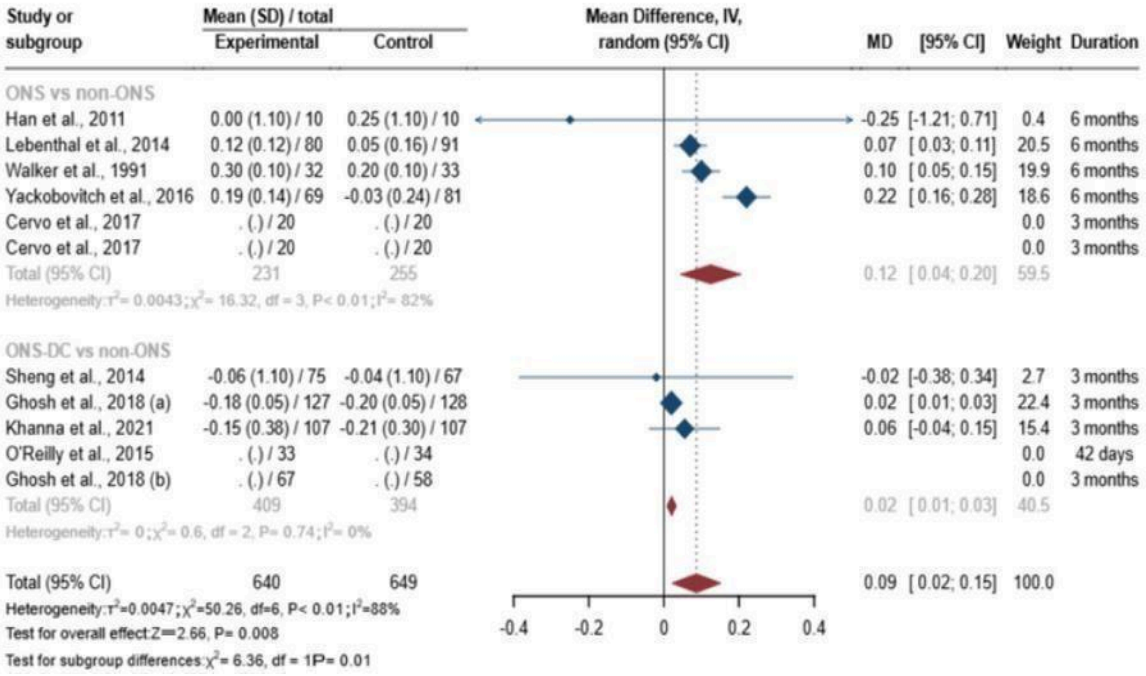

Figure 5: Forest plot comparing the effect of ONS vs control on LAZ.

Outcomes Changes on Weight for Length (WLZ)

Six comparisons were pooled to analyze the outcome of the weight-for-length Z-score (WLZ). ONS significantly improved WLZ compared with the control group (pooled MD 0.17 [95% CI 0.06-0.28], p = 0.003), although considerable heterogeneity was observed across studies (I^2 = 98%). Subgroup analysis demonstrated a significant improvement in the ONS-DC group (pooled MD 0.21 [95% CI 0.06-0.36]), whereas the pooled effect in the ONS-only group was not statistically significant (pooled MD 0.10 [95% CI -0.00 to 0.21]). However, the difference between subgroups was not statistically significant (p = 0.25) (**Figure 6**).

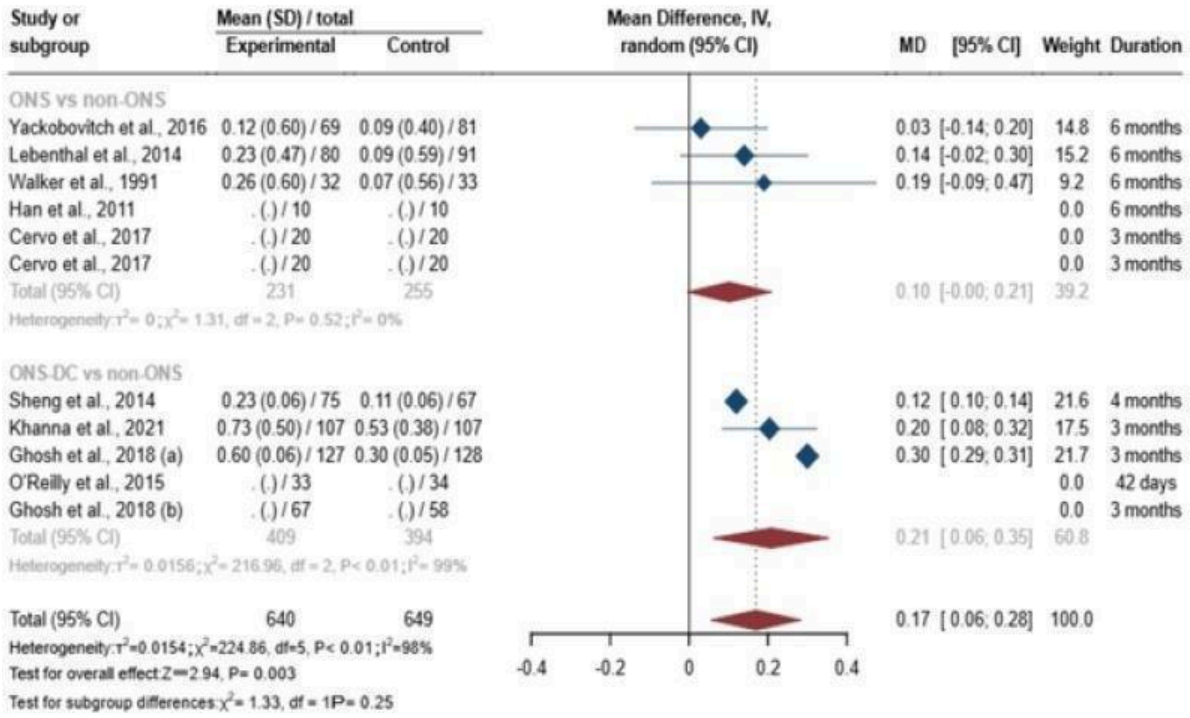

Figure 6: Forest plot comparing the effect of ONS vs control on WLZ.

Outcome Serum IGF-1 Levels

Only four studies evaluated serum Insulin-like Growth Factor-1 (IGF-1) following oral nutritional supplementation (ONS) **(Table 2)**. Because the included studies reported IGF-1 using different outcome measures, including absolute serum concentrations, changes from baseline, and IGF-1 standard deviation scores (SDS), quantitative synthesis was not performed. Overall, the available evidence suggests that ONS may improve IGF-1 levels; however, the magnitude and consistency of this effect varied across studies, likely reflecting differences in study populations, intervention duration, ONS formulations, and IGF-1 assessment methods. For instance, Han et al. (2011) reported increase in serum IGF-1 concentrations from 180 ± 45 ng/ml to 788 ± 181 ng/ml after 12 months of ONS intervention, while the control group reached 666 ± 178 ng/ml. Similarly, Widjaja et al. (2024) observed greater increases in IGF-1 among severely stunted children (Δ6.72 ± 11.06) than among children with normal stature (Δ0.07 ± 10.89). Given the limited number of studies and methodological heterogeneity, these findings should be considered exploratory and interpreted with caution.

Table 2: Outcome serum IGF-1 levels.

No	Author (year)	Population	IGF-1 (ng/ml)	
			Intervention	Control
1.	Han et al., 2011[21]	ONS 1 kcal/ml vs. Usual Diet	Baseline, 180 ± 45 6 mon, 326 ± 93 12 mon, 788 ± 181 18 mon, 605 ± 124	Baseline, 187 ± 41 6 mon, 252 ± 46 12 mon, 666 ± 178 18 mon, 638 ± 154
2.	Yackobovitch et al., 2016[22]	ONS 1.5 kcal/ml vs. low-caloric	IGF-1 SDS -135 ± 1.50	IGF-1 SDS -1.04 ± 1.50

3.	Soliman et al., 2021[23]	ONS 1 kcal/ml (Control) vs. ONS 1,5 kcal/ml (Intervention)	Baseline -0.48 ± 0.5 After 360 days 1.5 ± 0.6	Baseline -0.6 ± 0.3 After 360 days 0.35 ± 0.16
4.	Widjaja et al., 2024[24]	ONS 1 kcal/ml vs. ONS 1 kcal/ml	Increments day 0-90 Change of IGF-1 (Δ) based on LAZ/HAZ Normostature, 0.07 ± 10.89 Stunted, 1.68 ± 5.64 Severely stunted, 6.72 ± 11.06 Increments day 0-90 Change of IGF-1 (Δ) based on WAZ Normoweight, 1.18 ± 9.61 Underweight, 3.39 ± 10.41 Severely underweight, 19.94 ± 1.44 Increments day 0-90 Change of IGF-1 (Δ) based on WLZ/WHZ Normoweight, 1.58 ± 9.77 Underweight, 6.38 ± 8.71 Severely wasted, 0.93 (p=0.950)	Increments day 0-90 Change of IGF-1 (Δ) based on LAZ/HAZ Normostature, 0.07 ± 10.89 Stunted, 1.68 ± 5.64 Severely stunted, 6.72 ± 11.06 Increments day 0-90 Change of IGF-1 (Δ) based on WAZ Normoweight, 1.18 ± 9.61 Underweight, 3.39 ± 10.41 Severely underweight, 19.94 ± 1.44 Increments day 0-90 Change of IGF-1 (Δ) based on WLZ/WHZ Normoweight, 1.58 ± 9.77 Underweight, 6.38 ± 8.71 Severely wasted, 0.93 (p=0.950)

Abbreviations: ONS = Oral Nutritional Supplement, IGF-1 = Insulin-like Growth Factor 1, SDS = Standard Deviation Score, LAZ/HAZ = Length-for-Age-Z-score / Height-for-Age Z-score, WAZ = Weight-for-Age Z-score, WAZ = Weight for Age Z-score, WLZ/WHZ = Wight-for-Length Z-score / Weight-for-Height Z-score.
The IGF-1 findings summarized in this table should be considered exploratory because only four studies evaluated this outcome, and the reported IGF-1 measures were methodologically heterogenous (absolute serum concentrations, changes from baseline, and IGF-1 standard deviation scores), quantitative synthesis was not performed and the findings are presented narratively.

Discussion

Childhood undernutrition is a global issue associated with high mortality and morbidity.[34] Reduction of undernutrition incidence can be accomplished through evidence-based interventions.[14] ONS intervention proved to provides clinical benefits in the management of undernutrition in children.[35] In this study, we conducted a systematic review and meta-analysis of scientific evidence focusing on the effects of ONS on anthropometric status and serum IGF-1 level of undernourished children. We found that ONS administration for undernourished children had significant positive effects on weight and height increment compared to non-ONS administration. Furthermore, WAZ, WHZ, and LAZ in the intervention group showed significant improvements, suggesting that ONS is able to promote catch-up growth. Although several individual studies included in the meta-analysis reported effect estimates with confidence intervals crossing the line of no effect, the overall pooled estimates consistently favored ONS. This apparent inconsistency is likely attributable to clinical and methodological heterogeneity among the included studies rather than the absence of a treatment effect. The analysis we performed assessed the impact of ONS administration throughout a minimum intervention of 3 months and maximum intervention period of 6 months. Our results are consistent with prior studies. Interventions strategy in children with undernutrition largely focused on increasing nutritional intake. However, it is important to provide nutritional counseling in an effective way that facilitates lifestyle modifications and yields long-term health outcomes.[36]

In this study, subgroup analyses were performed to compare the effects of ONS alone and ONS + dietary counseling (DC). Both interventions were associated with improvements in several growth outcomes. Although the pooled effect estimates differed numerically for some outcomes, formal tests for subgroup differences were not statistically significant for body weight, WAZ, and WLZ. Therefore, the available evidence does not support the conclusion that ONS-DC is consistently more effective than ONS alone. A statistically significant subgroup difference was observed only for LAZ, whereas the difference for length increment was borderline significant. Furthermore, although the pooled effects for height increment and LAZ appeared smaller in the ONS-DC subgroup than in the ONS-only subgroup, these findings should be interpreted cautiously because the between-subgroup differences were not consistently statistically significant across outcomes. This pattern may also reflect the biological characteristics of linear growth, which generally responds more slowly to nutritional intervention than weight gain. Previous studies have shown that improvements in nutritional status following nutritional interventions are often reflected earlier by gains in body weight than by measurable changes in linear growth.[35,37,38]

Zhang et al. conducted a study in 2021 that explored the effects of ONS on anthropometric status, and their findings were consistent with those observed in our study. This research demonstrated that the mean changes in several key anthropometric indicators, including

weight, WAZ, weight-for-age percentile (WAP), WHZ, and height-for-age percentile (HAP), were significantly greater at 90 days post-ONS intervention compared to 30 days. The intervention group showed marked improvements in these measures over time, which were notably greater to those observed in the control group. This underscores the importance of sustaining nutritional supplementation for an extended duration to achieve meaningful improvements in growth parameters. Based on these findings, it can be inferred that providing nutritional supplementation for at least 90 days is essential to facilitate optimal catch-up growth, particularly in terms of height. This highlights the critical role of prolonged interventions in addressing growth deficits and ensuring long-term improvements in child health outcomes.[35]

Another important outcome as anthropometric status is the IGF-1 level following ONS intervention. In a previous study, An et al. performed a systematic study on nutritional biomarkers following ONS intervention in undernourished children, indicating that numerous factors may influence the assessment of these biomarkers.[39,40] IGF-1 is a biomarker that can be utilized to evaluate nutritional status in children and adolescents.[21,40] In addition, IGF-1 is more sensitive and specific compared to prealbumin, transferrin, and retinol-binding protein (RBP) as a biomarker of nutritional status.[40] Both short-term and long-term changes in nutritional status can affect IGF-1 concentration.[19] Adequate protein and energy intake provided through ONS may stimulate the growth hormone-IGF-1 axis, thereby enhancing hepatic IGF-1 production and supporting linear growth, providing a biological rationale for the observed effects of nutritional supplementation.

Only four studies evaluated serum IGF-1 following ONS intervention. Direct comparison among studies was challenging because IGF-1 was reported using different outcome measures, including absolute serum concentrations, changes from baseline, and IGF-1 standard deviation scores (SDS). Therefore, the findings should be considered exploratory rather than conclusive. One of these studies, conducted in 2011, provided compelling evidence of the long-term benefits of ONS on IGF-1 levels. This study found that daily ONS resulted in significantly higher serum IGF-1 levels at both 12 months and 18 months post-intervention when compared to baseline levels, with the differences being statistically significant. These findings emphasize the critical role of consistent and prolonged nutritional supplementation in boosting IGF-1 levels, a key biomarker linked to growth and development in children with undernutrition.[21] Another study observed an increase in IGF-1 level after nutritional intervention, but there was no significant difference compared to baseline IGF-1 level.[24] The observed variability among studies is likely multifactorial. In addition to differences in intervention methods and study populations, heterogeneity may also reflect variations in baseline nutritional status, intervention duration, ONS formulations, laboratory methods, and the outcomes measures use to report IGF-1. These methodological differences precluded quantitative pooling and warrant cautious interpretation of the available evidence. Additionally, inconsistencies in the collection, handling, and processing of blood samples for IGF-1 level assessment also play a significant role in influencing the reliability of the findings.[41]

When the subjects were categorized by age, a study demonstrated a significant positive correlation between anthropometric measures and IGF-1 levels, emphasizing the importance of IGF-1 in growth and body composition. Specifically, in children aged three to four years, higher IGF-1 levels were strongly associated with improved Z scores for weight and body mass index (BMI), indicating better overall growth and nutritional status within this age group. In contrast, among children aged four to five years, the study found a different pattern of correlation. In this slightly older age group, IGF-1 levels showed a significant positive association with the Z score of triceps skinfold thickness, a measure of subcutaneous fat, as well as the Z score of arm muscle area. These findings highlight the nuanced role of IGF-1 in influencing different aspects of growth and body composition depending on the child's age.[20] Although the current evidence suggest that ONS may increase serum IGF-1 levels, the available data remain limited because only four studies evaluated this outcome using heterogeneous methodologies. Therefore, the present findings should be regarded as promising but still limited evidence, highlighting the need for additional well-designed RCTs using standardized IGF-1 outcome measures to better define the effect of ONS on the growth hormone-IGF-1 axis.

To our knowledge, this is the first systematic review and meta-analysis conducted to evaluate the impact of ONS on IGF-1 levels and anthropometric status in children with undernutrition. While our study provides valuable insights into the potential benefits of ONS, several limitations should be acknowledged. Several pooled analyses demonstrated substantial statistical heterogeneity, particularly for body weight, WAZ, and WLZ. This heterogeneity is likely attributable to important clinical and methodological differences among the included studies rather than a single underlying factor. Accordingly, the pooled effect estimates should be interpreted with caution, as the observed heterogeneity may reduce the precision of the summary estimates and limit their applicability across different clinical settings and populations. The included trials enrolled children across a broad age range and with varying baseline nutritional status, including underweight, wasted, stunted, or at-risk children. In addition, the ONS interventions differed with respect to formulation, caloric and protein composition, dosing regimens, intervention duration, and the concomitant use of dietary counseling, all of which may have influenced the magnitude of treatment effects.

Although sensitivity analysis and meta-regression could have provided further insight into the robustness of the pooled estimates and potential sources of heterogeneity, these analyses were not feasible because of the limited number of studies available for each pooled outcome and the insufficient availability of study-level covariate data. Furthermore, formal publication bias assessment using funnel plots and Egger's regression test was not performed because most pooled analyses included fewer than ten studies, limiting the reliability and interpretability of these methods. In addition, the limited number of eligible studies and relatively short intervention durations for some outcomes may restrict the generalizability and durability of the findings. These limitations should be considered when interpreting the

pooled estimates and underscore the need for large, well-designed RCTs using more standardized intervention protocols and outcome measurements.

Conclusion

This systematic review and meta-analysis demonstrates that ONS improves anthropometric outcomes in children with undernutrition, supporting its role as an effective nutritional strategy to promote growth and address nutritional deficiencies. Evidence regarding the effect of ONS on serum IGF-1 is promising but remains limited because only a small number of methodologically heterogenous studies have evaluated this outcome. The findings should therefore be interpreted with caution. Current evidence is further constrained by substantial clinical heterogeneity, variations in ONS formulation and intervention protocols; and limited number and duration of available studies. Further well-designed RCTs using standardized IGF-1 assessment methods, longer intervention durations, follow-up protocols, and comparative evaluations of high-density ONS formulations (1kcal/ml vs 1.5 kcal/ml) is warranted to strengthen the evidence base and guide evidence-based strategies for improving child health outcomes globally.

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