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Effectivity and cost-effectiveness of oral nutrition supplement on malnourished children: A Literature review

Siti Helmyati[1, 2*], Maria Wigati[1, 2], Yuliana Novita Rachmawati[2], Cut Alima Syarifa[2], Gifani Rosilia[2], Renita[2]

[1]Department of Nutrition and Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Center for Health and Human Nutrition, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Correspondence: helmyati@ugm.ac.id

ABSTRAK

Latar Belakang: *Kekurangan gizi pada anak adalah masalah global yang berpotensi diatasi dengan dukungan pangan olahan untuk keperluan medis khusus, salah satunya yaitu suplemen gizi oral (oral nutrition supplement/ONS).*
Tujuan: *Tinjauan literatur ini bertujuan untuk mengkaji efektivitas ONS pada anak malnutrisi dilihat dari indikator pertumbuhan, lama rawat inap, dan kejadian efek samping, serta mengeksplorasi efektivitas biaya ONS dalam menangani malnutrisi pada anak.*
Metode: *Artikel dikumpulkan dari database elektronik yang meliputi PubMed, ProQuest, dan Google Scholar dengan tambahan artikel dari mesin pencari Google. Artikel dimasukkan dalam tinjauan literatur jika subjek adalah anak di bawah lima tahun yang berisiko kurang gizi, kurang gizi, pascaoperasi, atau dirawat di rumah sakit dan diresepkan ONS; merupakan penelitian eksperimental dengan atau tanpa kelompok pembanding atau kelompok kontrol; dan meneliti status gizi, luaran lain yang secara langsung atau tidak langsung berhubungan dengan malnutrisi, dan efektivitas biaya.*
Hasil: *Terdapat 16 artikel yang ditinjau dari hasil pencarian. Anak yang mengonsumsi ONS, memiliki konsumsi ONS yang baik, dan mengonsumsi ONS dengan kepadatan yang lebih tinggi mengalami kenaikan berat dan tinggi badan, peningkatan status gizi yang lebih baik, serta lama rawat inap yang lebih singkat dibandingkan dengan anak yang tidak diberi ONS, memiliki konsumsi ONS yang buruk, dan mengonsumsi ONS dengan kepadatan yang lebih rendah, meskipun ditemukan beberapa efek samping konsumsi ONS, seperti gejala gangguan pencernaan, diare, dan muntah. Bukti tentang efektivitas biaya ONS dalam menangani anak malnutrisi sangat terbatas. Namun, perbaikan luaran medis akibat konsumsi ONS berpotensi menurunkan biaya medis langsung.*
Kesimpulan: *Konsumsi ONS dapat memberikan hasil pertumbuhan dan hasil medis yang diharapkan. ONS dapat menjadi intervensi gizi untuk penanganan malnutrisi anak yang efektif biaya karena biayanya yang relatif rendah, kemampuannya untuk meningkatkan luaran medis, serta bukti efektivitas biayanya pada populasi lain.*

KATA KUNCI*: anak; efektivitas biaya; indikator pertumbuhan; malnutrisi; suplemen gizi oral*

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ABSTRACT

Background: *Child undernutrition has been a global problem that could be potentially treated with the support of food for special medical purposes, including oral nutrition supplements (ONS).*

Objectives: *This literature review aims to examine the effectiveness of ONS administration for malnourished children as seen from growth indicators, length of stay, and adverse events occurrence, and explore ONS cost-effectiveness in treating child malnutrition.*

Methods: *Articles were collected from electronic databases including PubMed, ProQuest, and Google Scholar, with additional articles from Google search engine. Articles were included if it included children under five at risk of malnutrition, with malnutrition, post-surgery, or hospitalized and prescribed with ONS; were experimental research with or without comparison or control group; and examined nutrition status, other outcomes directly or indirectly related to malnutrition, and cost-effectiveness.*

Results: *This review summarized findings from 16 articles. Children who consumed ONS, had good ONS consumption, and consumed higher ONS density experienced better weight and height gain, better improvements in nutrition status, and shorter length of stay compared to children who didn't receive ONS, had poor ONS consumption, and consumed lower ONS density, although several adverse events of ONS consumption such as gastrointestinal symptoms, diarrhea, and vomiting were also recorded. Evidence on ONS cost-effectiveness in treating child malnutrition is limited. However, improved medical-related outcomes due to ONS consumption could potentially result in lower direct medical cost.*

Conclusions: *Studies suggest that ONS administration results in expected growth outcomes and medical-related outcomes. ONS could be a potential cost-effective nutrition intervention for child malnutrition treatment due to its relatively low cost, its ability to improve medical related-outcomes, and its cost-effectivity in other populations.*

KEYWORD*:* *children; cost-effectiveness; growth indicators; malnutrition; oral nutrition supplements*

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INTRODUCTION

Child undernutrition remains a global problem, especially in developing countries. In 2020, the WHO mentioned that over 149 children under five were estimated to be stunted and 45 million were wasted (1). In the continuous efforts to address child undernutrition around the world, a recent report by the WHO mentioned the number of 38 million wasted and severely wasted children in 15 of the worst-affected countries (2).

The negative impacts of child undernutrition on their long-term health and development as well as the effects on family and the country are already known (2). For instance, undernutrition is associated with a high risk of mortality and complications such as pneumonia, diarrhea, heart failure, decreased cognitive and motor skills. In the long term, it is associated with productivity reduction in adults (3–6). If there is a high prevalence of malnourished children in a country, it can be an impetus for slower economic growth as the result of a higher burden on health and social costs (7) The complexity of causes and effects of child malnutrition cost 2-3% of the Gross Domestic Product (GDP), perpetuating a cycle of poverty and illness (1,3,7–9).

One of the alternatives to treat child undernutrition is by providing food for special medical purposes (FSMPs). International Special Dietary Food Industries defined FSMPs as foods for special dietary uses which were specially formulated, processed, and presented for the dietary management of patients with limited or impaired capacity to take, digest absorb, or metabolise ordinary foodstuffs or certain nutrients; intended for exclusive or partial feeding; and may

be used only under medical supervision (10). Among available FSMPs is oral nutrition supplements (ONS) which provides additional calories, protein, and micronutrients for malnourished or at risk of malnourished people (11,12).

The potential of ONS to treat child undernutrition in health facilities is interesting to be explored. Oral Nutrition Supplement (ONS) could come in a variety of types, flavours, textures, and tastes and could be adapted to certain types of conditions, thus making it easily suitable for everyone's needs and liking (13). Additionally, ONS may provide functional benefits, including increased muscle strength, activity levels, and weight; decreased risk to fall, depression, and fatigue; and significantly reduced hospital admissions/readmission and length of stay which improves patients' quality of life (14).

The authors suggested the need to review the effectivity of ONS prescription for undernourished children (11,15,16). The efficiency of ONS prescription can be assessed by looking at changes in the budget and outcomes. The evaluation can also be done at the macroeconomic level to see the potential benefits and losses of the use of ONS in society. This is important since FSMPs development should be followed by a careful review of the current evidence so that the provision of the formula could enhance the success of the intervention in the broader population. That being said, this review aims to explore the effectiveness of ONS by examining the effects of ONS on growth indicators, length of stay, and adverse events, and explore the cost-effectiveness of ONS as an alternative to treat child malnutrition.

MATERIALS AND METHODS

Research Strategy

This review focused on the use of ONS for malnourished children. To obtain relevant studies, a research strategy is developed based on the PICO (population, intervention, comparison, and outcome) terms as follows:

a. Population: at risk or malnourished children indicated for ONS consumption
b. Intervention: oral nutrition supplement
c. Comparison: malnourished children not receiving oral nutrition supplement or receiving modified ONS formula
d. Outcome: nutrition status, other outcomes directly or indirectly related to malnutrition, and cost-effectiveness

Literatures were searched on three electronic databases: PubMed, ProQuest, and Google Scholar. Relevant to the PICO terms above, the search queries used the following keywords: diet therapy OR dietary supplement OR oral nutrition supplements OR food supplement OR nutrition OR diet OR foods, specialised; malnutrition OR undernutrition OR malnourishment OR nutritional status; and children OR child, preschool.

Study Inclusion Criteria

Studies were included in this review if it specifically evaluated the effect of ONS on children under the age of five, including those at risk of malnutrition, clinically diagnosed with malnutrition, post-surgery, or hospitalized and prescribed with ONS. Studies which included children older than five were also included if it includes children under five. Only original articles with experimental study design with or without comparison or control group were included in this review. Studies that have no full texts available were excluded. Studies included in this review are restricted to those written in English. To capture all available studies regarding the topic in this review, there was no publication year limitation for the literature search.

Data Extraction

Collected articles from the databases were processed using Rayyan.ai. Before the articles were screened, duplicate articles were detected and eliminated. Four reviewers (YNR, CAS, GR, and R) separately screened and assessed the articles. Articles were screened by examining the titles, abstracts, and/or full texts, then assessed by the reviewers so included articles adhere to the inclusion and exclusion criteria.

Additional Resources

To enrich the discussion in this review, search for additional articles was done using Google search engine on the following topics: nutrient dense formula intervention on length of stay, nutrient dense formula intervention on weight gain, nutrient dense formula intervention adverse events, oral nutritional supplements and cost-

effectiveness, and stunting on children with allergy. Retrieved articles were subject to the same inclusion and exclusion criteria. The process of article selection are described in **Figure 1**.

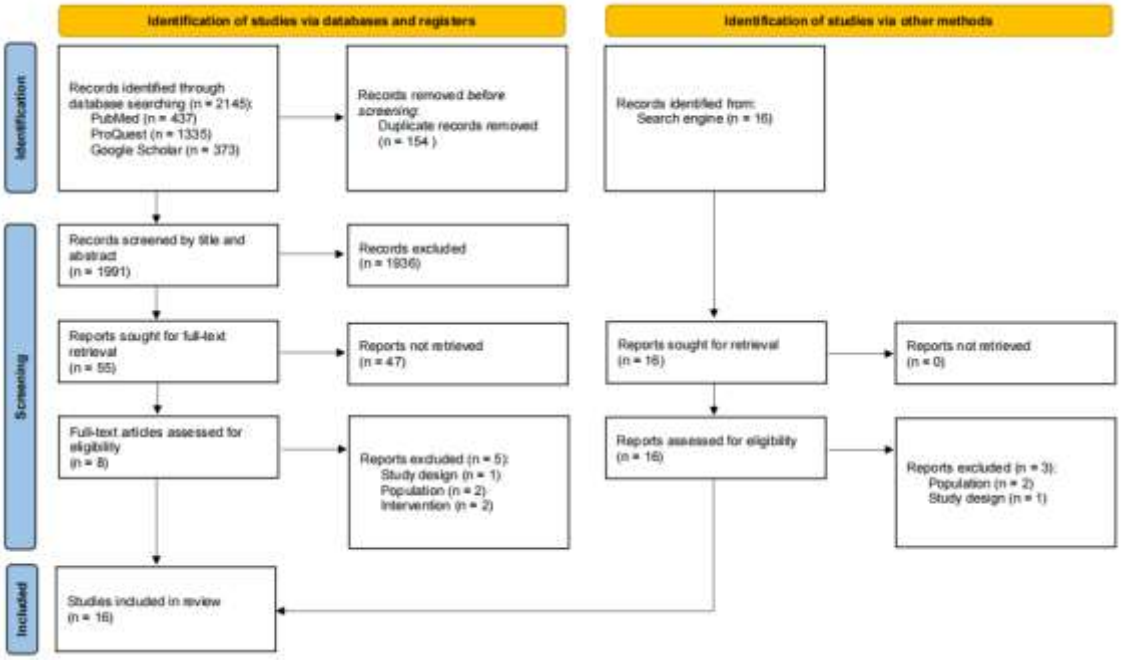


Figure 1. PRISMA Flow Diagram

RESULTS AND DISCUSSIONS

Oral Nutrition Supplements and Growth Indicators

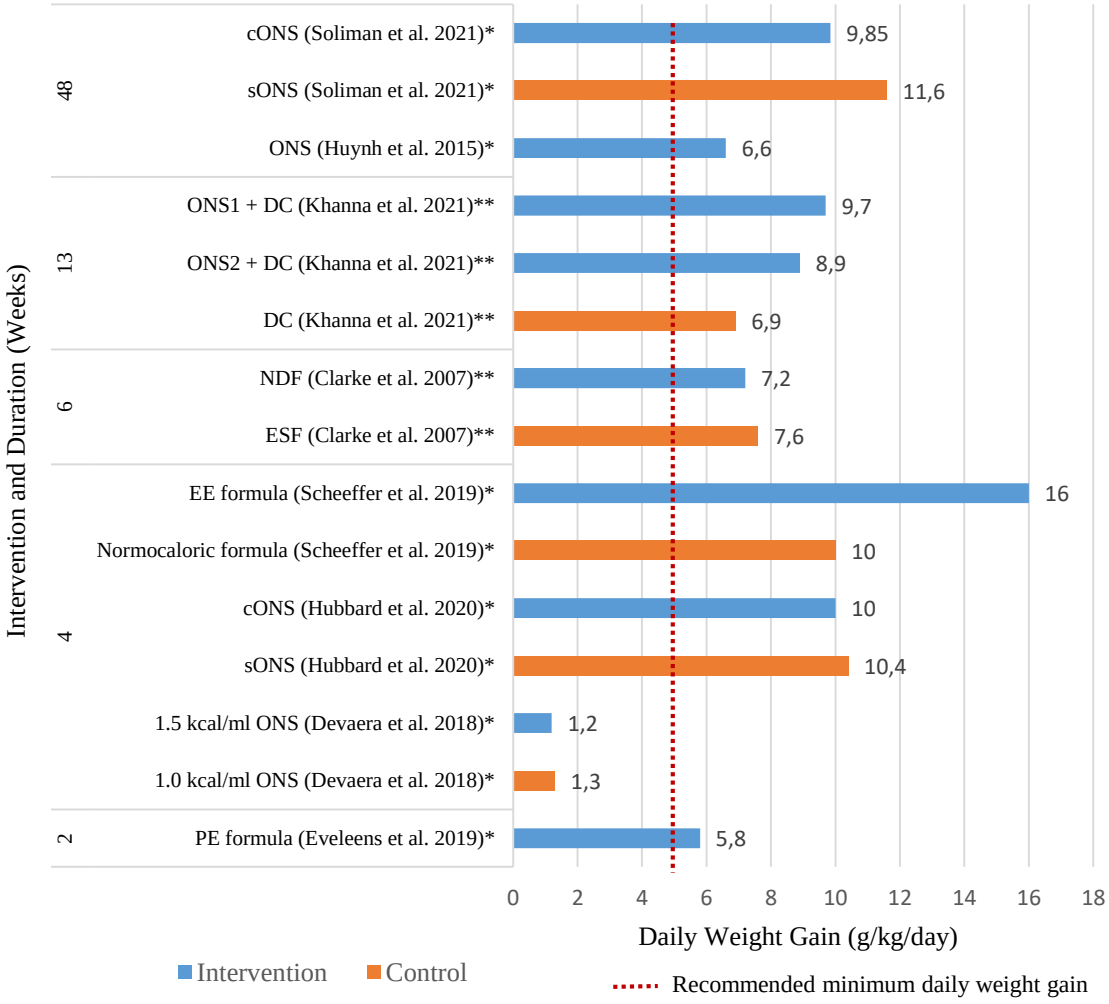
According to the consensus of the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition, recommended indicators to monitor child malnutrition, specifically undernutrition, include z-scores for weight-for-length/height, length/height-for-age, mid-upper arm circumference, or body mass index-for-age when a single data point is available or weight gain velocity (for children <2 years), weight loss (for children aged 2-20 years), retardation in weight-for-length/height z-score, and inadequate nutrient intake (17).

Effect of ONS on Weight and Weight-for-Age Z-Scores (WAZ)

Weight and weight-for-age measurement offer diagnostic parameters for acute undernutrition (17). During malnutrition treatment, achieved weight and weight gain velocity are monitored to trace the progress and identify the failure to respond ((18)). Sphere Standards recommends that diets for moderately malnourished children should support a daily weight gain of at least 5 g/kg/day (19).

To our knowledge, 8 studies reported the effectiveness of ONS administration on malnourished children on weight gain, as illustrated in **Figure 2**. Among 8 studies, 7 studies reported that ONS administration could meet the Sphere Standards by resulting more than 5 g/kg weight gain per day, all of which were conducted in a hospital setting ((20–26)), in which the result is significant in 4 studies (21,22,25,26). A study in a community setting also found a weight increase although insignificant (27). The British Association for Parenteral and Enteral Nutrition (BAPEN) declared that ONS may be prescribed either in the short term (less than 3 months) or long term (more than 6 months). ONS consumption should be observed regularly throughout the duration of their treatment every 3 months or, for those with longer term ONS requirements (28). It may examine the prolonged clinical need for ONS and continued properness of the product (29). The benefits of ONS on weight improvements are generally seen within 2-3 months of consumption. A research by Huynh et al (21) showed that children had more

weight increasement in the first two months of consumption with an average of 0.5 kg in the first and 0.3 kg in the second 4 weeks. It was supported by other studies that reported during a 3 months study, daily ONS consumption plus dietary counselling improved greater in weight and weight-for-age significantly from the first month until the third month compared to dietary counselling alone (25,30). Meanwhile, after 3 months, the body weight increase seemed to be lower compared to the first 3 months (0.2-0.3 kg per 8 weeks) (21). However, a study by Soliman et al (26) stated that the ONS consumption resulted in significantly increased mean total weight from baseline after 6 months and 1-year consumption. Although ONS can increase weight early, a longer period of consumption may be important to assure a significant improvement and to maintain the required weight gain (21,31), considering that there was a tendency for the weight and weight-z-score not to persist after supplementation stopped and even return to baseline (26,32).



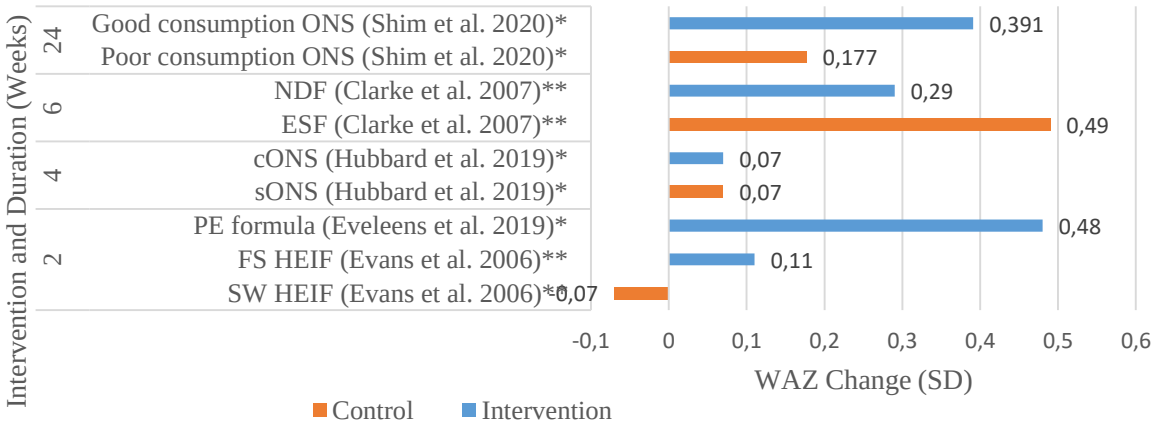
cONS, high-caloric density oral nutrition supplement; DC, dietary counselling; EE Formula, energy-enriched formula; ESF, energy-supplemented formula; NDF, nutrient-dense formula; ONS, oral nutrition supplement; ONS1, milk-based oral nutrition supplement; ONS2, lactose-free oral nutrition supplement; PE formula, protein and energy enriched nutritional formula; sONS, standard oral nutrition supplement
*mean
**median

Figure 2. Effect of ONS consumption on daily weight gain in malnourished children

ONS administration could also help provide nutritional support to children needing intensive care to avoid acute and chronic malnutrition due to their restricted body reserves and their higher nutrient needs for growth and development (22). Eveleens et al (22) reported that administering ONS enriched with a protein and energy in infants below the age of 12 months with a prolonged paediatric intensive care unit (PICU) stay resulted in weight increasement between 3.28–9.04 g/kg/day (median 5.8). ONS with a high energy formula (containing 100 kcal/100 mL) was found to be more effective to prevent weight loss (-16 g vs -181 g, p=0.001) and improve nutritional status after surgery compared to ONS with a standard energy formula (containing 67 kcal/100 mL) (33). These findings are also supported by a research by El-Ganzoury et al (34) who found that two-week perioperative nutritional prehabilitation programs have significantly higher mean weight gain than those receiving one-week nutritional prehabilitation programs.

Different energy densities of ONS also demonstrated different effects on weight gain. Gradually enhancing caloric density can be beneficial in some children because children tend to be reluctant to have their feeding volume increased, yet they are recommended to receive an addition of 20-50% calorie intake for catch-up accretion in children with growth faltering (35) Soliman et al (26) reported that the use of high caloric density ONS (cONS) on older children and young adolescents (aged 10±4 years) resulted in significantly greater mean total weight gain per day after 6 months and 1 year, compared to standard ONS (sONS) group (14.13±7.78 vs 8.65±3.98 g/day and 11.6±6.58 vs 9.85±4.71 g/day, respectively). Another study by Scheeffer et al (23). In children under 2 years of age found that the mean daily weight gain was better in those receiving energy-enriched formula (EE formula) containing 1 kcal/mL compared to those receiving normocaloric formula containing 0.67 kcal/mL although the disparity was not statistically significant (16 g/day vs 10 g/day respectively, p=0.32). However, this is not always the case. Research in a community setting by Devaera et al (27) found no significant differences in total and daily weight gain over the 4-week intervention between children who received ONS with an energy density of 1.5 kcal/mL and 1.0 kcal/mL. A study by Clarke et al (20) also found no significant difference in median weight gain (7.2 g/kg/day vs 7.6 g/kg/day, respectively) between those who received nutrient-dense formula (NDF) and energy-supplemented formula (ESF). Similarly, Hubbard et al (24) reported that after 28 days of intervention, although cONS containing 2.4 kcal/mL resulted in a significant weight increase of 0.28 kg (p=0.007) from baseline while no significant weight increase was observed in those receiving sONS containing 1.5 kcal/mL, the differences in mean weight were not significant [cONS 19.6 kg (SD 6.9) vs sONS 15.5 kg (SD 8.1), Δ4.1 kg, per protocol] between cONS and sONS group. Thus, ONS with various energy densities can be tolerated and was found to be effective in improving malnourished children's weight.

Besides resulting in weight gain, ONS administration also results in WAZ improvements in the majority of studies found, as illustrated in **Figure 3**.



cONS, high-caloric density oral nutrition supplement; ESF, energy-supplemented formula; FS HEIF, full strength high-energy infant formula; good consumption ONS, consumption of more than 60% of recommendation; poor consumption ONS, consumption of less than 60% of recommendation; NDF, nutrient-dense formula; ONS, oral nutrition supplement; PE formula, protein and energy enriched nutritional formula; sONS, standard oral nutrition supplement; SW HEIF, stepwise high-energy infant formula
*mean
**median

Figure 3. Effect of ONS on WAZ changes in malnourished children from baseline

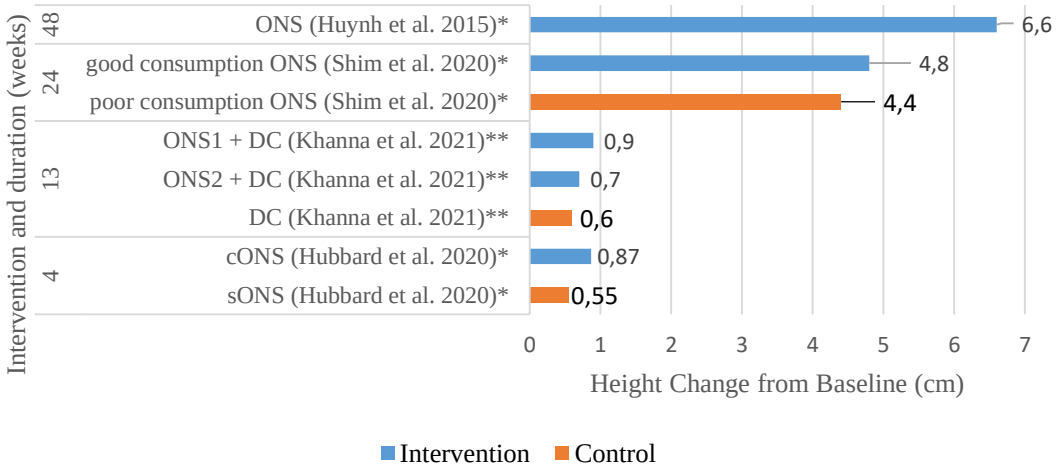
Evans et al.(36) reported that the introduction of high-energy formulas from day 1 over 2 weeks study period had a slight increase in WAZ, in contrast with the stepwise introduction over 3 days that had a slight decrease in WAZ (0.11 vs -0.07, respectively).Similarly, ONS enriched with protein and energy administered resulted in a 0.48 increase in mean WAZ.(22) ONS consumption >60% of the recommended dose of the formula also showed significant improvements in weight and WAZ compared to low consumption of ONS after 2, 4, and 6 months of supplementation (35). On the contrary, Hubbard et al (24) reported that cONS containing 2.4 kcal/mL resulted and sONS containing 1.5 kcal/mL resulted in similar WAZ changes and insignificant WAZ difference [cONS – 1.79 (SD 1.21) vs sONS -1.88 (SD 1.16), Δ0.09, per protocol]. Similarly, Clarke et al (20) also concluded that no significant difference in WAZ median improvement between NDF and ESF was present (0.29 vs 0.49, respectively, p=0.26).

.It should also be noted that ONS consumption compliance can also be affected by ONS energy density, in which children tend to have lower ONS volume intake when presented with high-energy density ONS (27). However, studies in our findings reported that both high energy density and low energy density had a high level of compliance (consumed more than 75%) (24,26,27).

Effect of ONS on Height and Height-for-Age Z-Scores (HAZ)

Height and height-for-age measurement represent linear growth that offers diagnostic parameters for chronic undernutrition (17). We found that among 4 studies (**Figure 4a**) with different intervention durations, ONS administration on malnourished children results in height gain (21,24,25,35). A study by Huynh et al (21) reported that long-term use of ONS and initial dietary counseling (DC) led to better linear growth during the maintenance growth phase and promoted ponderal growth in the catch-up phase, thereby promoting and sustaining proportional growth. This study also found that height continuously improved over the study period, with a mean rate of 0.5 cm every 4 weeks (21) Khanna et al (25) also found that after 90 days, ONS provision (milk-based or lactose-free) with additional dietary counseling (DC) resulted in a higher median height change compared to DC only, although insignificant (milk-based ONS 0.9 cm vs lactose-free ONS 0.7 cm).

A study by Hubbard et al (24) found that cONS with an energy density of 2.4 kcal/mL resulted in a significantly higher mean height and HAZ compared to sONS with an energy density of 1 kcal/mL after 28 days of intervention (mean height: 114.4 cm SD 18.2 versus 99.3 SD 24.4 Δ15.1 cm, per protocol, respectively; HAZ: cONS -1.25 (SD 1.19) versus -sONS -1.55 (SD 0.99), Δ0.3, per protocol). These findings were similar with the outcomes of a systematic review and meta-analysis of ONS intervention by Zhang et al (37) that found the administration of ONS had significant beneficial effects on height growth and weight gain. Although the majority of studies found that ONS administration results in height gain, most of studies found that there was a decrease in HAZ in malnourished children after different durations of ONS administration (**Figure 4b**).

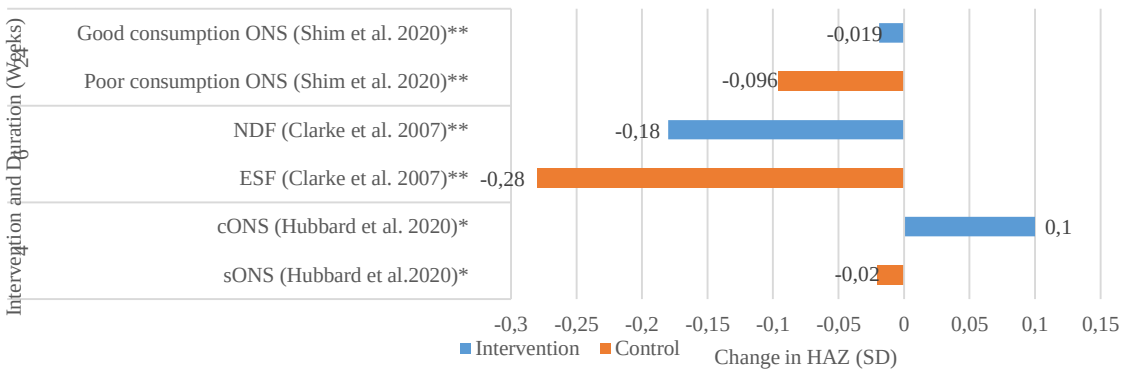


cONS, high-caloric density oral nutrition supplement; DC, dietary counselling; good consumption ONS, consumption of more than 60% of recommendation; poor consumption ONS, consumption of less than 60% of recommendation; ONS, oral nutrition supplement; ONS1, milk-based oral nutrition supplement; ONS2, lactose-free oral nutrition supplement; sONS, standard oral nutrition supplement
*mean
**median

Figure 4a. Effect of ONS on height changes in malnourished children

A study by Shim et al (35) found that ONS consumption either good or poor, had no significant difference in HAZ changes after 24 weeks. Clarke et al (20) also reported that 6 weeks supplementation using NDF and ESF showed a lower length z-score, but only the reduction in the ESF was statistically significant. Hubbard et al (24) also found that sONS administration also resulted in HAZ decrease. These findings were also in line with the study by Ghosh et al (38) that found a decrease in HAZ over the 90-day period ($p<0.05$), although the reduction of HAZ was lower in those receiving ONS and dietary counselling.

Only cONS administration resulted in an increase in HAZ as reported by Hubbard et al (24). Similarly, a study by Huynh et al (21) also found that ONS administration over 40 weeks resulted in a steady increase in height-for-age percentile (HAP) from 14.4 to 17.0. Meanwhile, no improvement in HAP from time to time was also demonstrated in the study by Khanna et al (25) It seems that the decreasing trend or stagnancy of HAZ in malnourished children receiving ONS might be due to the insufficiency of height increment to catch up with height recommendations according to the children's age.



good consumption ONS, consumption of more than 60% of recommendation; poor consumption ONS, consumption of less than 60% of recommendation; ESF, energy-supplemented formula; NDF, nutrient-dense formula; ONS, oral nutrition supplement
*mean
**median

Figure 4b. Effect of ONS Consumption on HAZ changes from Baseline in Malnourished children

Effect of ONS on Weight-For-Length/Height Z-Score (WHZ) and Mid-Upper Arm Circumference (MUAC)

According to the WHO and UNICEF, child nutrition status can be identified by weight-for-length/height z-score (WHZ) and/or mid-upper arm circumference (MUAC) (39). WHO protocols for SAM treatment intended to rapidly recover the WHZ and/or MUAC deficits (18). Thus, rapidly restoring WHZ and/or MUAC deficits could become a proxy in malnutrition treatment. We found three studies that explore the effect of ONS provision on WHZ changes (Figure 5). The majority of studies suggest that the provision of ONS may improve WHZ.

Study by Sheng et al (40) reported a significantly greater increase in WHZ among children who received nutrition supplement (NS) plus nutrition counselling (NC) than NS only. Similarly, a study by Khanna et al (25) showed a better weight-for-height percentile improvement after 90 days of daily ONS consumption with dietary counseling (DC), compared to DC only. Shim et al (35) also found that good ONS consumption resulted in a higher WHZ increase compared to those with poor consumption, although the difference is not significant. However, although both resulted in a WHZ increase above 0.4 SD, administering 1 kcal/mL or 1.5 kcal/mL ONS showed no significant differences in the increase of WHZ and the percentage of children who reached a WHZ of more than -1 over 4 weeks (27).

Meanwhile, several studies have also shown that the administration of ONS resulted in a significant MUAC enhancement (Figure 6). It should be noted that the daily MUAC gains were stated in median in the researches by Clarke et al (20), Evans et al (36), Khanna et al (25), and Moghadam et al (41) while stated in mean in the study of Shim et al (35).

A study of Clarke et al (20) showed a significant increase of median MUAC for all groups after 6 weeks, but the increase was not significantly different between the NDF and ESF groups, even when analysed by gender. Increased MUAC was found in the boys receiving NDF (0.4 cm/week) and in those receiving ESF (0.26 cm/week) (20). However, there was no significant difference in the MUAC change of the girls in either group (20). Similarly, in the study of Shim et al (35) the ONS provision for 6 months increased MUAC significantly ($p<0.001$), but there was no difference in MUAC changes between those who had good consumption of ONS and those who had poor consumption of ONS. The study of Evans et al (36) also showed that there was an increase of MUAC in both groups after 2 weeks, but the difference was not significant between the group receiving FS HEIF [median 0.5 (range 0-1.4)] versus SW HEIF [median 0.6 (range 0.1-1.5)]. Study by Khanna et al (25) found a significant difference in MUAC changes between the group receiving ONS versus the group receiving dietary counseling only, after 60 days and 90 days of intervention. Similarly, Moghadam et al (41) showed that ONS given over 12 weeks improved MUAC significantly ($p=0.001$).

Oral Nutrition Supplements and Length of Stay (LoS)

LoS is defined as a key indicator for the efficiency of an intervention or health system (42). There were 4 studies in this review that evaluated LoS in terms of hospital LoS and ICU LoS in patients given ONS (23,34,43,44). Minimising hospital LoS and ICU LoS were important in reducing resources utilised for patient care without sacrificing the quality of care. More resources such as human, material, and financial resources will be reduced for patients who have a shorter LOS in the hospital (45,46). Cui et al (43) compared LoS in the infant after congenital heart surgery given PE formula and standard formula group (S-group). The study showed that the differences of ONS formula did not significantly affect the hospital LoS and ICU LoS after congenital heart surgery (43). This result was different from other studies that showed shorter

LoS in the intervention group. El Ganzoury et al (34) evaluated the effect of perioperative nutritional prehabilitation duration on growth and surgical outcomes in malnourished children with CHD. The study found that the 2 weeks Perioperative Nutritional Prehabilitation (1 kcal/mL high energy-dense formula) can shorten hospital LoS and postoperative ICU LoS compared with the 1 week (34). Study by Scheeffer et al (23) also evaluated a reduction in hospital LoS and ICU LoS in the enriched formula group. After congenital heart surgery, the ICU LoS in 1 kcal/mL formula group was 8 days and the hospital LoS was 14 days while the ICU LoS in 0.67 kcal/mL formula group was 10 days and they discharged after 20 days. The reduction of LoS was about 28,67% in the energy-enriched group (23). The result in the study by Scheeffer et al (23) is in line with the result of Lakdawalla et al (44) that found an association between ONS use with a shorter LoS by 14.8%. From those result, it can be said that nutrition intervention with a proper duration and formula has a potential to decrease hospital LoS and ICU LoS. However, the LoS did not only vary by nutrition-related aspect, but it also influenced by other factors such as severity of illness and diagnostic diversity (46).

Oral Nutrition Supplements and Occurrence of Adverse Events (AEs)

Adverse events (AEs) are defined as unfavorable or harmful outcomes occurred during or after an intervention, but are not always caused by intervention (47). AEs can range from mild to severe and can be life-threatening. For this reason, AEs of ONS should be described. It will help to understand what a risk may have occurred after the intervention (48). There were 6 studies from 19 studies in this review that evaluated the AEs of ONS (Figure 7). The most frequently reported AEs were gastrointestinal symptoms in 5 studies (23–25,38,43), diarrhoea in 3 studies (23,40,43), vomiting in 3 studies (23,24,43), respiratory tract-related events, and pyrexia.

In the post-operative patients intervention, Cui et al (43) reported AEs including intolerable diarrhoea, intolerable vomit, and intolerable gastric retention. They reported lower AEs in the protein and energy-enriched formula group compared with the standard, with 0.49 of odds ratio (OR) (43). The percentage of AEs in the study of Cui et al (43) was higher than the percentage of AEs reported by Scheeffer et al (23) which gave an EE-Formula to the intervention group. In the setting of nutritional risk and picky eating children, the highest percentage of AEs was reported in the study of Sheng et al (40) that gave NC with a nutritional milk for intervention group. Sheng et al (40) reported AEs including upper respiratory tract infection, pyrexia, and diarrhoea. On the other hand, a lowest percentage of AEs was found in standard ONS by Hubbard et al (24). The study of Hubbard et al (24) reported AEs including gastrointestinal symptoms only when the others also reported respiratory tract events.

It has been understood that introducing high-energy feeding for infants has the risk of osmotic diarrhoea and vomiting (36). Therefore, it is necessary to evaluate the tolerance of the infants to the use of ONS. There were 4 studies in this review that reported the tolerance of ONS feeding (20,27,36,43). Indicators used in the studies include stool volumes, stool frequency or bowel actions, stool consistency, and vomiting. A study by Cui et al (43) showed significantly higher stool volumes and stool frequencies in 3 days after an intervention of protein-energy-enriched formula, compared with the standard. Clarke et al (20) reported no significant difference between the NDF and ESF in daily stool frequency and daily vomit. In a study by Devaera et al (27) there are no significant difference in stool characteristics, stool frequency, and consistency between 1.5 kcal/mL and 1 kcal/mL ONS group. Meanwhile, Evans et al (36) evaluated the feeding tolerance of a 1 kcal/mL formula for infants with growth faltering when administered at full strength from day 1 compared with stepwise introduction in 3 days. In the first 2 days, the number of bowel action in full strength introduction group was higher than the group receiving stepwise introduction (36). It appeared that the use of ONS in most studies was well tolerated and had no significant impact on vomiting or stool volume and frequency. However, this result should be interpreted carefully as it was not stated in the studies whether the adverse events are caused by ONS administration or as a result of the disease.

Cost-Effectiveness of ONS Use for Child Malnutrition

The cost-effectiveness of ONS should not be overlooked in the discussion as it could give insights into whether the cost of prescribing ONS to treat child malnutrition is worth the health benefits. The cost-effectiveness of ONS could be determined by comparing the cost of child malnutrition treatment using ONS and the health benefits of ONS use in malnourished children. When determining the cost of child malnutrition treatment using ONS, using the societal perspective by taking account direct medical, direct non-medical (e.g. transportation, day care for siblings), indirect (e.g. time lost from work of caregivers), and intangible (e.g. pain and suffering) costs are advised to gain results as a whole (49).

To our knowledge, studies that examined the cost-effectiveness of ONS in malnourished children are scarce. With the assumption that hospitalised children who received ONS were malnourished or at risk of malnutrition, we only found one study that explored the cost-effectiveness of ONS in malnourished children. Lakdawalla et al (44) conducted a retrospective analysis in the United States including 557,348 hospitalised children aged 2-8 years whose ONS indications were not stated. The study reported that the use of ONS was associated with an $8568 (95% CI, $8415-$8723) or 66,8% increase of episode cost from $12,833 to $21,401.(44) However, an instrumental variable (IV) analysis of a matched sample of 11,031 episodes showed that hospitalizations with ONS use resulted in a 9.7% lower cost [$16,552 vs $18,320; $1768 (95% CI, $1924-$1612)]. It was estimated that $1768 of episode cost was saved due to ONS use, which includes any avoided complications and is net of the cost of providing ONS. In the study, it was then estimated, based on reports that more than 3 million children were hospitalised nationally in the United States every year, assuming that 1.09% of the patients received ONS, and assuming that the sample in their study was nationally representative, ONS use among paediatric inpatients were associated with a total cost savings of approximately $57.8 million annually (44).

The cost-effectiveness of ONS may be due to the lower administration cost of ONS. This is supported by findings by Marino et al (50) that found that the total cost of administering ONS in the form of energy-dense ready-to-use infant feed (RTU formula) was lower than administering fortified powdered infant formula (PIF) in hospitalised undernourished infants aged < 12 months. RTU formula indeed had a higher actual cost compared to PIF with sunflower oil and PIF with medium triglyceride oil (MCT) (€1.62/100 mL, €0.18/100 mL, and €0.45/100 mL, respectively). However, when preparation and delivery costs were accounted for, the cost to provide 800 mL of feed per day is lower for RTU formula compared to PIF with sunflower oil and PIF with MCT (€12.51 vs €16.52 and €19.61) (50).

Other studies that examined the effectiveness of ONS in malnourished children mostly only report its medical-related outcomes without performing its cost-effectiveness analysis nor its cost analysis, yet those medical-related outcomes could still offer insights about the effect of ONS administration on hospitalisation cost. Improved medical-related outcomes such as shorter duration of mechanical ventilation (34), shorter ICU stay (34) shorter total duration of hospital stay (23,34), and less frequent antibiotic use (23) due to longer duration of ONS administration in infants suffering moderate or severe malnutrition (determined by WAZ ≥ -2) (34) and 30 days of EE ONS administration in 59 children aged < 2 years old after congenital heart surgery (23) could potentially result in lower direct medical cost, ergo, in lower children hospitalisation cost.

Despite the lack of evidence in the population of malnourished children, the cost-effectiveness of ONS use has been demonstrated in other populations. Economic modelling of ONS administration in adults by NICE reported that ONS has a cost per QALY €8,024 and is cost-effective (51) Caccialanza et al (52) found that ONS has positive and encouraging cost-effectiveness in paediatric and adult cancer patients. Meanwhile, a study by Freijer and Nuijten (53) in patients undergoing abdominal surgery in the Netherlands found that the use of ONS reduced the costs with a €252 (7.6%) cost saving per patient. The hospitalisation costs were

reduced from €3,318 to €3,044 per patient, which was an 8.3% cost saving and corresponds with 0.72 days reduction in length of stay (53). It was estimated that the use of ONS would lead to an annual cost saving of a minimum €40.4 million per year.

The findings of this review must be interpreted carefully since this review has several limitations. First, several studies in this literature review have at-risk of malnutrition children as its subject instead of clinically-diagnosed malnourished children, which such condition is making the studies prone to other variables that might confound the results. Second, the differences in study interventions, the duration of ONS administration, ONS consumption compliance, the subjects' age, and the initial conditions of subjects in existing studies make it difficult to compare the study results. Therefore, further studies exploring the effect of ONS administration strictly on clinically-diagnosed malnourished children should be conducted. More studies on the topic could be the basis for deciding the optimum duration and dose of ONS administration to support malnourished children. Furthermore, further research on the cost-effectiveness of ONS administration in malnourished children is needed to help policymakers decide whether an ONS prescription is advisable for child malnutrition treatment.

CONCLUSIONS AND RECOMMENDATIONS

The majority of studies in this literature review found that ONS administration as one type of Food for Special Medical Purposes (FSMPs) in malnourished children results in expected growth outcomes, including weight and height gain and improvements in WAZ, WHZ, and MUAC, but not in HAZ. While longer ONS administration and higher density of ONS administered in malnourished children results in shorter LoS, ONS administration is also related to the occurrence of several AEs. Meanwhile, despite the limited evidence on the cost-effectiveness of prescribing ONS to malnourished children as presented in this literature review, it is suggested that ONS might potentially be a cost-effective solution for child malnutrition treatment since ONS has a relatively low cost, improves medical-related outcomes that could potentially result in lower direct medical cost, and is found to be cost-effective in other populations.

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Declaration of interest.

The authors declare that they have no competing interests.

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