Clinical Nutrition 47 (2025) 157–168

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

The effects of nutritional supplementation for children and adolescents with sickle cell disease: A systematic review and meta-analyses

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ARTICLE INFO

Article history:
Received 25 September 2024
Accepted 13 February 2025

Keywords:
Sickle cell disease
Dietary supplements
Children
Adolescents
Systematic review
Meta-analysis

SUMMARY

Background & aims: Sickle cell disease (SCD), a neglected chronic genetic blood disorder that severely impacts the pediatric population, often leading to premature death, is associated with compromised nutritional status. This study aimed to evaluate the effect of nutritional supplementation in SCD-related complications.

Methods: A systematic review with searches in PubMed, Scopus and Web of Science was performed. Randomized controlled trials (RCT) assessing diet or supplements as complementary therapy for children and adolescents with SCD were included (PROSPERO:CRD42024532369). The data for outcomes of interest (efficacy, safety) were pooled by means of pairwise and network meta-analyses with ranking (p-score) analysis. The results were presented as odds ratio or mean differences with 95 % confidence intervals (NMAstudio2.0).

Results: Twenty RCTs were included (2002–2023) (n = 2058), analyzing 9 dietary supplements on different regimens. All patients were in use of hydroxyurea as active treatment. Supplementation with fatty acids (n = 3 studies) and L-arginine (n = 4) presented higher efficacy and safety, significantly improving pain intensity, vaso-occlusive crises (VOC) and inflammation when compared to usual care/placebo ($p < 0.05$). Vitamin D3 (n = 6) at different dosages may reduce respiratory complications and length of hospital stay, yet further studies are needed to confirm its significant effects. Evidence is limited and of poor quality regarding the effects of add-on vitamin A (n = 2), magnesium sulfate (n = 2) and zinc (n = 4) for this population.

Conclusions: The complementary use of certain supplements (fatty acids, L-arginine, vitamin D3) can enhance the management of VOC and improve patients' physiological functions. These supplements are often affordable and can contribute towards the reduction of opioid use and shorten patients' hospital stays - especially in low/middle-income countries where resources are scarce. Although further studies are needed to refine these findings (e.g., appropriate doses/regimens), practical guidelines and decision-makers may benefit from updated evidence.

1. Introduction

Sickle cell disease (SCD) is a genetic blood disorder characterized by the production of abnormal hemoglobin S (HbS) due to a mutation in the β-globin chain. This mutation results in distorted, C-shaped erythrocytes, leading to a range of symptoms and clinical

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https://doi.org/10.1016/j.clnu.2025.02.016

consequences, including hemolytic anemia, recurrent infections, painful vaso-occlusive crises (VOC), strokes, acute chest syndrome (ACS), and organ damage [1–3].SCD is an autosomal recessive Mendelian disorder in which homozygous individuals (HbSS) typically experience the most severe symptoms, while heterozygous individuals (HbAS) are usually asymptomatic. Other genotypes, such as HbSC and HbSβ-thalassemia, can result in varying clinical phenotypes, ranging from mild to severe. Besides the influence of SCD genotype, factors such as the presence of α-thalassemia and hemoglobin F levels also affect the condition's severity and should be considered when evaluating the efficacy of interventions [1–3].

Although considered a neglected disease, the global burden of SCD is increasing and now affects an estimated 20 million people worldwide [4]. This condition is especially life-threatening in children under five, with mortality rates reaching up to 50 % in Africa and as high as 90 % in some Sub-Saharan countries, where around 500 children die prematurely premature every day due to delayed diagnosis and lack of access to comprehensive care [5].

A definitive cure for SCD remains a subject of debate. While curative options such as bone marrow or stem cell transplantation exist, they are costly and difficult to access. Other non-pharmacological treatments as chronic blood transfusions can also be used to reduce symptoms; however, these procedures are associated with several challenges including patients' eligibility, therapy access, and related complications. Moreover, although the pipeline for SCD has recently expanded from hydroxyurea to include newer [yet more expensive] drugs such as voxelotor and crizanlizumab, there remains a significant unmet need for alternative and complementary treatments – especially for the pediatric population [3,6,7].

Nutritional imbalances are common in SCD, often resulting from poor dietary intake and absorption (e.g., undernutrition). This deficiency has recently been recognized as a significant risk factor to increased SCD severity [8,9], as it adversely affects clinical outcomes, overall patients' well-being, and vital processes (e.g., children's growth) through mechanisms of chronic inflammation, immune system dysfunction, and oxidative stress [2,10]. This scenario has led to a growing interest in promoting dietary strategies as a complement to adequate treatment of SCD. Additionally, integrating this approach into medical services and care could be particularly valuable in low- and middle-income countries, where resources are scarcer [11].

However, updated comparative evidence on the effects of different supplements for managing SCD comes primarily from few clinical trials and preliminary pairwise meta-analysis, frequently limited to assess specific physiological effects (e.g., hemolysis) or restricted to some classes of nutrients/substances (e.g., vitamins) [12–17]. As results are often incomplete and conflicting, the benefit, or otherwise, of such supplementation remains uncertain for this population [2,14,15,18,19].

Thus, given these literature gaps, this study aims to synthesize the evidence on the role of different dietary supplementation regimens as complementary approaches for managing SCD complications in children and adolescents by means of a broad systematic review with network meta-analysis.

2. Material and methods

This study was performed in accordance with the Cochrane Collaboration recommendations and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [20–22]. The protocol is available in PROSPERO (CRD42024532369). Two authors independently conducted all steps of the studies' selection and data extraction. A third author was consulted in case of discrepancies (BCO, DG, NEK).

2.1. Search strategy and eligibility criteria

A comprehensive literature search was conducted to identify relevant records in PubMed, Scopus and Web of Science without timeframe nor language filters (last updated on August 1st, 2024) to avoid selection bias. A manual search in the reference lists of included studies, other systematic reviews and registration databases (clinicaltrials.gov) was also performed was also conducted to identify additional relevant studies (published as peer-reviewed articles) and to complement any data not covered by the scientific publications included in the review. The complete search strategies for each database are available in supporting information material.

Registers retrieved from the databases were allocated into Rayyan [23], where duplicate records were removed. Two reviewers independently performed the screening (title/abstract reading) and full-text evaluation of the studies also in this platform. This systematic review included articles meeting the following criteria (PICOS' acronym).

- Population: children or adolescents (<18 years) diagnosed with SCD, regardless of previous treatment (previously treated or naïve patients). Studies including young adults (ages 19 to 24) were included only if this population represented less than 20 % of the participants and the mean age was inferior to 18 years old.
- Intervention: dietary supplements or nutritional interventions (food intake) used as complementary approaches to prevent or mitigate SCD-related symptoms and complications - either on their own or with other active treatment regimens.
- Comparator: any other supplement or placebo or no treatment.
- Outcomes: studies assessing at least one of the following outcomes as SDC-related complications such as pain, VOC, ACS (frequency, duration, intensity); analgesics use; hospital admission and length of stay; patients' nutritional status, physical and sexual growth; interventions' safety (adverse events and tolerability) and patients' health-related quality of life (QoL).
- Study design: randomized controlled trials (RCTs) published as peer-reviewed articles.

Studies focused on curative approaches (e.g., transplantation, gene therapy), pharmacological treatments (e.g., drugs), blood transfusion, supportive care (e.g., analgesics), assessments of malaria incidence/prevalence, or other study designs (such as observational studies, reviews, pharmacokinetic studies, or non-randomized trials) were excluded, as were studies without results and articles fully written in non-Roman characters (e.g., Cyrillic, Arabic, Chinese).

2.2. Data extraction and quality assessment

A standardized form Microsoft Excel (Redmond, WA) was used to extract information on: articles' overall data (authors name, year of publication, country, study design, sample size, patients' characteristics [age, sex, diagnosis]), details of the intervention and comparators (regimen, duration, follow-up) and outcomes results.

The risk of bias of the included RCTs was assessed using the Cochrane Collaboration's tool for assessment of risk of bias (RoB-2.0) [20]. The tool evaluates the risk of bias for each outcome of interest, based on the domains of selection, performance, detection, attrition and reporting bias. The results of each domain are pooled to provide an overall bias by outcome: low risk of bias, some

concerns or high risk of bias. This assessment was performed by two authors independently.

2.3. Statistical analyses and data synthesis

A narrative synthesis of the included studies, based on type of intervention, population characteristics and outcome of interest was performed. When possible, pairwise and network meta-analyses (integrating both direct and indirect evidence within a single model), as recommended by the International Society for Pharmaeconomics and Outcome Research (ISPOR) [24,25] were conducted to compare the effects among different treatments. For the pairwise meta-analyses (intervention vs. placebo), both Mantel-Haenszel and Inverse of Variance statistical methods were tested using random-effect models. Dichotomous outcomes were reported as odds ratio (OR) and continuous data as standard mean differences (SMD), both with a 95 % confidence interval (CI). Between-study heterogeneity was measured using τ^2 index and considered relevant when >50 %; $p < 0.05$. For the network meta-analyses, transitivity assessments were performed before including the studies in the network by comparing the population, interventions, controls, and outcome definitions among trials. A standard heterogeneity parameter was assumed for all comparisons. By means of a random-effect consistency model, pooled-effects sizes (reported as OR or SMD with 95 % confidence intervals - CI) were obtained for each treatment comparison within an outcome of interest. A conservative analysis of non-informative priors was used. To increase the estimated precision of the relative effect sizes of comparisons in the network, rank analyses of all treatment options were built for each outcome (data reported as p-score). To assess the robustness of the networks, node-splitting analyses were conducted, testing the inconsistency of evidence on specific nodes (p-values below 0.05 indicate significant differences between the pooled direct and indirect evidence for a particular comparison). Analyses were performed in NMAStudio2.0 [26]. When necessary, data were additionally calculated or converted from the raw information available in the trials using the tool PlotDigitizer [27].

2.4. GRADE

The certainty of the evidence was determined with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [28]. Outcomes for a given comparison were rated as with high quality and then downgraded based on five domains (risk of bias, imprecision, indirectness, heterogeneity and publication bias). The main comparator was fixed as placebo.

3. Results

We retrieved 951 records from the databases of which 669 were screened after duplicates removal, with 601 being considered irrelevant to the study. From the 61 articles read in full, 36 were excluded due to wrong population, study design, wrong intervention and lack of outcome of interest (see complete list of excluded studies with reasons for exclusion at supporting information material). Finally, 25 records [29–53] referring to 20 RCTs met the eligibility criteria and were included for synthesis (PACTR201611001864290 trial was reported in 3 different articles [48–50]; V-FIT trial (NCT01718054) was published by Cox, 2018 [34] and Marealle, 2018 [45] and ISRCTN80844630 trial was reported in two different publications [35,36]. See the complete PRISMA flowchart in Fig. 1. No record was included after manual search.

The characteristics of the included RCTs are presented in Table 1. These trials were published between 2002 and 2023, mostly by authors from the USA (n = 12; 60 %), followed by Nigeria (n = 3; 15 %); 6 trials (30 %) were multicenter. Half of the trials were restricted to patients with homozygous alleles (HbSS genotype). In the studies also including patients with sickle cell trait (HbAS genotype) or beta thalassemia, the homozygous HbSS genotype comprised at least 58 % of the randomized patients. Three trials [33,38,39] included healthy patients (with no diagnosis of SCD) for baseline comparisons (this data was not analyzed as part of this systematic review). Overall, 2058 participants were assessed in the included RCTs, with a mean age of 9.66 years old, ranging from 1 to 24 years old. Seventeen trials (85 %) evaluated dietary supplements as vitamins (A, D2 D3), omega-3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]), L-arginine, magnesium sulfate ($MgSO_4$) and zinc in different regimens and routes of administration. The other three studies assessed lime juice, RUSF (ready-to-use-supplementary food enhanced with arginine and citrulline) and SC411 (a purified DHA supplement with delivery system). Placebo was assessed as comparator in most studies (n = 13; 65 %). Duration of supplementation varied between 5 days and 12 months. In all included studies, all patients were treated with hydroxyurea as the baseline approach (both in the interventions and placebo groups). The most reported outcomes were pain – assessed using the Visual Analogic Scale (VAS), a validated scale for pain intensity, ranging from 0 to 10 [54], VOC, length of hospital stay, adverse events, changes in molecular serum levels and anthropometric measurements related to growth (Z-scores and body mass index [BMI]).

Results from the risk of bias assessment of the included RCTs are available in supporting information material. Studies were overall well performed and reported, with half of them having a low risk of bias for all outcomes [29,31–33,42–44,47–50,52]. Almost all trials (n = 18; 90 %) were judged as having low risk of bias for the domain of randomization; only two (10 %) had some concerns in this criterion as authors lack on informing about patients' allocation process [30,53]. Three (15 %) [34,46,51] and one (5 %) [35] studies presented some concerns and high risk of bias, respectively, on the domain of deviations from intended interventions, as information on study blinding and subjects' removal from the study were scarce. Few studies (n = 4; 20 %) [35,37,38,51] presented important methodological concerns regarding missing outcome data. All RCT were assessed as having a low risk of bias on the domain of outcome measurements for the objective outcomes. Conversely, seven trials (35 %) did not provide a study protocol or register, which may impact on the reported results (domain 5) [30,35,38,40,41,51,53]. No other potential sources of bias were found in the studies.

We were able to build four meta-analyses for the following outcomes: overall safety as incidence of any adverse event (n = 6 trials) [34,37,42,46,50,52], VOC (n = 3 trials) [37,43,52], length of hospital stay (LOS) (n = 7 trials) [32,40,42,43,46,50,52] and pain score – VAS scale (n = 5 trials) [29,43,46,48,52]. Network plots for each outcome are shown in Fig. 2, where each node represented one intervention, and the connecting lines represented direct comparisons. Between-trials heterogeneity was found to be low ($I2 < 20$ %) and no inconsistency was detected in the networks (see node-split analysis in supporting information material). The forest plots referring to the comparison of the interventions vs. placebo (i.e., the most reported control) are presented in Fig. 3. Complete network meta-analysis results are available in supporting information material.

Both the pairwise and network meta-analyses on overall safety showed no significant differences between L-arginine (100 mg), the combination of arginine/citrulline, omega fatty acids (DHA), $MgSO_4$

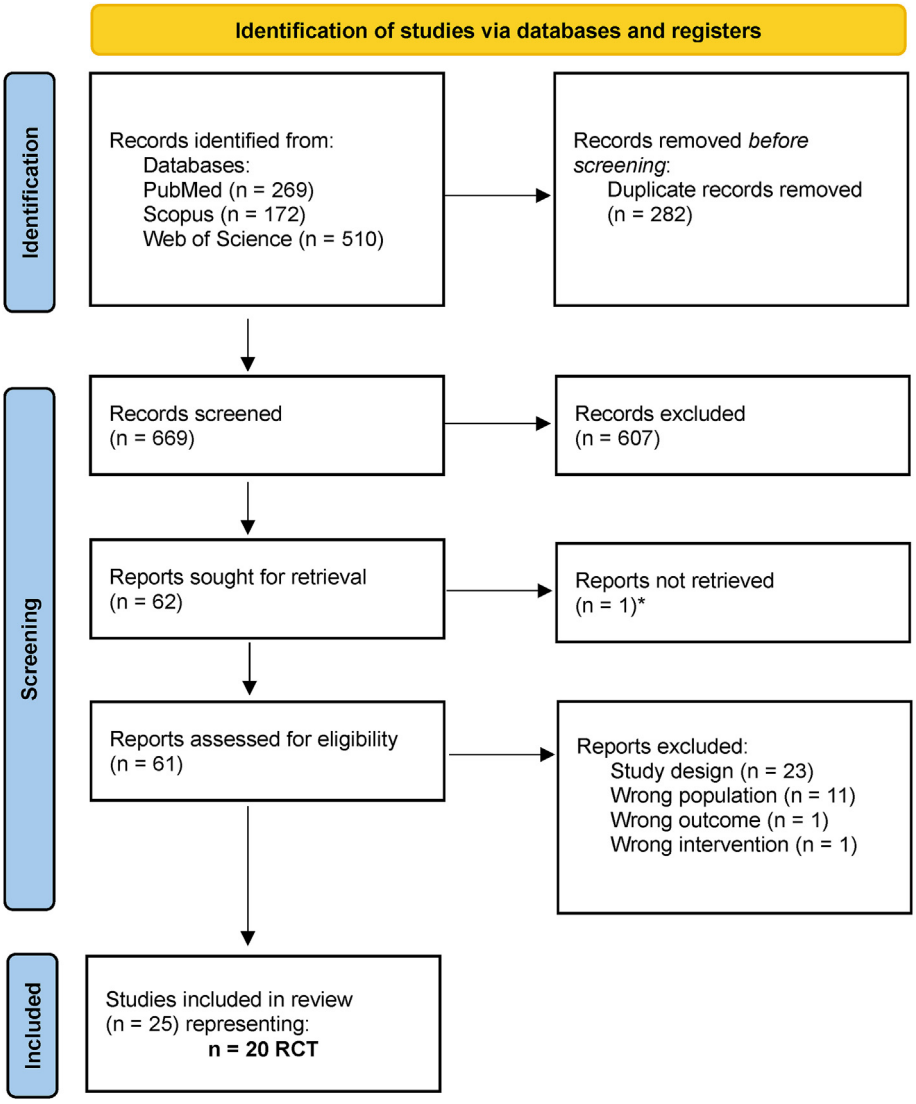

Fig. 1. PRISMA flowchart.

and placebo (other supplements were not evaluated for this outcome - no data available in the trials). Yet, according to the probability rank, the use of $MgSO_4$ may be more associated with adverse events (p-score 77 %) when compared to the other agents (values ranging 43–49 %) and placebo (32 %) (see Table 2). Very common events following the use of $MgSO_4$ [42] included pain infusion (incidence of around 15 %) and nausea/vomiting (between 5 and 10 %). Depending on the dose, L-arginine [34,46,50,52] can lead to mild yet well tolerated adverse events as headache (incidence around 20–40 %), nausea (20–45 %), abdominal pain (20–25 %), anemia and fever (around 20 %). Vitamin D3 [43,44] and zinc can frequently cause fever (20–30 % of cases reported in the trials), while omega fatty acids may cause anemia (incidence around 15 %). No severe nor life-threatening adverse events potentially associated with these supplements were reported. Other events including rash, stroke and death were uncommon (incidence around 1 %) (see Table 3 for the most reported adverse events).

The supplementation with L-arginine 100 mg led to a statistically significant reduction of 0.65 points [95 % CI −1.27, −0.02] in the pain score (VAS) in hospitalized patients during VOC compared to placebo ($p < 0.05$). L-arginine 200 mg and fatty acids (EPA and DHA) also reduced pain (−0.25 points [95 % CI −1.22, 0.72] and −0.23 points [95 % CI −1.20, 0.75], respectively) (see Fig. 2). No further differences among interventions were observed for this outcome (see complete network meta-analyses in supporting information material). Although no significant differences were found between interventions on the number of VOC cases *per se*, supplementations with vitamin D3, fatty acids (DHA) or L-arginine 100 mg potentially reduced the incidence of this event when compared to placebo (OR 0.23 [95 % CI 0.04, 1.31]; OR 0.38 [95 % CI 0.12, 1.18]; OR 0.65 [95 % CI 0.10, 4.12], respectively) (see Fig. 2). Vitamin D3 and L-arginine 100 mg were also associated with reductions in hospital LOS of 0.15 days [95 % CI −0.79, 0.49] and 0.10 days [95 % CI −0.38, 0.18] days compared to placebo, respectively (see Fig. 2 and complete network meta-analyses available in supporting information material). A decrease in respiratory events (up to 50 %) was reported after one year of bolus doses of vitamin D 100,000 IU monthly. Overall, L-arginine 100 mg was ranked as the best alternative to reduce pain score (86 % probability) and hospital LOS (72 %), alongside with vitamin D3 (around 70 %). Both vitamin D3, omega fatty acids (DHA) and L-arginine 100 mg were fairly associated with less incidence of VOC (see Table 2).

Table 1
Overall characteristics of the included studies (n = 20).

Author, year	Trial	Country	Multicenter	Study design	Genotype	Interventions	N	Mean age (SD)	% Male	Treatment duration	Primary outcome
Abdelhalim, 2022 [29]	NCT04301336	USA Saudi Arabia	Yes	RCT	HbSS	EPA (300–400 mg/day) + DHA (200–300 mg/day) + usual care	50	8.5 (4.0)	60	10 months	Number of painful crises
						Vitamin D (1500–3500 IU/day) + usual care	50	10.5 (3.5)			
						Usual care	50	11 (5.5)			
Adegoke, 2013 [30]	NR	Nigeria	Yes	RCT	NR	Lime juice + usual care	58	4.74	50.4	6 months	Significant painful crises, febrile illnesses, presence of hepatomegaly, splenomegaly, pallor, jaundice, hospital admissions and blood transfusions
						Usual care	55	(2.13)			
Adekunle, 2021 [31]	PACTR20180 3003160262	Nigeria	No	RCT	NR	Vitamin D2 (5000 IU/week)	69	1–18	NR	6 weeks	Effect of oral vitamin D on serum 25(OH)D and calcium levels and adverse events
						Vitamin D3 (50,000 IU/week)	70				
Brousseau, 2015 [32]	NCT01197417	USA	Yes	RCT	HbSS (>90 %)	IV MgSO4 (40 mg/kg)	101	13.4	48.5	6 doses/discharge	Length of stay from the time of first drug infusion until 12 h after the last IV opioid dose or time of discharge
						Placebo	103	(4.6)			
Brownell, 2020 [33]	NCT03632876	USA	No	RCT	HbSS	Vitamin A (3000 IU/day)	10	13.8	59	8 weeks	Changes in serum retinol, RBP and TTR after supplementation with vitamin A
						Vitamin A (6000 IU/day)	11	(3.3)			
Cox, 2018 [34] Marealle, 2018 [45]	V-FIT (NCT01718054)	United Kingdom	No	Cross-over RCT	HbSS	RUSF-v (fortified with arginine and citrulline)	61	10.01	59.7	12 months	Differences in mean plasma aminoacid concentrations between groups and height and BMI as Z-scores-for-age combined
						RUSF-b (base formula)	58	(1.25)			
Daak, 2013 [35] Daak, 2015 [36]	Current controlled Trials ISRCTN80844630	United Kingdom/ Sudan	No	RCT	HbSS	EPA (39 mg) + DHA (277,8 mg)	67	8.1 (4.6)	56.4	12 months	Annual rate of vaso-occlusive crises
						Placebo	61	7.8 (5.5)			
Daak, 2018 [37]	SCOT (NCT02973360)	USA	Yes	RCT	HbSS (76 %)	SC411 (20–60 mg/kg)	50	11.8 (2.6)	52.4	8 weeks	Change in the total blood cell membrane DHA and EPA concentration
						Placebo	17	12.6 (3.7)			
Dougherty, 2015 [38] Dougherty, 2020 [39]	NR	USA	No	RCT	HbSS	Vitamin D3 (4000 IU/day)	12	10.8 (4.0)	43	12 weeks	Changes in serum 25(OH)D levels, anthropometric measurements, hematological parameters and adverse events
						Vitamin D3 (7000 IU/day)	9				
Dougherty, 2012 [40]	NR	USA	Yes	RCT	HbSS	Vitamin A (1000–2000 IU/day)	23	7.7 (2.9)	52	12 months	Number of hospitalizations over 12 months
						Vitamin A (1000–2000 IU/day) + zinc (10–20 mg/day)	18				
						Placebo	21				
Fung, 2002 [41]	NR	USA	No	RCT	HbSS	Zinc (10 mg/day)	20	7.1	52.6	12 months	Changes in serum zinc levels, anthropometric measurements, dietary intake and hematological parameters
						Placebo	22	(1.6)			
Goldman, 2013 [42]	NCT00313963	Canada	No	RCT	HbSS (58.8 %)	IV MgSO4 (100 mg/kg)	51	12.4	46	Discharge	Reduction in length of stay
						Placebo	53				
Gregoire-Pelchat, 2021 [43]	NCT03417947	Canada	No	RCT	HbSS (72 %)	Vitamin D3 (300,000 IU single dose) + vitamin D3 (1000 IU/day)	18	9.4 (3.4)	60.5	3 months	Changes in serum 25(OH)D to sufficient levels after 3 months
						Placebo + vitamin D3 (1000 IU/day)	20	10.8 (3.8)			
Lee, 2018 [44]	ViDAS trial (NCT01443728)	USA	No	RCT	HbSS (87 %)	Vitamin D3 (100,000 IU/month)	31	9.9 (3.9)	48	12 months	Annual rate of respiratory events, asthma exacerbations or ACS
						Vitamin D3 (12,000 IU/month)	31				
Morris, 2013 [46]	NCT01796678	USA	No	RCT	HbSS (73 %)	Oral or IV L-arginine (100 mg/kg)	26	13.9 (4.0)	48	15 doses/discharge	Length of stay
						Placebo	28				
Namazzi, 2023 [47]	ZIPS (NCT03528434)	Uganda	No	RCT	HbSS	Zinc (10 mg)	124	32.3 (13.4) months	47.2	12 months	Incidence of severe or invasive infections
						Placebo	124	32.6 (13.8) months			
Onalo, R. Cilliers,	Pan African clinical trial	Nigeria	Yes	RCT	HbSS	L-arginine (100 mg/kg)	35		56	5 days/discharge	
						Placebo	33				

(continued on next page)

Table 1 (*continued*)

Author, year	Trial	Country	Multicenter	Study design	Genotype	Interventions	N	Mean age (SD)	% Male	Treatment duration	Primary outcome
A., 2021 [48] Onalo, R. Cooper, P., 2021 [50] Onalo, 2022 [49]	Registry (PACTR20161100 1864290)							10.7 (3.2) 10.5 (3.5)			Changes in analgesic use (MQS score) and blood pressure dynamics during vaso-occlusive crises
Osunkwo, 2012 [51]	NR	USA	No	RCT	HbSS	Vitamin D3 (40,000 −100,000 IU/ week) + usual care (vitamin D3 200 IU + calcium 500 mg/ day) Placebo + usual care (vitamin D3 200 IU + calcium 500 mg/ day)	20 19	13.2 (3.1)	41	6 weeks	Changes in serum (25OHD) levels and pain intensity, quality of life and adverse events
Reyes, 2022 [52]	NCT02536170	USA	No	RCT	HbSS (65 %)	IV L-arginine (IV L-arginine (200 mg/kg) Placebo	36 36 36	12.6 (3.82)	48	Discharge	Total amount of parenteral opioid use in mg/kg of IV morphine equivalents
Zemel, 2002 [53]	NR	USA	No	RCT	HbSS	Zinc (10 mg/day) Placebo	20 22	7.1 (1.6)	52.4	12 months	Changes in serum zinc and copper levels, anthropometric measurements, growth and dietary intake

ACS: Acute Chest Syndrome; BMI: body-mass index; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; IU: international unit; IV: intravenous; $MgSO_4$: magnesium sulfate; MQS: Medication Quantification Scale; NR: not reported; RBP: retinol-binding protein; RCT: randomized controlled trial; RUSF: ready-to-use-supplementary food; SD: standard deviation; TTR: transthyretin; USA: United States of America; 25(OH)D: 25-hydroxy vitamin D.

Five RCTs additionally assessed analgesic use during VOC in hospitalized patients, with three of them supporting the efficacy of L-arginine supplementation in reducing opioid consumption (no meta-analyses performed given the heterogeneity of data). In Reyes et al., 2022 [52], patients receiving IV L-arginine (100 mg and 200 mg) used less IV morphine equivalents compared to the placebo group (1.77 mg/kg and 1.95 mg/kg, respectively, vs. 2.36 mg/kg). Similarly, Onalo et al., 2021 [50] found lower morphine equivalent usage in the L-arginine group (3.8 mg/kg) compared to placebo (5.1 mg/kg), which is also corroborated by Morris et al., 2013 [46] (1.9 mg/kg vs. 4.1 mg/kg, respectively). Other RCTs evaluated the impact of zinc (n = 3) [41,47,53] and vitamin A (n = 2) [33,40] supplementation on children's growth, using the height-for-age Z score [55]. Zinc supplementation showed an increased height in SCD patients after one year of treatment ($p = 0.004$) [53], but there was no significant difference in Z-score between the intervention and placebo groups ($p > 0.05$). No further relevant clinical effects of these supplements were reported in the studies.

Few trials assessed patients' QoL, mostly measured as school absence days of children and adolescents in school age. Patients treated with omega fatty acids presented a score of 0 day (IQR 7.6) vs. 4.3 days (IQR 21.1) in the placebo group after one year of treatment [35]. Daak et al., 2018 [37] similarly reported that the use of SC411 — a purified fatty acid DHA - can reduce school absence and visits to medical facilities in comparison to placebo, although statistical meaningfulness was not achieved. The use of MgSO4 [32] was not related with improved QoL ($p > 0.05$) in this population. Evidence on the effects of vitamins in this outcome were conflicting; while one trial showed that high dose of vitamin D3 significantly improves pain, fatigue and QoL in children with SCD by the PROMIS pediatric short forms and Paediatric Quality of Life Inventory [PedsQL version 4.0], other two studies found no significant effects [39,43,51].

The GRADE assessment comparing different interventions to placebo on the main reported outcomes showed a low certainty in the evidence from the outcomes LOS, VOC and pain score, and a moderate certainty regarding the incidence of adverse events. These results are due the methodological quality of the trials, the small number of studies, the limited sample size, and imprecision of confidence intervals. This means that new published trials can possibly change the evidence regarding to the use of supplements for these SCD-related complications (see full assessment at supporting information material).

4. Discussion

This systematic review with network meta-analysis synthesized the evidence from 20 RCT assessing 9 nutritional supplements as add-on therapies for managing SCD in children and adolescents. Given that sickling dynamics may vary across SCD phenotypes, treatments should be tailored to each patient's needs. While HbAS typically requires no active treatment beyond lifestyle guidance, both HbSS (the most prevalent genotype in the included trials) and HbSC require similar management strategies, though HbSS is often associated with more frequent and severe crises [56,57]. Hydroxyurea, used as the base treatment in all included trials, along with supportive care, is the only commonly employed approach, with blood transfusions considered when necessary [3]. Therefore, updated evidence on alternative management options for SCD is critical, given the existing gaps in knowledge, as well as the potential for integrating nutrition into SCD healthcare services, such as recommended daily allowances, dietary reference intakes and supplements regimens for specific populations [9,58] - especially in low- and middle-income regions with higher frequencies of food insecurity and housing instability (i.e., social determinants of health) [59].

Previous studies demonstrated that patients with SCD commonly have multiple nutrient deficiencies which are directly associated with increased disease severity [60].In Canada, over 55 % of a cohort of children with SCD had zinc and vitamins deficiencies, which were associated with increased number of pain crises ($p = 0.001$) and hospitalization ($p = 0.01$) [61]. In another

Fig. 2. Network meta-analyses plots for the outcomes of interest. The nodes represent different interventions connected by lines (direct comparisons). DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; $MgSO_4$: magnesium sulfate; vitA: vitamin A; vitAzinco: vitamin A/zinc; vitD3: vitamin D3.

observational study (n = 29 children in Italy) the combination of inadequate nutritional intake, weight and BMI were correlated with SCD severity indices (hospitalization and fetal hemoglobin (HbF) levels [62]). Key factors contributing to this increased severity include chronic inflammation and oxidative stress, both part of the diseases' complex pathophysiology, consisting of a snowball effect, starting with distorted sickled erythrocytes that cause vaso-occlusion, leading activation of nociceptors and pain [58,63]. Recent studies highlight the complex interplay of environmental (e.g., diet) and genetic factors contributing to gut dysbiosis in children with SCD [64,65]. Gut microbiome alterations are prevalent in this population, driven by both nutritional deficiencies and ischemia-reoxygenation damage from VOC, leading to altered microbiota density, adhesion, translocation, affecting nutrient absorption, metabolic balance, hormonal regulation and immunity [66–68].

In our study, although evidence is limited and of low-to-moderate certainty, we found that the supplementation of SCD children and adolescents with some specific nutrients, namely L-arginine (known to have antioxidant, immunomodulatory and analgesic effects [14]), vitamin D (related to calcium regulation, erythropoiesis, pain perception [12]) and fatty acids (omega-3 acts in cell membrane synthesis, neural development and inflammation) [1] may significantly reduce disease complications and resources use in this population who are consistently treated with hydroxyurea (potential synergistic effect), while maintaining or even increasing patients' QoL. The effects of other nutrients including vitamin A and zinc were poorly documented and showed inconsistent results on SCD-related complications and patients' growth; thus, their role remains unclear for this population [16,18,53]. Trials assessing MgSO4 supplementation showed no significant clinical benefit and higher probabilities of serious adverse events, suggesting this approach should be avoided in practice [17]. Other studies not included in our review due to their design may provide valuable insights into the use of additional supplements in children with SCD and encourage further research in this area. A quasi-experimental study and a cohort conducted in Jamaica found that while folate supplementation significantly reduced mean cell volume, no significant differences were observed between the intervention and usual care regarding infection incidence or pain episodes and VOC [69,70].

Although most hospital visits (60 %) and admissions (90 %) [42,71] of pediatric SCD are due to VOC, few standardized procedures for crisis and pain management are available [63,72]. The complementary use of L-arginine could improve these figures [13]. This therapy is expected to increase nitric oxide production, leading

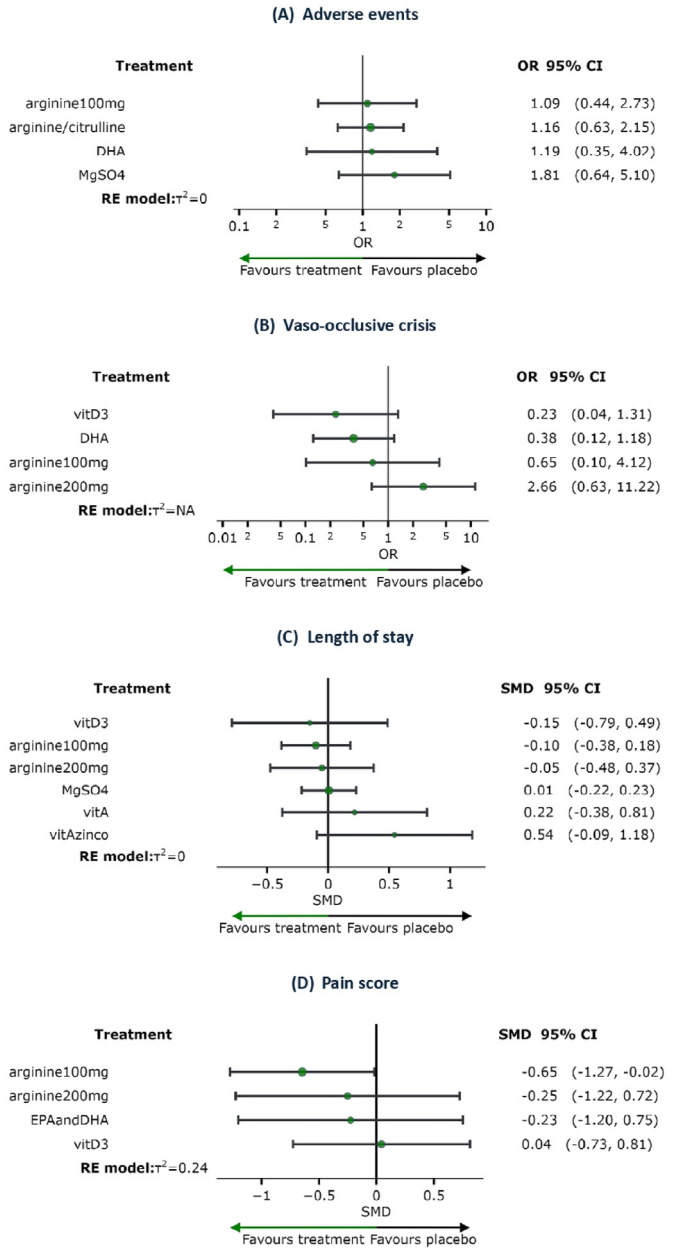

Fig. 3. Forest plots (inverse variance method/random effects model) for the outcomes of interest. CI: confidence intervals; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; MgSO4: magnesium sulfate; OR: odds ratio; RE model: random effects model; SMD: standard mean differences; τ^2: tau-squared; vitA: vitamin A; vitAzinco: vitamin A/zinc; vitD3: vitamin D3.

to improved vasodilation and oxygen delivery [14]. In our study, L-arginine 100 mg led to significant reduction on pain intensity compared to placebo (0.65 points), as well as reduction in VOC rates (77 % lower chance of experiencing the event) and analgesic usage (reductions vs. placebo varying from 0.60 to 2.20 mg/kg of opioids equivalents) in the hospital setting – which impacted in reduced LOS (around one day). A previous systematic review also advocated for the use of L-arginine combined with hydroxyurea to reduce HbF levels and VOC [14], reinforcing that the prevention of the onset of pain leads to better outcomes [71,73]. Yet, while overall safe, L-arginine may cause mild adverse events (e.g., gastrointestinal discomfort, anemia, fever [around 20–40 % according to our review]), which should be monitored to avoid treatment discontinuation. Although L-arginine doses of 100 mg demonstrate a better risk-benefit ratio compared to higher doses (200 mg), adjustments may be necessary to tailor treatment [3].

Table 2
Ranking analysis for outcomes of interest.

Intervention	Change in pain score	Impact on LOS	VOC	AE
Arginine + Citrulline	–	–	–	49 %
DHA	–	–	27 %	49 %
EPA + DHA	53 %	–	–	–
L-arginine 100 mg	86 %	72 %	46 %	43 %
L-arginine 200 mg	53 %	62 %	96 %	–
$MgSO_4$	–	53 %	–	77 %
Vitamin A	–	33 %	–	–
Vitamin A + Zinc	–	7 %	–	–
Vitamin D3	29 %	71 %	15 %	–
Placebo	30 %	54 %	67 %	32 %

AE: adverse events; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; LOS: length of hospital stay; $MgSO_4$: magnesium sulfate; VOC: vaso-occlusive crises.

It is known that SCD patients often have decreased protection from antioxidants, possibly due to lipid peroxidation, which results from its interaction with ferroptosis, and compromises antioxidant competence. In this scenario, the supplementation with fatty acids and vitamins may be promising. We found DHA, EPA and vitamin D fairly associated with reduced number of VOC (62 % and 35 % lower chances vs. placebo, respectively), pain and hospital LOS. Although few studies are available on the subject, these supplements have also been associated with an improvement in children's QoL, by reducing absenteeism from social and academic activities [74] – an important benefit given the complexity of the disease [75]. Previous studies similarly suggest that omega-3 favors both clinical and humanistic outcomes in people with SCD, by decreasing episodes of painful crisis, cell adhesion and hemolysis [76–78]. A 10-months cost-effectiveness analysis in Egypt assessed the benefits of adding daily omega-3 and vitamin D supplements to the standard therapy (hydroxyurea and folic acid) for children with SCD [79]. Authors found that the incremental costs of both interventions were offset by their significant efficacy, with an incremental cost-effectiveness ratio (ICER) of around US$115 for reducing VOC episodes and US$70 for lowering VOC intensity compared to the control group [79]. The implementation of these interventions could result in economic savings in the long term, especially considering the annual healthcare costs for managing SCD can reach up to US$1500 in individuals with over three VOC/year in Africa [80]. In the USA, the direct medical costs of care and from facility-only charges (excluding physician or professional fees) are estimated in approximately US$490 million for around 100,000 SCD-related hospitalizations [81,82]. These figures are similar in Europe, where the mean annual costs for managing 100 SCD patients represent € 25,000 vs. € 3000 for controls [83].

Yet, little has been discussed regarding the most appropriate dietary reference intakes, nutritional interventions and their inclusion in therapeutic guidelines as supplementary care for SCD [9,58]. We observed significant heterogeneity among clinical trials regarding, among others, therapies dosage/regimens (e.g., vitamin D ranging from the usual 4000–5000 IU/weekly to high doses of 40,000–100,000 IU/weekly) and the limited evidence on the effects of dietary interventions, such as specific foods or diets (e.g., lime juice). This may hamper the comparison of their effects and the translation of findings into clinical practice.

Thus, considering that the standard management of SCD incurs significant costs, representing substantial economic burden on health systems and on patients' families, complementary interventions as dietary supplementation, while not disease-specific, may lead to clinical benefits and costs reduction on hospitalizations [84,85]. Further research including well-designed RCT and

Table 3
Summary of most reported adverse events (n = 20 studies).

Author, year	Intervention Control	N Int N Control	Abdominal pain	Anemia	Death (any cause)	Diarrhea	Fever/ Pyrexia	Headache	Rash	Stroke	Nausea
Abdelhalim, 2022 [29]	EPA (300–400 mg/day) + DHA (200–300 mg/day) + usual care Vitamin D (1500–3500 IU/day) + usual care Usual care	50 50 50	–	–	–	–	–	–	–	–	–
Adegoke, 2013 [30]	Lime juice + usual care Usual care	58 55	–	–	–	–	–	–	–	–	–
Adekunle, 2021 [31]	Vitamin D2 (5000 IU/week) Vitamin D3 (50,000 IU/week)	69 70	–	–	–	–	–	–	–	–	–
Brousseau, 2015 [32]	IV MgSO4 (40 mg/kg) Placebo	101 103	–	–	–	–	–	–	–	–	–
Brownell, 2020 [33]	Vitamin A (3000 IU/day) Vitamin A (6000 IU/day)	10 11	–	–	–	–	–	–	–	–	–
Cox, 2018 [34] Marealle, 2018 [45]	RUSF-v (fortified with arginine and citrulline) RUSF-b (base formula)	61 58	0 (0.0 %) 1 (1.72 %)	–	–	1 (1.64 %) 0 (0.0 %)	4 (4.82 %) 1 (1.20 %)	0 (0.0 %) 1 (1.72 %)	–	1 (1.64 %) 0 (0.0 %)	–
Daak, 2013 [35] Daak, 2015 [36]	EPA (39 mg) + DHA (277,8 mg) Placebo	67 61	–	2 (2.85 %) 10 (14.29 %)	–	–	–	–	–	0 (0.0 %) 2 (2.85 %)	–
Daak, 2018 [37]	SC411 (20–60 mg/kg) Placebo	50 17	4 (8.0 %) 1 (5.9 %)	–	–	2 (4.0 %) 1 (5.9 %)	1 (2.0 %) 2 (11.76 %)	5 (10.0 %) 2 (11.8 %)	–	–	3 (6.0 %) 0 (0.0 %)
Dougherty, 2015 [38] Dougherty, 2020 [39]	Vitamin D3 (4000 IU/day) Vitamin D3 (7000 IU/day)	12 9	–	–	–	–	–	–	–	–	–
Dougherty, 2012 [40]	Vitamin A (1000–2000 IU/day) Vitamin A (1000–2000 IU/day) + zinc (10–20 mg/day) Placebo	23 18 21	–	–	–	–	–	–	–	–	–
Fung, 2002 [41]	Zinc (10 mg/day) Placebo	20 22	–	–	–	–	–	–	–	–	–
Goldman, 2014 [42]	IV MgSO4 (100 mg/kg) Placebo	51 53	–	–	–	–	–	–	–	–	2 (4 %) 2 (4 %)
Gregoire-Pelchat, 2020 [43]	Vitamin D3 (300,000 IU single dose) + vitamin D3 (1000 IU/day) Placebo + vitamin D3 (1000 IU/day)	18 20	–	–	–	–	5 (27.78 %) 3 (15.0 %)	–	–	–	–
Lee, 2018 [44]	Vitamin D3 (100,000 IU/month) Vitamin D3 (12,000 IU/month)	31 31	–	2 (6.45 %) 4 (12.90 %)	–	–	7 (22.58 %) 4 (12.90 %)	–	–	–	–
Morris, 2013 [46]	Oral or IV L-arginine (100 mg/kg) Placebo	26 28	–	–	–	–	–	–	–	–	–
Namazzi, 2023 [47]	Zinc (10 mg) Placebo	124 124	–	–	2 (1.61 %) 7 (5.65 %)	–	35 (28.23 %) 23 (18.55 %)	–	–	0 (0.0 %) 2 (1.61 %)	–
Onalo, R. Cilliers, A., 2021 [48] Onalo, R. Cooper, P., 2021 [50] Onalo, 2022 [49]	L-arginine (100 mg/kg) Placebo	35 33	2 (6 %) 4 (12 %)	–	0 (0 %) 1 (3 %)	–	5 (14 %) 5 (15 %)	1 (3 %) 2 (6 %)	1 (3 %) 3 (9 %)	–	20 % 3 %
Osunkwo, 2012 [51]	Vitamin D3 (40,000–100,000 IU/week) + usual care Placebo + usual care	20 19	–	–	–	–	–	–	–	–	–
Reyes, 2022 [52]	IV L-arginine (100 mg/kg) IV L-arginine (200 mg/kg) Placebo	3 36 36	9 (25.0 %) 9 (25.0 %) 9 (25.0 %)	7 (19.44 %) 7 (19.44 %) 8 (22.22 %)	–	3 (8.33 %) 4 (11.11 %) 1 (2.78 %)	7 (19.44 %) 10 (27.78 %) 6 (16.67 %)	14 (38.39 %) 10 (27.78 %) 9 (25.0 %)	0 (0.0 %) 1 (2.78 %) 0 (0.0 %)	–	15 (41.67 %) 17 (47.22 %) 13 (36.11 %)
Zemel, 2002 [53]	Zinc (10 mg/day) Placebo	20 22	–	–	–	–	–	–	–	–	–

ACS: Acute Chest Syndrome; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; IU: international unit; IV: intravenous; $MgSO_4$: magnesium sulfate; RUSF: ready-to-use-supplementary food.

observational studies conducted by multidisciplinary teams should explore additional supplements and focus on developing tailored nutritional plans that incorporate cost-effective supplements while considering patients' characteristics and preferences, therapy accessibility, and costs. Additionally, studies on treatment patterns are needed to improve supplement regimens for this population.

Our study has limitations. The systematic review included few studies, most of which had small sample sizes and some concerns regarding their risk of bias. Yet, these studies represent the available evidence on the impact of nutritional supplements for SCD. The scarcity of studies in this field may be partly due to SCD being a neglected condition, primarily affecting low- and middle-income populations. As is often the case with such conditions, there is still limited research and financial support for conducting new trials [86,87]. We also acknowledge that some inconsistency among RCT may exist, as is common in many clinical areas, due to the inherent differences in population characteristics, sample sizes, interventions and external validity along with the lack of standardized outcome measurements and reporting – which restricted our statistical analyses to a limited number of outcomes. However, we followed all international recommendations for conducting and reporting both pairwise and network meta-analyses, tried to minimize systematic errors by including only comparative data and ensuring transitivity in the meta-analyses, and found that the I2 index (between-study heterogeneity index) remained consistently below 20 % in all analyses indicating a low level of variability between studies (i.e., consistent results). Whenever possible, findings were synthetized in narrative texts and tables to improve data interpretability. Network meta-analysis has limitations, as its validity depends on how treatment effects vary across different comparisons; therefore, treatment rankings should be interpreted in the context of these relative effects. We excluded studies that included both adults and children when the adult population exceeded 20 % of the participants or when the mean age was over 18 years. This decision does not suggest a lack of evidence for children with SCD but rather reflects our review's design criteria to maintain population homogeneity. While our systematic review specifically targeted the pediatric population, further evidence syntheses are needed to assess the efficacy and safety of dietary supplements in adults with SCD [88].

5. Conclusion

Integrating specific nutritional interventions as L-arginine, vitamin D and fatty acids into the standard treatment for SCD in children and adolescents can significantly enhance clinical outcomes (including reducing painful crisis, shortening hospital stays, and improving physiological functions) and overall health-related QoL. These supplements are often affordable, which is especially beneficial for low- and middle-income countries where resources are limited, and the burden of the disease is substantial. Although further research is needed to refine these findings (e.g., appropriate doses/regimens), practical guidelines and decision-makers may benefit from the updated evidence synthetized in this systematic review.

CRediT statement

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Daniela Gorski: Validation, Formal analysis, Writing (Review & Editing).

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Funding

This work was partially supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and by FCT/MCTES (UIDB/05608/2020 and UIDP/05608/2020) – H&TRC. Funders have no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, nor approval of the manuscript; decision to submit the manuscript for publication.

Conflict of interest

The authors declare to have no competing interests regarding this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.02.016.

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