REVIEW

The Effect of Nutrients and Dietary Supplements on Sperm Quality Parameters: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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ABSTRACT

Infertility, which affects ∼15% of the world's population, is a global public health issue recognized by the WHO. Therefore, it is of major clinical and public health importance to investigate whether modifiable lifestyle factors—such as stress, drug use, smoking, alcohol intake, and diet—may influence human fertility. A systematic review and meta-analysis of randomized clinical trials (RCTs) from the MEDLINE-PubMed database was conducted to assess the effect of nutrients, dietary supplements, or food on sperm quality parameters. In total, 28 articles were included for qualitative analysis and 15 for quantitative meta-analysis. Total sperm concentrations [expressed as mean differences (MDs); 95% CIs, in spermatozoa (spz)/mL] were increased by selenium (3.91×10^6 spz/mL; 3.08, 4.73 spz/mL), zinc (1.48×10^6 spz/mL; 0.69, 2.27 spz/mL), omega-3 (*n*–3) fatty acids (10.98×10^6 spz/mL; 10.25, 11.72 spz/mL), and coenzyme Q10 (CoQ10) (5.93×10^6 spz/mL; 5.36, 6.51 spz/mL). Sperm counts were increased by ω-3 fatty acids (18.70×10^6 spz/mL; 16.89, 20.51 spz/mL) and CoQ10 supplementation (10.15×10^6 spz/mL; 8.34, 11.97 spz/mL). Sperm total motility was increased by selenium (3.30%; 2.95%, 3.65%), zinc (7.03%; 6.03%, 8.03%), ω-3 fatty acids (7.55%; 7.09%, 8.01%), CoQ10 (5.30%; 4.98%, 5.62%), and carnitines (7.84%; 6.54%, 9.13%), whereas sperm progressive motility was increased only after supplementation with carnitines (7.45%; 6.24%, 8.67%). Finally, sperm morphology was enhanced by selenium (1.87%; 1.50%, 2.24%), ω-3 fatty acid (0.91%; 0.69%, 1.13%), CoQ10 (1.06%; 0.72%, 1.41%), and carnitine (4.91%; 3.68%, 6.15%) supplementation. This meta-analysis of RCTs suggests that some dietary supplements could beneficially modulate sperm quality parameters and affect male fertility. However, results must be cautiously interpreted due to the limited sample size of the meta-analyzed studies and the considerable observed interstudy heterogeneity. The present study and the corresponding search protocol were registered at the PROSPERO registry at http://www.crd.york.ac.uk/PROSPERO as CRD42017058380. *Adv Nutr* 2018;9:833–848.

Keywords: diet, nutrition, nutrients, food, sperm quality, male infertility, RCT

Introduction

Infertility, which affects ∼15% of the world's population, is a global public health issue recognized by the WHO (1). In the case of male fertility, a recent meta-regression analysis reported a significant worldwide decline in total sperm counts between 1973 and 2011 (2). These data strongly suggest a significant decline in male reproductive health, with crucial implications for human reproduction and perpetuation of the species. Research aimed at revealing the causes and implications of this decline is therefore urgently needed.

Investigating modifiable lifestyle factors that influence human fertility—such as stress, drug use, smoking, alcohol intake, and diet—is of major clinical and public health importance for understanding the problem. Indeed, several observational studies that explored the associations between dietary patterns, food and nutrient consumption, and sperm quality suggest that adhering to a healthy diet (e.g., the Mediterranean diet) may improve male sperm quality parameters (3). In addition to observational studies, which are important for creating new hypotheses, randomized clinical trials (RCTs) are also needed. Such trials are considered the gold standard in terms of scientific evidence if the quality of design of the interventions and the execution of the trial are high, because they enable strong conclusions to be drawn and can be used for future clinical and public health recommendations. Several RCTs have tested the effect of food and nutrients on male fertility parameters. Differences in

supplements tested, study duration and design, as well as the different interventions, populations, and measured outcomes make it extremely difficult to compare these trials.

One systematic review of clinical trials recently attempted to summarize knowledge in this field (4). Unfortunately, the authors of the review merged observational studies and RCTs, did not take into account certain relevant articles, and included others that were of low quality or that contained a high risk of bias (ROB), which made it difficult to draw strong conclusions.

The aims of the present systematic review of RCTs that have tested the effect of nutrients, dietary supplements, or food on sperm quality parameters were as follows: *1*) to update scientific evidence on the topic by assessing the ROB in all the articles selected, and *2*) to meta-analyze the effect of similar interventions on selected endpoints.

Methods

Protocol and registration

The present study and the corresponding search protocol have been registered in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO) as PROSPERO 2017: CRD42017058380.

Literature search strategy

A systematic, comprehensive search of the literature published between the earliest available online indexing year and October 2017 by searching the MEDLINE-PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) and handsearching the reference lists of the retrieved papers was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (5, 6).

With the use of Medical Subject Headings and keywords, 2 search subsets were used: the first subset comprised male infertility-related keywords [fertility OR infertility OR male infertility OR male fertility OR sperm dysfunction(s) OR sperm DNA damage OR varicocele OR asthenozoospermia OR oligozoospermia OR oligoasthenozoospermia OR oligoasthenoteratozoospermia OR teratozoospermia]; and the second subset comprised nutrition and/or diet-related keywords [diet OR nutrients OR food OR food supplement OR dietary supplement OR probiotic OR nuts OR vitamin C OR vitamin E OR zinc OR antioxidants OR cereals OR meat OR vegetable OR fruit OR fishes OR legumes OR milk OR yogurt OR cheese OR seeds OR eggs OR dairy product(s) OR micronutrient(s) OR vitamins OR alcohol consumption OR l-carnitine OR n-acetylcysteine OR glutathione OR coenzyme q10 OR selenium OR fatty acids OR sugar]. The following inclusion filters were applied in the search: Classical Article, Clinical Conference, Clinical Study, Clinical Trial, Clinical Trial-Phase I, Clinical Trial-Phase II, Clinical Trial-Phase III, Clinical Trial-Phase IV, Controlled Clinical Trial, English Abstract, Journal Article, Letter, Meta-Analysis, Multicenter Study, Pragmatic Clinical Trial, Evaluation Studies, Case Reports, Congresses, Dataset, Introductory Journal Article, Abstract, Humans, English, and Male. The complete search strategy is available in **Supplemental Appendix 1**.

Eligibility criteria and study selection

The titles and abstracts of all the preselected articles were screened for eligibility by 2 independent researchers (AS-H and NR-E), who are specialists in male (in)fertility and human nutrition, respectively. Any discrepancies were re-evaluated together with a third author (JS-S). After primary screening (to evaluate the scope of the study), the full texts of the selected articles were obtained. Only RCT studies in which fertile/infertile men were well defined (men with or without sperm disorders, sperm DNA damage, or idiopathic infertility) were included for the qualitative analysis. The primary outcomes of the selected studies had to have referred to the following semen quality parameters: semen volume, ejaculate pH, total sperm count or concentration, sperm vitality, sperm motility (progressive or total motility), sperm morphology, acrosome resistance, sperm DNA fragmentation (SDF) or damage, sperm chromatin integrity, sperm reactive oxygen species (ROS), sperm aneuploidies, sperm function parameters, or hormonal levels. Exclusion criteria were as follows: case-control, cross-sectional, observational prospective or retrospective studies, animal or in vitro studies, review articles, studies conducted on individuals with varicocele or other fertility-related diseases, studies with drug interventions, studies with $\leq$15 participants per intervention, uncontrolled intervention studies, and studies with a high ROB (see the ROB section). Finally, RCTs testing the effect of food extracts, botanic extracts, or drugs have also been excluded from the present review.

Data extraction

With the use of a standardized model, the following information from each study was extracted: authors, year of publication, journal, title of the article, location of the study, age, population studied, sample size, study design (parallel or crossover), interventions, primary outcomes, and main conclusions. Data were first extracted and further checked

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Supplemental Figures 1 and 2 and Supplemental Appendix 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: CoQ10, coenzyme Q10; FSH, follicle-stimulating hormone; iOAT, idiopathic oligoasthenoteratozoospermia; LAC, L-acetyl carnitine; LC, L-carnitine; LH, luteinizing hormone; MD, mean difference; OS, oxidative stress; RCT, randomized clinical trial; ROB, risk of bias; ROS, reactive oxygen species; spz, spermatozoa.

by the researchers for discrepancies in order to minimize the possibility of errors.

ROB

Analyzing all the data extracted, the quality of the studies selected was evaluated through a ROB index based on 7 categories (7). ROB was assessed in parallel by 2 authors (AS-H and NR-E) and discrepancies were re-evaluated together with a third author (JS-S). Applying this system, the ROB of individual studies was assessed with the use of the following criteria: *1*) random sequence generation (due to inadequate generation of randomized sequences); *2*) allocation concealment (due to inadequate concealment of allocations before assignment); *3*) blinding of participants and personnel (due to knowledge of the allocated interventions by participants and personnel during the study); *4*) blinding of outcome assessment (due to knowledge of the allocated interventions by outcome assessors); *5*) incomplete outcome data (due to the amount, nature, or handling of incomplete outcome data); *6*) selective reporting (due to selective outcome reporting); and *7*) other bias (due to problems not covered elsewhere). Studies whose mean ROB was high were considered to be of low quality and therefore excluded, whereas those whose mean ROB was low or unclear were accepted for the systematic qualitative review and quantitative analysis.

Statistical analysis

Meta-analysis was conducted through the use of Review Manager (RevMan) software version 5.3 (http://community.cochrane.org/tools/review-production-tools/revman-5) in accordance with the Cochrane guidelines (7). The difference in the change from the baseline values for the intervention and placebo/control arms was derived from each trial. However, if the change from the baseline values was not available, end-of-treatment values were used. When necessary, an imputed SD or SE for the between-treatment difference was calculated. In crossover trials, to impute SD for between-treatment differences, correlation coefficients between baseline and end-of-treatment values within each trial were derived via a published equation (8). When multiple intervention arms were present in a single trial, intervention arms were pooled to obtain a single pairwise comparison to mitigate unit-of-analysis error. To evaluate the differences in sperm quality parameters between the intervention and the control groups, the data were pooled through the use of the inverse variance method with the fixed effects model and the results were expressed as mean differences (MDs) with 95% CIs. Statistical significance was set at $P < 0.05$. Heterogeneity between the studies was evaluated via a chi-square test and the I^2 index with the significance level set at $P < 0.10$. I^2 values <50% were deemed moderate, ≥50% to <75% were deemed substantial, and ≥75% were deemed of considerable heterogeneity (7).

Results

Study characteristics

A total of 2381 articles were identified after a primary search of MEDLINE-PubMed and 1 study from other sources (**Supplemental Figure 1**). After analyzing every abstract ($n = 2382$), 2240 articles were excluded because they were beyond the scope of the present study (did not assess the effect of nutrients, supplements, or food on sperm quality parameters). A total of 142 articles were collected as full texts and their inclusion/exclusion criteria and ROB were assessed: of these articles, 110 were excluded because they did not meet the inclusion/exclusion criteria (no control group, $n = 34$; small sample size, $n = 26$; non-RCT, $n = 22$; did not meet primary outcome, $n = 5$; studies with animals or nonmale subjects, $n = 3$; in vitro studies, $n = 2$; participants with varicocele, $n = 5$; other fertility-related diseases, $n = 8$; using intervention with drugs, $n = 3$; 2 interventions at the same time, $n = 1$; and using a food extract, $n = 1$), and 4 were excluded because they were classified as having a high ROB. After applying all the eligibility parameters, 28 articles were included for qualitative analysis. When ≥2 studies had analyzed the same exposures and outcomes, the results were meta-analyzed. Therefore, 15 were quantitatively analyzed via a meta-analysis approach.

The articles included subjects ($n = 2900$) from 11 countries: Australia, England, Germany, Iran, Italy, Kuwait, Netherlands, Saudi Arabia, Scotland, Spain, and the United States. The age of the participants ranged from 18 to 52 y. There were 26 parallel-group RCTs and 2 crossover RCTs.

Qualitative analysis

Eight of the 28 articles assessed antioxidant supplements (9–16). Four articles evaluated folic acid and/or zinc (17–20), 2 articles evaluated omega-3 fatty acid supplements (21, 22), 5 articles assessed coenzyme Q10 (CoQ10) supplements (23–27), 3 assessed carnitines (28–30), and 6 assessed some other dietary supplements (31–36). All the studies evaluated had sperm parameters and quality as study outcomes (**Table 1**).

Antioxidant supplements. The vast majority of the RCTs were conducted with the use of antioxidants or cocktails of antioxidants. The studies included in the qualitative analysis are shown in Table 1 (9–16).

Selenium supplements were tested in 3 studies (9, 10, 12). Whereas Hawkes et al. (9) reported that supplementation with 300 μg Se/d had no effect on conventional sperm parameters or serum hormones, Scott et al. (12) reported that 100 μg Se/d for 3 mo improved sperm motility and increased the chance of conception, and Safarinejad and Safarinejad (10) reported that 200 μg Se/d for 6 mo improved semen volume, total sperm count and concentration, and morphology. In the study by Scott et al. (12), adding vitamin C and vitamin E to the supplement had no synergic effect on these semen parameters. In the study by Safarinejad and Safarinejad (10), adding *N*-acetyl cysteine to the selenium supplement improved these parameters but also affected

TABLE 1 Summary of the RCT studies investigating the effect of nutrition on sperm quality parameters or sexual hormones[1]

Reference	Location	Age (y)	Population studied	Background diet controlled during the study?	Design	Intervention	Primary outcome	Principal conclusion	ROB1	ROB2	ROB3	ROB4	ROB5	ROB6	ROB7
Antioxidant															
Haghighian et al. (16)	Iran	Intervention (32.98 ± 5.35); placebo (34.12 ± 4.79)	44 patients with iA (23 intervention; 21 placebo)	No	Parallel	12 wk. α-Lipoic acid (600 mg) or placebo per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, vitality, and morphology)	α-Lipoic acid improves sperm count and concentration, and motility (progressive motility). No effect on semen volume, sperm vitality, or morphology.	LB	UB	LB	LB	LB	LB	UB
Hawkes et al. (9)	United States	18–45	42 healthy participants (22 intervention; 20 placebo)	No	Parallel	11 mo. Se (300 μg) or placebo (Se < 1.5 μg) per day	Semen parameters (semen volume, sperm count and concentration, sperm motility, and morphology) and serum hormones (T, LH, PSA)	Se has no effect on conventional sperm parameters or serum hormones.	UB	UB	LB	LB	LB	UB	UB
Safarinejad and Safarinejad (10)	Iran	Intervention Se (31 ± 9); intervention NAC (32 ± 10); intervention NAC + Se (31 ± 8); placebo (31 ± 9)	420 patients with iOAT (314 intervention [105 Se, 105 NAC, 104 NAC + Se]; 106 placebo)	No	Parallel	6 mo. Se (200 μg), NAC (600 mg), Se + NAC (200 μg + 600 mg respectively), or placebo per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), serum hormones (T, LH, FSH, inhibin B, PRL)	Se, NAC, or Se + NAC improve all conventional sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), except sperm motility in NAC group. Se, NAC, or Se + NAC increase T, LH, and inhibin B but decrease FSH. No effect on PRL serum hormone.	LB	UB	LB	LB	UB	LB	UB
Greco et al. (15)	Italy	ND	64 patients with idiopathic infertility (32 intervention and 32 placebo)	No	Parallel	2 mo. Vitamin C (1 g) + vitamin E (1 g), or placebo per day	Semen parameters (sperm count and concentration, sperm motility, and morphology), sperm DNA damage	Vitamin C and E improve sperm DNA fragmentation index. No effect on conventional semen parameters.	UB	LB	LB	LB	LB	UB	UB
Rolf et al. (11)	Germany	Intervention (36.1 ± 5.0); placebo (35.2 ± 4.8)	31 patients with astheno-zoospermia or moderate oligoastheno-zoospermia (15 intervention; 16 placebo)	No	Parallel	8 wk. Vitamin C (1000 mg) + vitamin E (800 mg), or placebo per day	Sperm parameters (semen volume, sperm concentration, sperm motility, sperm vitality, and morphology), serum hormones (T, FSH, LH, E2)	Vitamin C + E has no effect on conventional semen parameters or hormones.	LB	LB	LB	LB	LB	LB	UB
Scott et al. (12)	Scotland	Se intervention (32.6 ± 1.1); Se + vitamins intervention (33.9 ± 0.9); placebo (32.9 ± 1.5)	64 patients with astheno-zoospermia (46 intervention [16 Se, 30 Se + vitamins]; 18 placebo)	No	Parallel	3 mo. Selenium (100 μg), selenium + vitamin A (1 mg) + vitamin C (10 mg) + vitamin E (15 mg), or placebo per day	Sperm parameters (sperm concentration and motility), conception chance	Selenium improves sperm motility and chance of conception. No effect on sperm concentration.	LB	UB	LB	LB	UB	UB	UB

(*Continued*)

TABLE 1 *Continued*

Reference	Location	Age (y)	Population studied	Background diet controlled during the study?	Design	Intervention	Primary outcome	Principal conclusion	ROB1	ROB2	ROB3	ROB4	ROB5	ROB6	ROB7
Suleiman et al. (14)	Saudi Arabia	Intervention (27–52); placebo (22–45)	87 patients with astheno-zoospermia (52 intervention and 35 placebo)	No	Parallel	6 mo. Vitamin E (300 mg) or placebo per day	Sperm parameters (sperm motility) and pregnancy rate	Vitamin E improves sperm motility and pregnancy rate.	UB	UB	LB	LB	UB	UB	UB
Kessopoulou et al. (13)	England	32 (26–49)	30 healthy participants with high levels of ROS	No	Crossover	3 mo. 1 mo WO, 3 mo vitamin E interven-tion/placebo, 1 mo WO, 3 mo vitamin E interven-tion/placebo. Vitamin E (600 mg) or placebo per day	Sperm parameters (semen volume, sperm concentration, sperm motility, and morphology), zona binding test, ROS	Vitamin E improves the zona binding test. No effect on ROS or conventional sperm parameters.	UB	UB	LB	LB	UB	LB	UB
Folic acid and/or zinc															
Raigani et al. (19)	Iran	ND	83 patients with iOAT (65 intervention [20 folic acid, 24 zinc sulfate, 21 folic acid + zinc sulfate]; 18 placebo)	No	Parallel	16 wk. Folic acid (5 mg), zinc sulfate (220 mg), folic acid + zinc sulfate (5 mg + 220 mg, respectively), or placebo per day	Sperm parameters (sperm concentration, sperm motility, sperm vitality, and morphology), DNA damage, and chromatin damage	Zinc sulfate improves sperm chromatin integrity. Folic acid and/or zinc sulfate has no effect on conventional sperm parameters.	UB	UB	LB	LB	UB	LB	UB
Ebisch et al. (17)	Netherlands	Subfertile men 35.0 (32.3–37.0); fertile 34.0 (31.0–38.0)	87 participants (42 intervention [24 fertile, 18 subfertile] and 45 placebo [23 fertile, 22 subfertile])	No	Parallel	6 mo. Folic acid (5 mg) + zinc sulfate (66 mg), or placebo per day	Semen parameters (semen volume, sperm concentration, sperm motility, and morphology), serum hormones (T, FSH, inhibin B)	Folic acid + zinc sulfate improve sperm concentration. No effect on semen volume, sperm motility or morphology, or serum hormones.	LB	UB	LB	LB	UB	LB	UB
Wong et al. (18)	Netherlands	Subfertile men (34.3 ± 3.9); fertile men (34.2 ± 4.2)	193 healthy participants (99 fertile, 94 subfertile)	No	Parallel	6 mo. Folic acid (5 mg), zinc sulfate (66 mg), folic acid + zinc sulfate (5 mg + 66 mg, respectively), or placebo per day	Sperm parameters (semen volume, sperm count and concentration, motility, and morphology)	Folic acid + zinc sulfate improves sperm concentration and morphology; folic acid improves sperm morphology in subfertile patients. Zinc improves sperm morphology in fertile patients. No effect on semen volume, sperm count, or motility.	LB	LB	LB	LB	LB	LB	UB

(*Continued*)

TABLE 1 *Continued*

Reference	Location	Age (y)	Population studied	Background diet controlled during the study?	Design	Intervention	Primary outcome	Principal conclusion	ROB1	ROB2	ROB3	ROB4	ROB5	ROB6	ROB7
Omu et al. (20)	Kuwait	Intervention (37.8 ± 7.9); control (38.1 ± 8.2)	97 patients with astheno-zoospermia (49 intervention; 48 control)	No	Parallel	3 mo. Zinc (500 mg) per day, or no therapy	Sperm parameters (semen volume, sperm concentration, sperm motility, and morphology), HOS, serum hormones (T, FSH, LH, PRL), pregnancy, abortion, delivered or ongoing pregnancies	Zinc improves sperm concentration, sperm motility, sperm integrity membrane (HOS), fertilizing capacity, conception, and pregnancy.	UB	UB	UB	UB	LB	LB	UB
ω-3 Fatty acid															
Martínez-Soto et al. (21)	Spain	Intervention (35 ± 0.8); placebo (35.6 ± 1.0)	57 patients attending an infertility clinic (32 intervention; 25 placebo)	No	Parallel	10 wk. ω-3 DHA-enriched oil (990 mg DHA + 135 mg EPA) or placebo (1500 mg sunflower oil) per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), sperm DNA fragmentation	DHA reduces the percentage of spermatozoa with DNA damage. No effect on any conventional sperm parameter.	UB	UB	LB	LB	UB	LB	UB
Safarinejad (22)	Iran	Intervention (32 ± 9); placebo (32 ± 10)	211 patients with iOAT (106 intervention; 105 placebo)	No	Parallel	32 wk. ω-3 Group (1.12 g EPA + 0.72 g DHA) or placebo per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), serum hormones (T, LH, FSH, E2, PRL)	EPA and DHA improve sperm count and concentration, sperm motility, and morphology. No effect on semen volume or serum hormones.	UB	UB	LB	LB	UB	LB	UB
CoQ10															
Nadjarzadeh et al. (23)	Iran	Intervention (34.17 ± 4.52); placebo (34.67 ± 6.69)	47 patients with iOAT (23 intervention; 24 placebo)	Yes	Parallel	12 wk. CoQ10 (200 mg), or placebo (containing lactose) per day	Sperm parameters (sperm concentration, sperm motility, and morphology)	CoQ10 has no effect on conventional sperm parameters.	UB	UB	LB	LB	UB	LB	UB
Safarinejad et al. (24)	Iran	Intervention (31); placebo (32)	191 patients with iOAT (96 intervention; 95 placebo)	No	Parallel	6 mo. Ubiquinol, or reduced CoQ10 (200 mg), or placebo per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), and serum hormones (T, LH, FSH, inhibin B, PRL)	Ubiquinol improves sperm count, concentration, and motility, increases inhibin B, and reduces LH and FSH. No effect on semen volume, sperm morphology, T, or PRL.	LB	LB	LB	LB	UB	LB	UB
Nadjarzadeh et al. (25)	Iran	Intervention (34.17 ± 4.52); placebo (34.67 ± 6.69)	47 patients with iOAT (23 intervention; 24 placebo)	Yes	Parallel	12 wk. CoQ10 (200 mg), or placebo (containing lactose) per day	Sperm parameters (semen volume, pH, sperm count and concentration, sperm motility, and morphology)	CoQ10 has no effect on conventional sperm parameters.	UB	UB	LB	LB	UB	LB	UB
Balercia et al. (26)	Italy	32 (27–39)	55 patients with iA (28 intervention; 27 placebo)	No	Parallel	6 mo. CoQ10 (200 mg) or placebo per day	Semen parameters (sperm concentration, motility, and morphology)	CoQ10 improves sperm motility. No effect on sperm concentration or morphology.	UB	UB	LB	LB	LB	LB	UB
Safarinejad (27)	Iran	Intervention (28 ± 9); placebo (28 ± 10)	194 patients with iOAT (98 intervention; 96 placebo)	No	Parallel	6 mo. CoQ10 (300 mg) or placebo per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), acrosome-reacted spermatozoa, and serum hormones (T, LH, FSH, inhibin B, PRL)	CoQ10 improves sperm count and concentration, sperm motility, and morphology. Se reduces FSH and LH, and increases inhibin B and acrosome-reacted spermatozoa.	LB	UB	LB	LB	LB	LB	UB

(*Continued*)

TABLE 1 *Continued*

Reference	Location	Age (y)	Population studied	Background diet controlled during the study?	Design	Intervention	Primary outcome	Principal conclusion	ROB1	ROB2	ROB3	ROB4	ROB5	ROB6	ROB7
Carnitine															
Balercia et al. (28)	Italy	24–38	59 patients with iA (44 intervention [15 LC, 15 LAC, 14 LC + LAC]; 15 placebo)	No	Parallel	6 mo. LC (3 g), LAC (3 g), LC + LAC (2 g + 1 g, respectively), or placebo (malic acid, sodium benzoate, sodium saccharinate dihydrate, anhydrous sodium citrate, pineapple flavoring, and demineralized water) per day	Sperm parameters (semen volume, sperm concentration, sperm motility, and morphology)	LC, LAC, or LC + LAC improve sperm motility. LAC improves sperm concentration and LC sperm morphology. No effect on semen volume.	UB	UB	LB	LB	LB	LB	UB
Lenzi et al. (29)	Italy	20–40	56 patients with iOAT (30 intervention; 26 placebo)	No	Parallel	6 mo. LC (2 g) + LAC (1 g), or placebo per day	Sperm parameters (semen volume, sperm concentration, motility, and morphology)	LC + LAC improve sperm motility. No effect on semen volume, sperm concentration, or morphology.	UB	UB	LB	LB	LB	LB	UB
Lenzi et al. (30)	Italy	20–40	86 infertile patients	No	Crossover	2 mo WO, 2 mo LC interven-tion/placebo, 2 mo WO, and 2 mo LC interven-tion/placebo. LC (2 g), or placebo per day	Sperm parameters (semen volume, sperm concentration, motility, and morphology)	LC improves sperm concentration and motility. No effect on semen volume or sperm morphology.	UB	UB	LB	LB	UB	LB	UB
Dietary supplements															
Maretti and Cavallini (31)	Italy	Intervention (37; 32–42); placebo (36; 30–43)	41 patients with iOAT (20 intervention; 21 placebo)	No	Parallel	6 mo. Flortec (*Lactobacillus paracasei* B21060 5×10^9 CFUs + ara-binogalactan 1243 mg + oligo-fructosaccharides 700 mg + L-glutamine 500 mg) or placebo (alimentary starch) per day	Sperm parameters (semen volume, pH, sperm count and concentration, sperm motility, and morphology), serum hormones (T, LH, FSH, E2, PRL)	Flortec improves semen volume, sperm count, sperm concentration, progressive motility, and morphology, also improves FSH, LH, and T levels. No effect on PRL and E2.	LB	UB	LB	LB	LB	LB	UB

(*Continued*)

TABLE 1 *Continued*

Reference	Location	Age (y)	Population studied	Background diet controlled during the study?	Design	Intervention	Primary outcome	Principal conclusion	ROB1	ROB2	ROB3	ROB4	ROB5	ROB6	ROB7
Calogero et al. (32)	Italy	Intervention (28 ± 9); placebo (28 ± 10)	194 patients with idiopathic infertility (98 intervention; 96 placebo)	No	Parallel	3 mo. Inofolic (4 g MI + 400 μg folic acid) or placebo (400 μg folic acid alone) per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), acrosome-reacted spermatozoa, serum hormones (T, LH, FSH, inhibin B, PRL)	MI increases sperm count and concentration, motility (progressive motility), and T levels, and decreases acrosome-reacted spermatozoa, LH, and FSH levels. No effect on semen volume, PRL, or inhibin B.	UB	UB	LB	LB	LB	UB	UB
Kolahdooz et al. (33)	Iran	Intervention (31.5 ± 1.1); placebo (32.1 ± 0.8)	68 patients with idiopathic infertility (34 intervention; 34 placebo)	No	Parallel	2 mo. *Nigella sativa* seed oil (5 mg of *N. sativa* oil) or placebo (liquid paraffin) per day	Sperm parameters (semen volume, pH, sperm concentration, motility, and morphology)	*N. sativa* improves semen volume and pH, sperm concentration, motility, and morphology, and semen round cells in the ejaculate (reduction of this type of cells).	UB	LB	LB	LB	UB	LB	UB
Robbins et al. (34)	United States	Intervention (25.6 ± 4.0); control (24.8 ± 3.7)	107 healthy participants (55 intervention; 52 control)	Yes	Parallel	12 wk. Walnuts (75 g) or no tree nuts consumption (control) in the context of a Westernized diet	Sperm parameters (sperm concentration, motility, vitality, and morphology), and sperm aneuploidy (X, Y, 18)	Walnuts improve sperm motility, vitality, and morphology. No effect on semen volume, sperm concentration, or aneuploidy.	LB	UB	LB	LB	LB	LB	UB
Safarinejad et al. (35)	Iran	Intervention (28.4 ± 5.2); placebo (28.8 ± 5.6)	230 patients with iOAT (114 intervention; 116 placebo)	No	Parallel	6 mo. Saffron (60 mg *Crocus sativa*) or placebo per day	Sperm parameters (semen volume, sperm count and concentration, sperm motility, and morphology), serum hormones (T, LH, FSH, PRL, TSH)	Saffron has no effect on conventional sperm parameters or serum hormones.	UB	UB	LB	LB	UB	LB	UB
Tremellen et al. (36)	Australia	Intervention (37.1 ± 5.1); placebo (35.5 ± 4.3)	60 patients with idiopathic infertility attending an infertility clinic (n = ND)	No	Parallel	3 mo. Menevit (lycopene 6 mg, vitamin E 400 IU, vitamin C 100 mg, zinc 25 mg, selenium 26 μg, folate 0.5 mg, garlic 1 g, palm oil) or placebo (palm oil) per day	Sperm parameters (sperm concentration, sperm motility, sperm vitality, and morphology), SDF, and fecundability parameters (cleavage stage embryo quality, oocyte fertilization rate, and pregnancy rates)	Menevit improves pregnancy rates during IVF-ICSI treatment. No effect on conventional sperm parameters.	LB	UB	LB	LB	LB	LB	UB

[1] The studies are arranged by supplement compounds and from the most recent to the oldest study. The studies are classified and ordered as: antioxidant supplement studies, folic acid and/or zinc studies, ω-3 fatty acid studies, CoQ10 studies, carnitine studies, and dietary supplement studies. Age is given as mean ± SD or mean (range) where such data are available. CoQ10, coenzyme Q10; E2, estradiol; FSH, follicle-stimulating hormone; HOS, hypo-osmotic swelling; iA, idiopathic asthenozoospermia; ICSI, intra-citoplasmatic sperm injection; iOAT, idiopathic oligoasthenoteratozoospermia; IVF, in vitro fertilization; LAC, L-acetyl carnitine; LB, low risk of bias; LC, L-carnitine; LH, luteinizing hormone; MI, myoinositol; NAC, *N*-acetyl cysteine; ND, no data; PRL, prolactin; PSA, prostatic-specific antigen; RCT, randomized clinical trial; ROB1, random sequence generation; ROB2, allocation concealment; ROB3, blinding of participants and personnel; ROB4, blinding of outcome assessment; ROB5, incomplete outcome data; ROB6, selective reporting; ROB7, other bias; ROS, reactive oxygen species; SDF, sperm DNA fragmentation; T, testosterone; TSH, thyroid-stimulating hormone; UB, unclear risk of bias; WO, washout period.

certain sex hormones, increasing testosterone, luteinizing hormone (LH), and inhibin B and decreasing follicle-stimulating hormone (FSH).

No effect on conventional semen parameters and sex hormones has been demonstrated with the use of vitamin E or vitamin C + E supplementation (11, 13, 15), except in 1 RCT (14) in which the administration of 300 mg vitamin E significantly improved sperm motility after 6 mo. However, an improvement in fecundity capacity was reported with the use of the zona binding test after 3 mo of vitamin E supplementation (13) in sperm DNA fragmentation indexes after 2 mo of vitamin C + E supplementation (15) and in pregnancy rates after 3 mo of vitamin E supplementation (14).

Finally, supplementation for 12 wk with 600 mg α-lipolic acid improved total sperm count, concentration, and motility (progressive motility) but had no effect on semen volume, sperm vitality, or morphology (16).

Folic acid and zinc. Four studies investigated the effects of folic acid and/or zinc supplements on different semen variables (Table 1). Although the main conclusions are controversial, some of the results are worth emphasizing. Whereas the intake of folic acid + zinc sulfate led to improvements in sperm concentration (17, 18) and morphology (18), isolated folic acid or zinc supplementation improved other sperm-related parameters. Specifically, improvements in sperm chromatin integrity indexes (19) or sperm concentration, sperm motility, sperm integrity membrane through the hypo-osmotic swelling test, fertilizing capacity, conception, and pregnancy (20) were reported after supplementation with zinc sulfate in infertile patients with idiopathic oligoasthenoteratozoospermia (iOAT) and asthenozoospermia, respectively. Also, an improvement in sperm morphology was demonstrated after supplementation with folic acid (5 mg/d) in subfertile healthy patients (18).

ω-3 Fatty acids. Two parallel-group RCTs (Table 1) evaluated the effect of ω-3 fatty acid supplementation on sperm parameters (21, 22).

Supplementation with DHA + EPA (990 mg/d and 135 mg/d, respectively) for 10 wk demonstrated no effect on sperm parameters but improved SDF (21). Although supplementation with higher amounts of DHA + EPA (0.72 g/d and 1.12 g/d, respectively) led to significant improvements in total sperm count and concentration, sperm motility, and morphology, it had no effect on semen volume or serum sex hormone concentrations (22).

CoQ10. In terms of intervention (3–6 mo in length and 200–300 mg of supplementation/d), the most homogeneous group of studies are those that used CoQ10 (see Table 1) (23–27). The 2 articles by Nadjarzadeh et al. (23, 25) are considered as 1 study.

Studies testing the effect of supplementation with CoQ10 for a moderate-to-short-term intervention period ($\leq$3 mo) reported no effect on conventional sperm parameters (23, 25). On the other hand, RCTs that explored the effects after 6 mo of intervention reported improvements in classical sperm parameters such as sperm motility (26), total sperm count and concentration (24), and morphology (27). The 2 studies by Safarinejad et al. (24, 27) also described a peripheral increase in the inhibin-B hormone and a reduction in LH and FSH after CoQ10 supplementation. A reduction in acrosome-reacted spermatozoa in the ejaculate (an important parameter in the fecundation process) was also observed by Safarinejad (27) in 2009.

Carnitines. Three RCT studies with carnitines are summarized in Table 1 (28–30).

The administration of all types of isolated carnitines, such as L-acetyl carnitine (LAC), L-carnitine (LC), or complexes of both carnitines (LAC and LC), has been shown to increase sperm motility (28–30). Supplementation with between 2 and 3 g LC/d improved sperm concentration (30) and morphology (28). Finally, in the aforementioned study (28), 1 g LAC/d also improved sperm concentration, but no effect of carnitine intake on semen volume was reported in any of these studies.

Dietary supplements. Table 1 summarizes the effects of several dietary supplements on sperm parameters (31–36).

In idiopathic oligoasthenoteratozoospermic patients, improvements in semen volume; total sperm count, concentration, progressive motility, and morphology; and levels of FSH, LH, and testosterone were reported after 6 mo supplementation with 1 Flortec capsule/d (*Lactobacillus paracasei* B21060 5×10^9 CFUs/d + arabinogalactan 1243 mg/d + oligo-fructosaccharides 700 mg/d + L-glutamine 500 mg/d) (31).

After 3 mo supplementation with 4 g myoinositol/d, total sperm count and concentration, progressive motility, and testosterone levels increased and acrosome-reacted spermatozoa, LH, and FSH levels decreased (32).

Supplementation with Menevit, a complex enriched with many antioxidants (lycopene 6 mg/d, vitamin E 400 IU/d, vitamin C 100 mg/d, zinc 25 mg/d, selenium 26 μg/d, folate 0.5 mg/d, garlic 1 g/d, and palm oil), had no effect on any conventional parameter (36).

Nigella sativa was tested (33). After the intervention with this herb, improvements in several seminogram parameters in the ejaculate (including semen volume and pH, sperm concentration, motility, sperm morphology, and semen round cells) were reported.

One RCT that used saffron (*Crocus sativus*), an ancestral herbal remedy traditionally thought to improve semen parameters, as a supplement showed that consuming 60 mg of saffron/d for 26 wk had no effect on conventional sperm parameters or serum hormones (35).

To the best of our knowledge, the only food that has been tested in an RCT was walnuts (34). This study showed that consuming 75 g of raw walnuts/d in the context of a Western-style diet improved sperm motility, sperm vitality, and morphology in healthy individuals but that

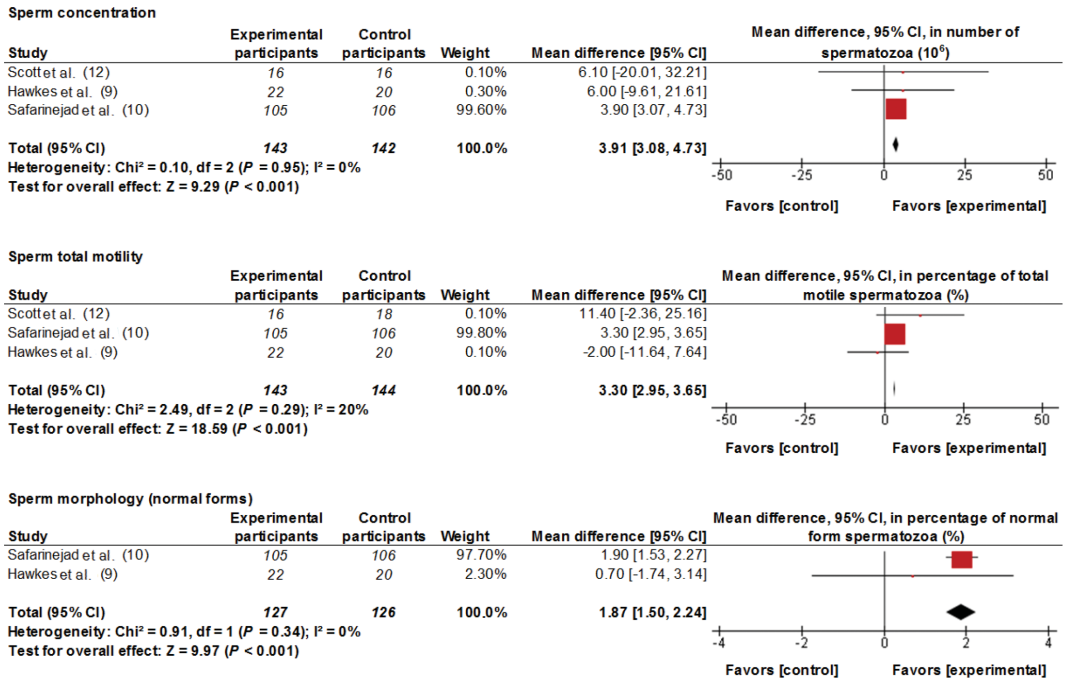

FIGURE 1 MDs and 95% CIs for the effects of selenium supplements on sperm concentration, sperm total motility, and sperm morphology. The forest plots of the studies use generic-inverse variance and a fixed-effects estimate method. The points for each study indicate the MD, the size of the boxes indicates the weight of the study, and the horizontal lines indicate the 95% CI for each study. The bold data represent the total number of participants for all studies, and the diamond represents the pooled MD. MD, mean difference.

supplementation with walnuts had no effect on semen volume, sperm concentration, or aneuploidy index.

Quantitative analysis

The relatively high number of RCTs that have used selenium, zinc, folic acid, ω-3, CoQ10, and carnitines as supplements and the homogeneity between them led us to conduct a meta-analysis to test the effect of these supplements on various sperm outcomes.

Selenium. Data from 3 studies have been meta-analyzed. Supplementation of 100–300 μg Se/d for between 3 and 11 mo improved (MD; 95% CI) sperm concentration [3.91 × 10^6 spermatozoa (spz)/mL; 3.08, 4.73 spz/mL; $P < 0.001$], total motility (3.30%; 2.95%, 3.65%; $P < 0.001$), and morphology (1.87%; 1.50%, 2.24%; $P < 0.001$) (**Figure 1**). Interstudy heterogeneity was nonsignificant ($I^2 \leq 20$, $P > 0.1$).

Zinc. Analyzing data from 3 studies, the present study found that 66–500 mg Zn supplementation/d for 3–6 mo improved (MD; 95% CI) sperm concentration (1.48 × 10^6 spz/mL; 0.69, 2.27 spz/mL; $P < 0.001$) and total motility (7.03%; 6.03%, 8.03%; $P < 0.001$) (**Figure 2**). Interstudy heterogeneity was nonsignificant ($I^2 \leq 1$, $P > 0.1$).

Folic acid. Data from 2 studies with folic acid have been meta-analyzed (**Supplemental Figure 2**). Supplementation with 5 mg folic acid/d for 3–6 mo did not improve sperm concentration, total motility, or morphology in fertile and subfertile participants ($I^2 = 0$, $P > 0.1$).

ω-3 Fatty acids. Administration of a supplement containing 1 g DHA/d and 1 g EPA/d for 10–32 wk improved (MD; 95% CI) total sperm count (18.70 × 10^6 spz; 16.89, 20.51 spz; $P < 0.001$), sperm concentration (10.98 × 10^6 spz/mL; 10.25, 11.72 spz/mL; $P < 0.001$), total motility (7.55%; 7.09%, 8.01%; $P < 0.001$), and morphology (0.91%; 0.69%, 1.13%; $P < 0.001$) (**Figure 3**). There was evidence of considerable and significant heterogeneity between the 2 meta-analyzed studies ($I^2 > 90$, $P < 0.001$).

CoQ10. Analyzing data from 4 RCTs, the present study found that supplementation with 200–300 mg CoQ10/d for 3–6 mo improved (MD; 95% CI) total sperm count (10.15 × 10^6 spz; 8.34, 11.97 spz; $P < 0.001$), sperm concentration (5.93 × 10^6 spz/mL; 5.36, 6.51 spz/mL; $P < 0.001$), sperm total motility (5.30%; 4.98%, 5.62%; $P < 0.001$), and morphology (1.06%; 0.72%, 1.41%; $P < 0.001$) (**Figure 4**). The effect on sperm progressive motility had substantial interstudy heterogeneity ($I^2 = 65\%$, $P = 0.09$), and there was considerable interstudy heterogeneity for other sperm parameters ($I^2 \geq 89\%$, $P < 0.001$). The 2 articles by Nadjarzadeh et al. (23, 25) were computed as 1 study.

Carnitines. Data from 3 studies have been meta-analyzed. Supplementation with 3 g LC/d and 1 g LAC/d for 2–6 mo significantly improved (MD; 95% CI) sperm progressive

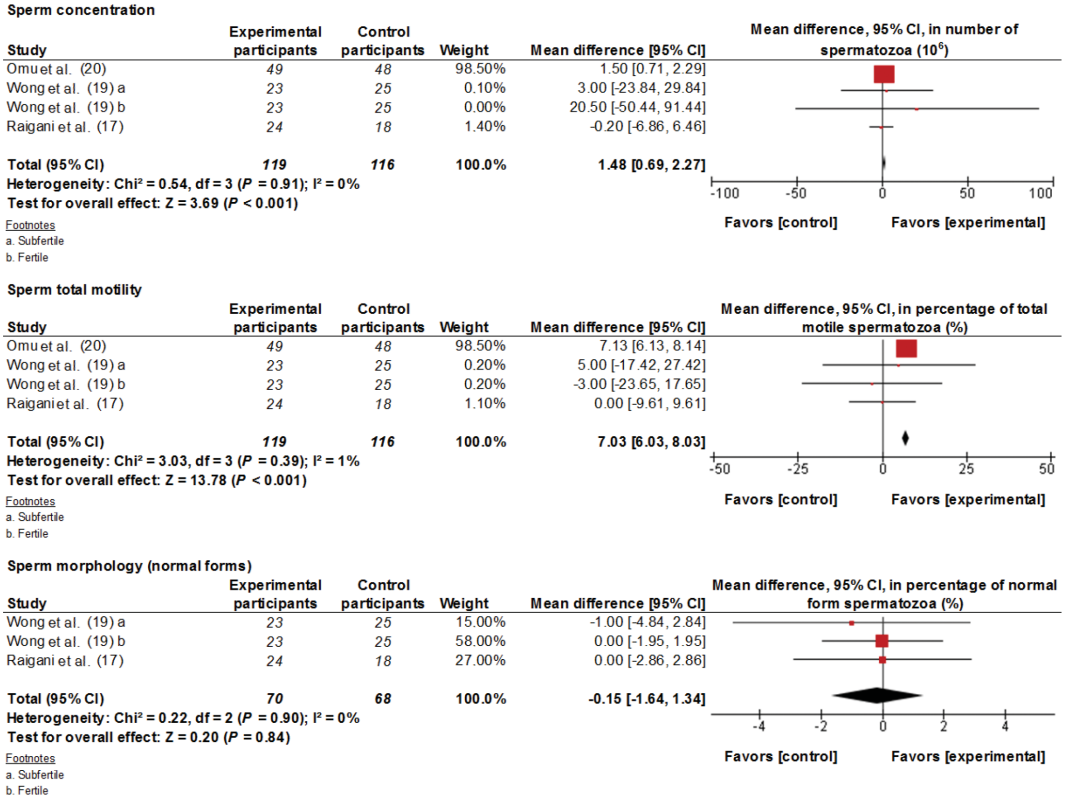

FIGURE 2 MDs and 95% CIs for the effects of zinc supplements on sperm concentration, sperm total motility, and sperm morphology. The forest plots of the studies use generic-inverse variance and a fixed-effects estimate method. The points for each study indicate the MD, the size of the boxes indicates the weight of the study, and the horizontal lines indicate the 95% CI for each study. The bold data represent the total number of participants for all studies, and the diamond represents the pooled MD. MD, mean difference.

motility (4.80%; 3.32%, 6.28%; $P < 0.001$), total motility (4.82%; 3.30%, 6.34%; $P < 0.001$), and morphology (2.98%; 1.10%, 4.87%; $P = 0.002$) (Figure 5). Except for sperm concentration, where homogeneity was very high ($I^2 = 9\%$, $P = 0.33$), there was evidence of considerable and significant heterogeneity between the studies for the motility and morphology parameters ($I^2 \geq 90$, $P < 0.001$).

Discussion

This systematic review of RCTs provides the most wide-ranging analysis to date for the effects of nutrients, supplements, or foods on sperm quality parameters. The meta-analysis included in the review revealed a significant beneficial effect on total sperm count from supplementation with ω-3 and CoQ10; on sperm concentration from supplementation with selenium, zinc, ω-3, and CoQ10; on sperm motility from supplementation with selenium, zinc, ω-3, CoQ10, and carnitines; and on sperm morphology from supplementation with selenium, ω-3, CoQ10, and carnitines. The review suggests that some dietary supplements may help to modulate male fertility.

Different underlying mechanisms could explain these results and therefore deserve comment. Oxidative stress (OS) is identified as one of the main mediators of male infertility. It causes sperm dysfunctions and is related to increased cellular damage triggered by ROS. This occurs naturally in sperm cells because high levels of sperm motility, in the case of the hyperactivation required in zona-pellucida binding, induce ROS (37). However, high levels of ROS were also strongly correlated with sperm DNA damage and low percentages of sperm motility (38), among other sperm-related outcomes. The ROS-DNA–damage sperm motility pathway may also act in the opposite direction, i.e., DNA damage induces ROS through the H2AX (H2A histone family, member X)–*Hox1* [NAD(P)H oxidase]/*Rac1* (Rac Family Small GTPase 1) pathway (39). In this scenario, the equilibrium between antioxidants and ROS may be key for achieving better sperm quality (mainly in terms of sperm motility, vitality, and DNA damage). This is why most of the RCTs in the literature tested antioxidant supplements in order to balance OS. Some supplements (vitamin E and zinc) proved beneficial for increasing the live birth rate in couples with male or unexplained subfertility and some (certain carnitine supplements) proved beneficial for increasing the pregnancy rate. Other supplements had no beneficial effects in this regard (40).

The main antioxidants tested as supplements with a positive effect on sperm quality parameters were selenium and zinc. On one hand, selenium is essential for the normal spermatogenesis of mammals and plays a pivotal role in

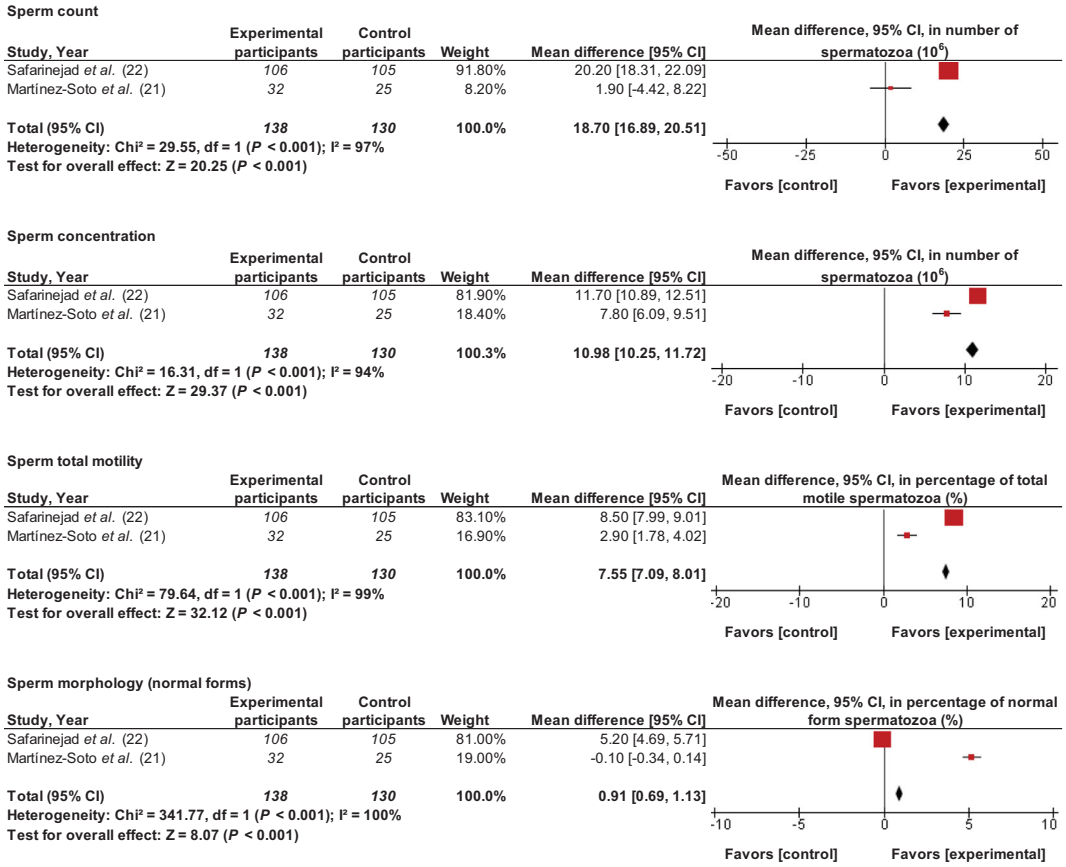

FIGURE 3 MDs and 95% CIs for the effects of ω-3 fatty acid supplements on total sperm count, sperm concentration, sperm total motility, and sperm morphology. The forest plots of the studies use generic-inverse variance and a fixed-effects estimate method. The points for each study indicate the MD, the size of the boxes indicates the weight of the study, and the horizontal lines indicate the 95% CI for each study. The bold data represent the total number of participants for all studies, and the diamond represents the pooled MD. MD, mean difference.

increasing glutathione peroxidase-1 expression and activity, which, in turn, destroys hydrogen peroxide molecules (41). On the other hand, zinc is also an antioxidant element with a membrane-stabilizing activity by inhibiting membrane-bound oxidative enzymes such as NAD(P) oxidase (42). A recent meta-analysis showed that the zinc content in the seminal plasma of infertile males was significantly lower than those of normal males, which indicates that zinc supplementation may significantly increase the sperm quality of infertile males (43). The present meta-analysis of RCTs in humans that used zinc and selenium as supplements reinforces this hypothesis. However, no consistent beneficial effects of other antioxidants, including folic acid, have been demonstrated.

ω-3 PUFAs are fatty acids with anti-inflammatory and antioxidant properties potentially modifying cell membrane composition and functionality. The mechanism by which ω-3 (and ω-6) PUFAs can affect spermatogenesis is their incorporation into the spermatozoa cell membrane. It has been demonstrated that the successful fertilization of spermatozoa depends on the lipid composition of the spermatozoa membrane (44). In line with this finding, the present RCT meta-analysis shows positive effects on sperm concentration after supplementation with ω-3 PUFAs. However, other RCTs conducted in large samples of participants are needed in order to definitively endorse the beneficial effect of ω-3 supplementation on sperm motility and pregnancy indicators.

CoQ10 is also an antioxidant molecule with a central role in the electron-transport system. As Balercia et al. (26) and Safarinejad (27) pointed out, CoQ10 inhibits organic peroxide formation in seminal fluid and may therefore reduce sperm-cell OS. In the last 2 decades, interest in this molecule as a supplement for treating infertile men and fecundability has grown. In a meta-analysis conducted in 2013 by Lafuente et al. (45) and in the present review, an overall improvement was shown in sperm parameters but not in live birth or pregnancy rates (45). However, high heterogeneity between the studies was reported, which indicates that more and larger studies are needed before supportive recommendations can be made.

The lack of clear effects of antioxidant supplements on sperm parameters in some of the studies included in our systematic review can be explained by the amount/dose of

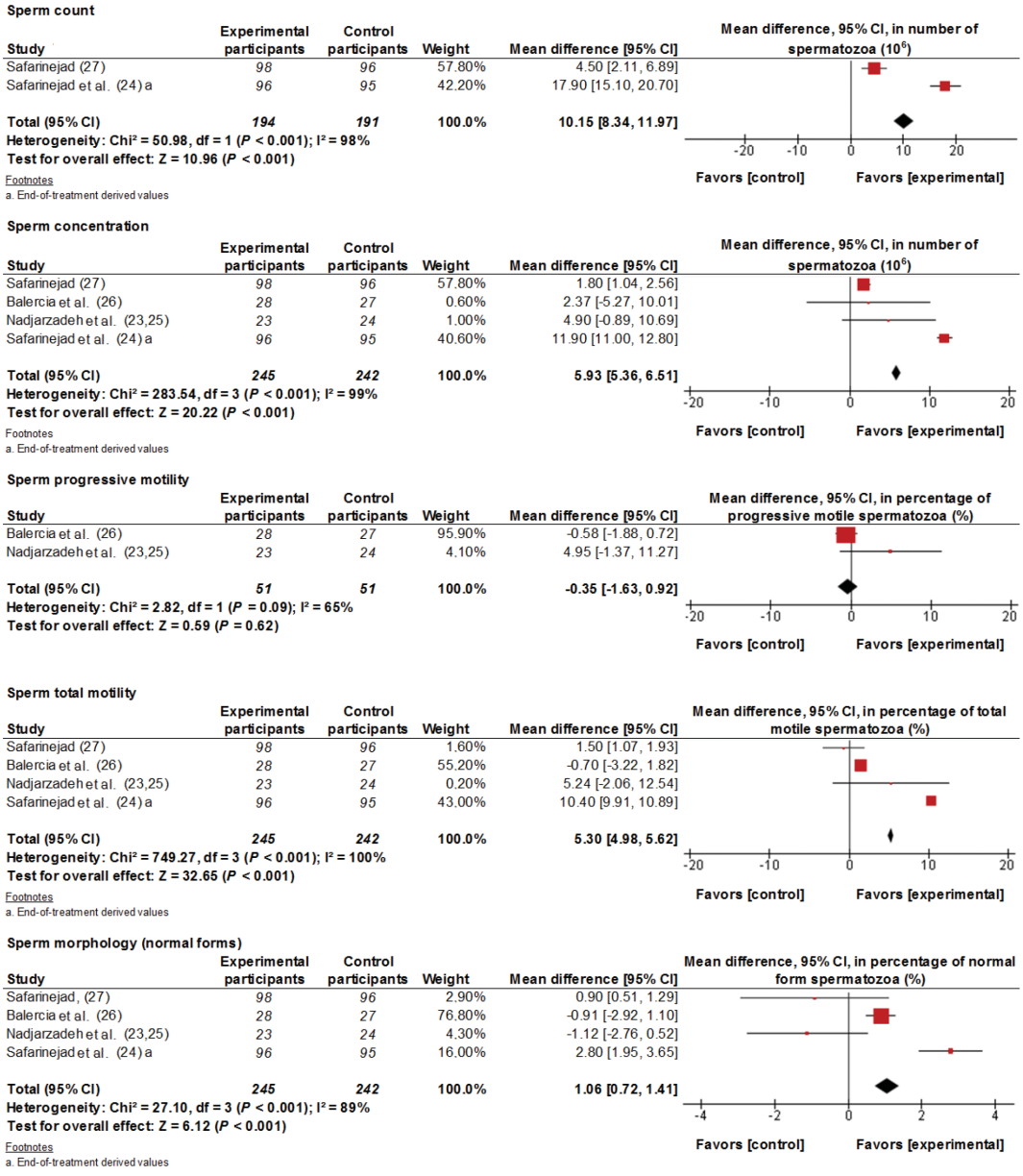

FIGURE 4 MDs and 95% CIs for the effects of coenzyme-Q10 supplements on total sperm count, sperm concentration, sperm progressive motility, sperm total motility, and sperm morphology. The forest plots of the studies use generic-inverse variance and a fixed-effects estimate method. The points for each study indicate the MD, the size of the boxes indicates the weight of the study, and the horizontal lines indicate the 95% CI for each study. The bold data represent the total number of participants for all studies, and the diamond represents the pooled MD. The 2 articles by Nadjarzadeh et al. (23, 25) are computed as 1 study. MD, mean difference.

antioxidant used, because long-term treatments with larger amounts of phenolic or other antioxidant compounds have proven to have pro-oxidant effects. In addition, the low amount/dose of antioxidants used in these studies may have been unable to beneficially affect sperm parameters (46, 47).

Majzoub and Agarwal (48) conducted a narrative review in relation to studies that used antioxidants in iOAT and concluded that additional randomized controlled studies are required to confirm the efficacy and safety of antioxidant supplementation in the medical treatment of idiopathic male infertility, as well as the dosage required to improve semen parameters, fertilization rates, and pregnancy outcomes in iOAT.

The present study shows that carnitine supplementation also has certain beneficial effects on spermatozoa motility and morphology, although there was also considerable heterogeneity between the 3 studies meta-analyzed. LC and LAC play important roles in sperm metabolism by providing immediate available energy for use by spermatozoa, which positively affects sperm motility, the spermatogenic process, and maturation (49). In addition, carnitines are involved in the transportation of long-chain fatty acids into the

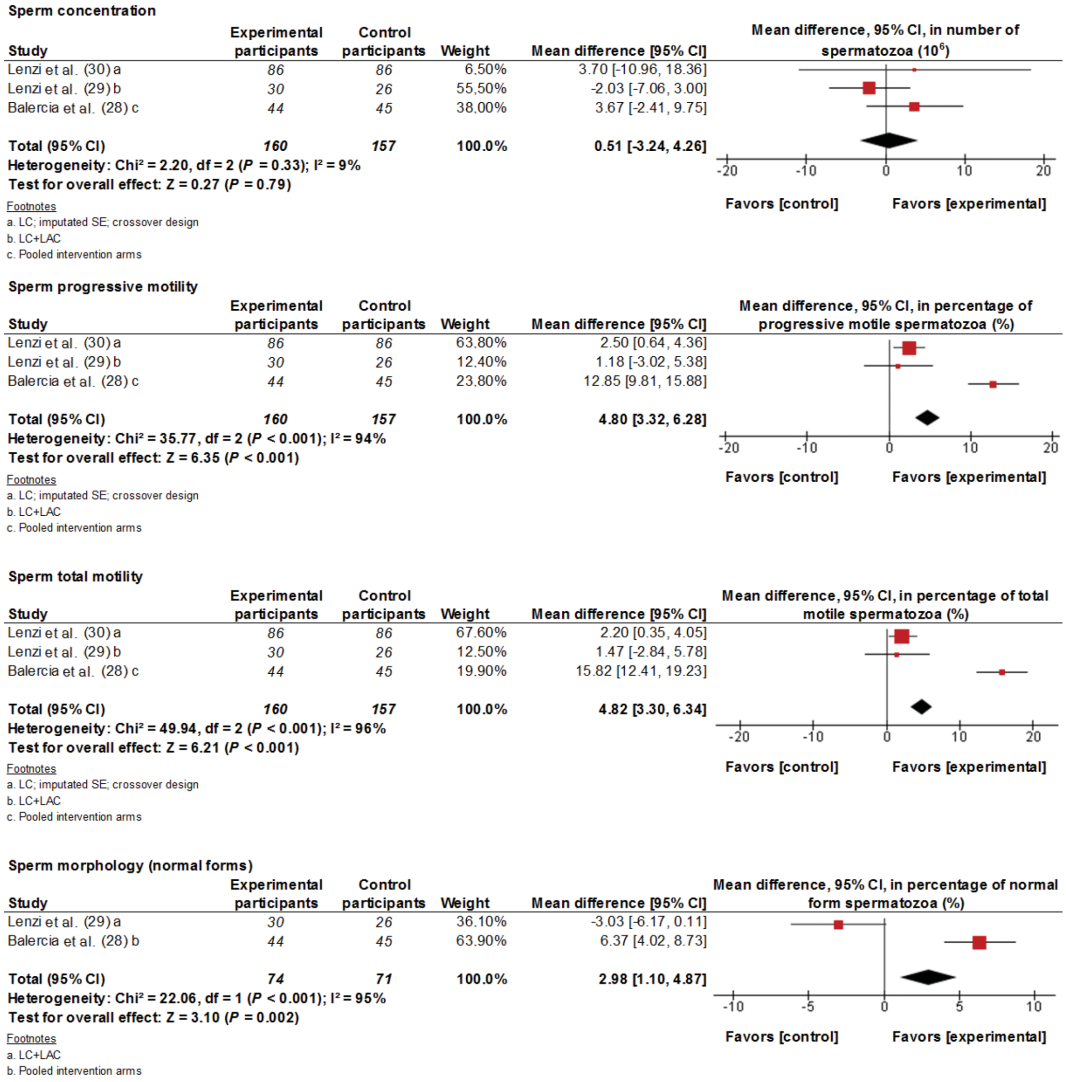

FIGURE 5 MDs and 95% CIs for the effects of carnitine (LC, LAC, or LC + LAC) supplements on sperm concentration, sperm progressive motility, sperm total motility, and sperm morphology. The forest plots of the studies use generic-inverse variance and a fixed-effects estimate method. The points for each study indicate the MD, the size of the boxes indicates the weight of the study, and the horizontal lines indicate the 95% CI for each study. The bold data represent the total number of participants for all studies, and the diamond represents the pooled MD. LAC, L-acetyl carnitine; LC, L-carnitine; MD, mean difference.

mitochondrial matrix for β-oxidation and exert antioxidant activity by increasing the expression of antioxidant enzymes (28). Finally, although studies with food extracts or botanic extracts may be of potential interest for fertility modulation, these types of supplements are outside of the scope of the present review and meta-analysis, and therefore these RCTs have not been included.

Strengths and limitations

Certain limitations of the present study should be acknowledged. The search strategy was limited to the MEDLINE-PubMed database or hand-searching and did not include other databases (e.g., EMBASE). Although our search strategy included a broad number of search terms, and the use of the most relevant scientific database combined with hand-searched reference lists, it is possible (although also improbable) that not all relevant publications were identified. It is also important to point out that, because few studies were included in the meta-analysis (<10 articles meta-analyzed/group), we were unable to assess the across-studies ROB with a post hoc analysis. Also, in the present meta-analysis considerable interstudy heterogeneity was observed for most outcomes, but this could not be explored with subgroup analysis because of the few studies included. It is therefore difficult to draw strong conclusions or to make evidence-based recommendations. Unfortunately, in our analyses we did not control for the background diet and/or any dietary changes that occurred during the intervention in most of the included RCTs. Indeed, whether the changes observed in some fertility parameters can be explained by

changes in the intervention diet remains to be elucidated, thus decreasing the level of scientific evidence derived from these studies. Furthermore, a potential source of bias could be derived from the fact that the studies included in this review did not report information about background medication and/or changes in medication during the trial. However, this is probably irrelevant because most of the studies were conducted in healthy young populations rarely receiving medication. The subfertile populations were heterogeneous and had different phenotypes (e.g., asthenozoospermic, oligoasthenozoospermic, or oligoasthenoteratozoospermic participants; patients with idiopathic infertility who attended infertility clinics). It is difficult, therefore, to generalize the results to other phenotypes of populations. Another limitation relates to judging the biological significance of the improvements observed in some sperm parameters because their effects on fertility need to be confirmed with other studies. Finally, in some studies, neither the manufacture reliability of the supplements used nor their bioavailability are clearly explained, making interpretation of the findings difficult.

The main strengths of the present study include its multistage design with multiauthor validation, the evaluation of ROB, and the possibility of replicating the systematic review and meta-analysis with the same system. Finally, the age range of the populations studied is quite low (18–52 y) and corresponds to the main male reproductive age.

Conclusions

This systematic review and meta-analysis of RCTs provides the most wide-ranging analysis to date of the effects of nutrients, supplements, and food on sperm quality parameters. The present study concludes that diet supplementation with certain antioxidants, especially selenium, zinc, ω-3 fatty acids, CoQ10, and carnitines, and certain foods rich in these supplements can beneficially modulate sperm quality parameters and affect male fertility. The small number of studies that have tested similar supplements, the small sample sizes included in those studies, and the high degree of interstudy heterogeneity across outcomes mean that further research may lead to a change in the effect estimates outlined in this meta-analysis. More RCTs with larger samples and clear inclusion/exclusion criteria are needed in future to test how these types of supplements affect not only sperm parameters but also fecundability.

Acknowledgments

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