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The Effects of Nutritional Supplements on Semen Quality And Pregnancy Rates in Patients with Male-Factor Infertility: A Systematic Literature Review and Network Meta-analysis

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Backgrounds

- Male infertility contributes to approximately 30–50% of infertility cases globally and affects around 7% of men (1). Individuals with fertility issues are often willing to explore multiple strategies recommended on the internet to improve fertility outcomes, with minimal awareness of the scientifically backed evidence.
- Since 2017, the Human Fertilisation and Embryology Authority (HFEA) has worked to reduce the use of add-ons during fertility treatment. The most common add-ons are medications or supplements (39%) according to the HFEA National Patient Survey 2024 (2).
- Despite the increasing use of supplements aimed at improving sperm parameters, the American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) advise that the clinical efficacy of these interventions remains uncertain due to inadequate data (3).
- The objective of this systematic literature review (SLR) and network meta-analysis (NMA) was to establish the relative efficacy of nutritional supplements on semen quality and pregnancy rates in patients with male-factor infertility.

Methods

Systematic Literature review

- Electronic databases, including Embase, MEDLINE, and Cochrane Library, were searched on 13th May 2025. A hand-search of the reference list from relevant SLRs and meta-analyses (MAs) was conducted to identify additional studies.
- The Population Intervention Comparator Outcome and Study design (PICOS) eligibility criteria are shown in Table 1.

Table 1. PICOS framework for the SLR of RCTs investigating supplements and male factor infertility

Element	Description
Population	Adult men diagnosed with male factor infertility (all types), subfertility or poor sperm quality.
Intervention	Nutritional supplements, available over the counter (OTC). Excluding multivitamins with >3 ingredients, foods, Chinese herbal remedies and prescription medications.
Comparison	Placebo or no treatment, or comparison with any nutritional supplement.
Outcome	Sperm parameters (count, motility) and pregnancy rates.
Study type	Randomised controlled trials (RCTs) with treatment duration ≥2 months.
Language	English language

- Data on the study design, patient population, data source, treatment details, and outcomes of interest (sperm parameters and pregnancy rate) were extracted into a data extraction table.

Network Meta-Analysis

- A Bayesian NMA was carried out in accordance with NICE guidelines. All models were run in WinBUGS, version 1.4.3, using codes adapted from the NICE Decision Support Unit Technical Support Document 2 (TSD2).
- Sperm parameters were analysed in the form of the change from baseline to 3 (±1) months, given that spermatogenesis takes approximately 74 days (4). Pregnancy rate was reported as a binary outcome (number of events in each arm) throughout follow-up. Due to frequently sparse event rate and the risk of bias by implementing continuity correction, pregnancy rates were analysed as a continuous outcome on the risk difference scale.
- Fixed and random effects models were implemented. Model selection was based on the model fit statistics (DIC, total residual deviance and the precision of the RE component estimation). Vague, non-informative priors were applied to all parameters.
- Heterogeneity and inconsistency were assessed using R. For direct evidence informed by at least two studies, the I^2 statistic was calculated, demonstrating the magnitude of heterogeneity between studies. Inconsistency between the direct and indirect evidence was assessed using the node splitting method.
- Results were reported as the median relative effects and 95% credible interval (CrI), estimated in the models: the mean difference (MD) (continuous outcomes) and the risk difference (RD) (binary outcome), of each supplement relative to placebo.
- Supplements were ranked using the SUCRA (Surface Under the Cumulative Ranking Curve). An overall SUCRA was derived from the three key sperm parameters (concentration, motility and morphology), assuming equal weighting across these three outcomes, which reflects an equivalent clinical relevance in assessing male fertility.

Results

- The overall PRISMA flow diagram for the SLR, including the reasons for publications being excluded at first and second pass, has been summarised in Figure 1. The SLR identified 66 publications on 64 studies that investigated 34 supplements or combinations of ≤3 supplements in patients with male factor infertility.
- Trials were conducted in Africa, Asia, Europe, North and South America, frequently in a single center. Trial duration ranged from 8 weeks to 12 months. The number of randomised participants ranged from 20 to 2370; over half the trials were <100 participants in size.
- 45 trials were included in at least one semen quality analysis; the overall network of evidence is presented in Figure 2.
- The relative effect between each supplement and placebo, on the change in sperm quality outcomes from baseline to 3 months, is presented in Table 2. The random effects model was the preferred candidate for all analyses.
- Relative to placebo, ALA was the only supplement which significantly increased the sperm concentration from baseline to 3 months, relative to placebo, MD (95%CrI) of 15.3x10⁶/ml (5.3, 25.4).
- Relative to placebo, two supplements demonstrated a significant improvement in sperm motility: ALA and selenium plus vitamins; associated with an MD (95%CrI) in the sperm motility of 13.3% (5.6, 21.2) and 12.0% (2.8, 21.1), respectively. The largest numerical effect was demonstrated by lycopene, 17.3% (-0.2, 34.7); however this difference did not reach statistical significance.

Figure 1. PRISMA diagram for the SLR of RCTs investigating nutritional supplements and male-factor infertility

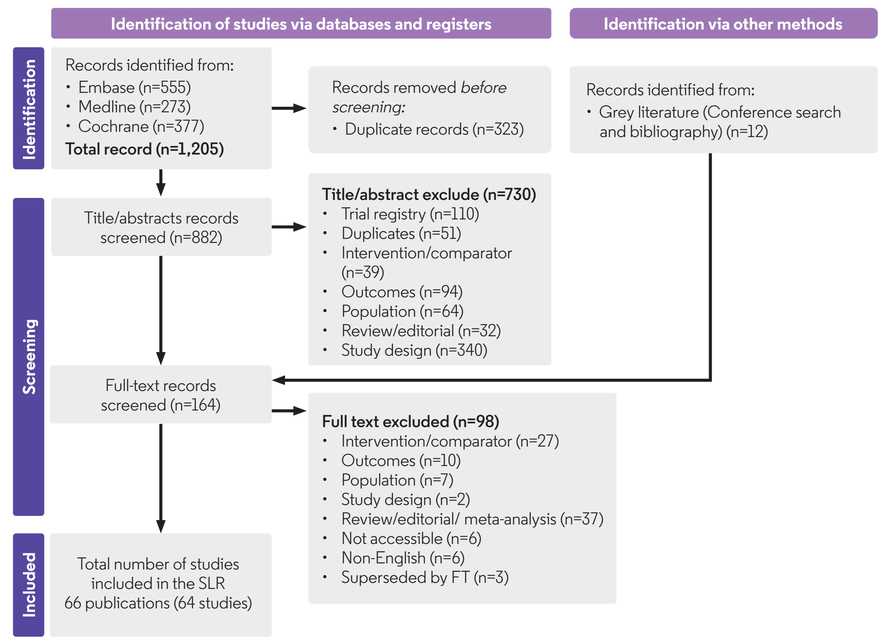
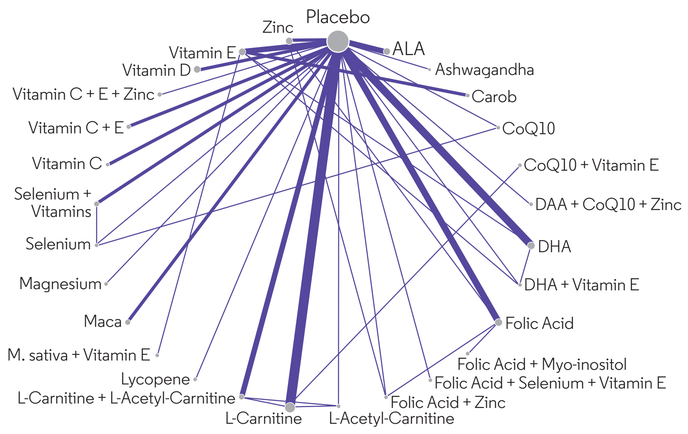


Figure 2. Network of evidence across all trials included in the analyses of at least one sperm parameter (N=45 studies included in the sperm parameter analyses at 3 ± 1 months)



- Two supplements showed significant improvement in sperm morphology: vitamin C and zinc. Relative to placebo, the mean change from baseline to 3 months in the percentage of sperm with normal morphology increased by a MD (95%CrI) of 12.7% (3.9, 21.4) and 4.6% (1.3, 7.9), with vitamin C and zinc, respectively.
- ALA was ranked the most effective treatment, based on the average SUCRA values estimated from the sperm concentration, motility and morphology analyses.
- No supplements demonstrated a statistically significant change in semen volume or DNA fragmentation from baseline to 3 months, when compared with placebo; 21 and 8 trials were included in these analyses, respectively.
- A moderate-high level of heterogeneity was present for most repeated comparisons. Significant evidence of inconsistency was identified in a small subset of the loops; hence the impact of inconsistency on the NMA is expected to be minimal.
- Outlier identification was outcome-dependent; trials which appeared as outliers for one sperm quality endpoint endpoint frequently did not demonstrate similar deviations in other analyses.

Table 2. Relative effect, MD (95%CrI), between all supplements and placebo, on semen quality outcomes after 3±1 months

Nutritional supplement	Sperm concentration (10⁶/ml)	Sperm motility (% motile)	Sperm morphology (% normal)	SUCRA RANK*	Semen volume (ml)	DNA fragmentation (%)
ALA	**15.3 (5.3, 25.4)**	**13.3 (5.6, 21.2)**	0.6 (-2.3, 3.7)	1	0.4 (-0.16, 0.94)	-1.9 (-15.7, 11.5)
Ashwagandha	13.8 (-2.3, 29.9)	8.9 (-4.5, 22.3)	N/A	2	0.65 (-0.22, 1.53)	NA
Carob	9.6 (-8, 27.5)	10.6 (-2, 24.3)	2.9 (-4.7, 9.8)	4	-0.13 (-1.29, 1.06)	NA
CoQ10	7,4 (-6.5, 21.2)	9.4 (-2.9, 21.4)	-1.1 (-7.4, 5.2)	10	NA	NA
CoQ10 + Vitamin E	-5.2 (-24.4, 13.9)	-1.1 (-16.2, 13.9)	1.9 (-5.1, 8.9)	26	NA	NA
CoQ10 + DAA + Zinc	2.1 (-22, 26.1)	1.1 (-14.4, 16.7)	-3 (-13.8, 7.8)	27	NA	NA
DHA	0.5 (-7.4, 8.3)	2.8 (-3.3, 9)	-0.1 (-3.2, 3)	24	0.09 (-0.36, 0.6)	-10.9 (-22.8, 2.2)
DHA + Vitamin E	2 (-11.5, 15.6)	4,4 (-6.7, 15.6)	0.1 (-5, 5.2)	18	0.05 (-0.67, 0.8)	NA
Folic Acid	8.4 (-1.3, 17.8)	2.1 (-5.5, 9.6)	0.3 (-3.1, 3.8)	16	NA	-1.4 (-20.2, 17.4)
Folic Acid + Myo-inositol	14.1 (-4.4, 32.2)	6.5 (-8.5, 21.3)	NA	5	NA	NA
Folic Acid + Selenium + Vitamin E	10.5 (-9.7, 30.7)	-2.5 (-17.9, 12.9)	-2.9 (-10.6, 4.8)	21	-0.02 (-0.95, 0.92)	NA
Folic Acid + Zinc	7.7 (-6.2, 21.4)	7.8 (-3.5, 19)	3.2 (-1.9, 8.3)	6	NA	NA
L-Acetyl-Carnitine	6.9 (-10.2, 24)	7.6 (-4.9, 20)	3.5 (-3, 10)	7	0.01 (-0.94, 0.94)	NA
L-Carnitine	2.4 (-7.3, 12)	4.8 (-2.4, 11.9)	2.5 (-1.3, 6.3)	11	-0.16 (-1.04, 0.7)	-1.1 (-20.1, 17.9)
L-Carnitine + L-Acetyl-Carnitine	2.7 (-9.6, 15.2)	5 (-4.1, 13.9)	2.4 (-2.5, 7.2)	12	-0.23 (-1.21, 0.74)	NA
Lycopene	8.8 (-7.7, 25.2)	17.3 (-0.2, 34.7)	-0.5 (-6.4, 5.2)	8	1.2 (-0.26, 2.66)	NA
M. sativa + Vitamin E	NA	NA	0.9 (-6.2, 7.9)	14	0.09 (-0.91, 1.14)	NA
Maca	2.4 (-8.7, 13.6)	1.8 (-11.2, 14.6)	0.4 (-5.5, 6.3)	19	-0.28 (-1.15, 0.58)	NA
Magnesium	2.9 (-14.5, 20.2)	-5.1 (-24, 13.8)	0.1 (-13.2, 13.4)	25	NA	NA
Selenium	5.7 (-7.5, 18.9)	10.6 (-0.2, 21.3)	-4.5 (-13.6, 4.7)	17	NA	NA
Selenium + Vitamins	-2.8 (-14.6, 9.1)	**12 (2.8, 21.1)**	0.7 (-5.1, 6.5)	15	-0.1 (-0.93, 0.74)	NA
Vitamin C	4.8 (-13.4, 23.1)	8.2 (-6.7, 23.2)	**12.7 (3.9, 21.4)**	3	NA	NA
Vitamin C + E	4.3 (-9.3, 17.9)	-0.1 (-11.7, 11.6)	-0.9 (-6.2, 4.5)	23	-0.2 (-1.74, 1.34)	-13.4 (-32.4, 5.9)
Vitamin C + E + Zinc	-0.7 (-16.4, 14.9)	2 (-11.8, 15.8)	0.1 (-5.7, 5.9)	22	-0.2 (-1.1, 0.69)	NA
Vitamin D	1.9 (-9.8, 13.4)	6.7 (-1.2, 14.6)	1.1 (-3.4, 5.7)	13	-0.05 (-0.56, 0.46)	NA
Vitamin E	1.3 (-8.1, 11)	2.9 (-5.1, 11)	0.3 (-3.6, 4.2)	20	0.09 (-0.48, 0.7)	NA
Zinc	6 (-1.9, 13.8)	-0.3 (-6.9, 6.2)	**4.6 (1.3, 7.9)**	9	NA	-4 (-22.7, 15.1)

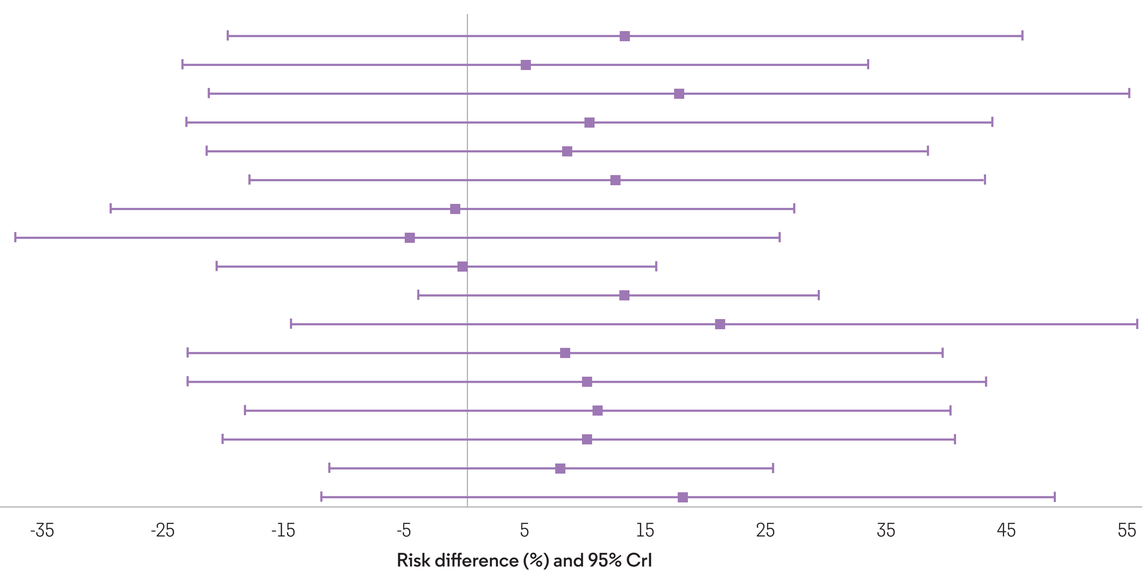
- Seventeen supplements were evaluated across 22 trials for their effect on pregnancy rate, excluding three trials with zero events in both arms. The treatment effect of each supplement relative to placebo, on the probability of pregnancy during follow-up, is shown in Figure 3.
- No supplement demonstrated significant evidence in improving the probability of pregnancy. Although most supplements demonstrated a numerically favourable effect on pregnancy rate compared with placebo, all treatment effects were estimated with considerable uncertainty. This imprecision is attributable to two factors:
  1. Moderate between-study heterogeneity was observed and few pairwise comparisons were repeated in the network, meaning the RE component was estimated with sparse data; the model fit statistics demonstrated a preference for the RE model.
  2. Eventhough modelling the outcome as a risk difference instead of odds ratio slightly attenuates the impact of low event rates, sparse data and low event rates propagate uncertainty through the model, resulting in wide credible intervals and reduced in the estimated treatment effects.

Abbreviations: CrI, credible interval. ALA, Alpha-Lipoic Acid. CoQ10, Coenzyme Q10. DAA, D-Aspartic Acid. DHA, Docosahexaenoic Acid. M.sativa, Medicago sativa. NA, not applicable. MD, mean difference. SUCRA, surface area under the curve.

Legend: **bold,** statistically significant evidence of a difference between supplement and placebo. Green, favouring the supplement over a placebo. Red, favouring the placebo over the supplement. *, based on the average SUCRA estimated from the sperm concentration, motility and morphology models.

Figure 3. Relative effect, RD (95%CrI), between all nutritional supplements and placebo on the probability of pregnancy at end of follow-up (including all treatment durations)

Intervention	RD (95% CrI)
ALA	13.15 (-19.75, 45.98)
Calcium + Vitamin D	4.96 (-23.6, 33.25)
Carob	17.67 (-21.42, 55.08)
CoQ10	10.24 (-23.18, 43.64)
DAA + CoQ10 + Zinc	8.33 (-21.51, 38.38)
Folic Acid	12.35 (-18.03, 43.04)
Folic Acid + Zinc	-0.92 (-29.37, 27.26)
L-Acetyl-Carnitine	-4.72 (-37.47, 26.08)
L-Carnitine	-0.22 (-20.61, 15.81)
L-Carnitine + L-Acetyl-Carnitine	13.17 (-4.04, 29.14)
M. sativa + Vitamin E	21.09 (-14.65, 55.8)
Maca	8.06 (-23.21, 39.45)
Magnesium	10.06 (-23.2, 43.14)
Selenium + Vitamins	10.84 (-18.36, 40.13)
Vitamin C + E + Zinc	10 (-20.29, 40.49)
Vitamin E	7.74 (-11.45, 25.38)
Zinc	18.3 (-11.93, 48.83)



Conclusions

- This is the first Bayesian NMA investigating nutritional supplements and male-factor infertility, to our knowledge. The comprehensive evidence synthesis considered treatment duration relative to spermatogenesis and carefully handled combination therapies via specific treatment labels to avoid generalised conclusions on combination therapies without the ability to isolate individual treatment effects.
- Substantial between-study heterogeneity in the treatment effects was observed and there was frequently a lack of dose-response consistency; where a supplement in monotherapy demonstrated a significant improvement however when used in combination with another numerically beneficial supplement, the effect was attenuated. Differences in the trial design, sparse data (small RCTs) on certain supplement combinations, or the difference in supplement dosages between mono-therapy and combination treatments, may all be plausible explanations. More concerningly, in the age of 'supplement stacking', the co-formulation of multiple nutrients may lead to treatment effect modification, possibly due to antagonistic interactions.
- While certain supplements show potential to improve semen quality over 3 months, these improvements were often limited to a single sperm parameter. No supplements demonstrated evidence of increasing the probability of pregnancy relative to a placebo. Several studies investigated the impact of supplements on sperm parameters, without establishing whether there is a concurrent benefit on the rate of pregnancies. Pregnancy is a key clinical outcome that should be included in future evaluations of male factor infertility treatments.

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