Drugs (2023) 83:531–546
https://doi.org/10.1007/s40265-023-01853-0

SYSTEMATIC REVIEW

Effectiveness of Nutritional Therapies in Male Factor Infertility Treatment: A Systematic Review and Network Meta-analysis

Mohammad Ishraq Zafar[1,2] · Kerry E. Mills[3,4] · Charles D. Baird[4] · Huahua Jiang[5] · Honggang Li[1,6]

Accepted: 20 February 2023 / Published online: 21 March 2023

Abstract

Background Nutritional therapies are effective alternative treatments for male infertility or subfertility. These are cost-effective and easily implementable, unlike other advanced invasive treatments. Even moderate improvements in sperm quality could improve spontaneous pregnancy.

Objective We aimed to compare the effectiveness of all nutritional therapies in male infertility/subfertility treatment and ranked their efficacy based on type and etiology. We intend to aid clinicians with an evidence-based approach to affordable and safer initial infertility treatment for those who mainly do not wish to have other advanced invasive treatments or could not afford or have access to them.

Methods We included 69 studies with 94 individual study arms identified from bibliographic databases and registries. We included studies in adult men with proven infertility or subfertility that investigated nutritional or dietary supplement therapies compared with control or placebo and at least reported on a sperm parameter. We undertook a network meta-analysis and performed a pairwise meta-analysis on all sperm parameter outcomes and meta-regression. No language or date restriction was imposed. A systematic article search was concluded on August 29, 2022.

Results Our network meta-analysis is the first to compare all dietary interventions in a single analysis, sub-grouped by intervention type and type of infertility. L-Carnitine with micronutrients, antioxidants, and several traditional herbal supplements showed statistically and clinically significant improvement in sperm quality. Meta-regression identified that improvement in the sperm count, motility and morphology translated into increased pregnancy rates ($p < 0.001$; $p < 0.001$; $p < 0.002$, respectively). In particular, L-carnitine with micronutrient therapy (risk ratio [RR]: 3.60, 95% CI 1.86, 6.98, $p = 0.0002$), followed by zinc (RR 5.39, 95% CI 1.26, 23.04, $p = 0.02$), significantly improved pregnancy rates. Men with oligozoospermia (RR 4.89), followed by oligoasthenozoospermia (RR 4.20) and asthenoteratozoospermia (RR 3.53), showed a significant increase in pregnancy rates.

Conclusion We ranked nutritional therapies for their ability to improve sperm quality in men with infertility. Nutritional therapies, particularly L-carnitine alone or combined with micronutrients, significantly improved sperm parameters and pregnancy rates even under severe conditions. We believe these affordable solutions may be valuable for people without access to or who do not wish to undergo more invasive and costly fertility treatments.

✉ Kerry E. Mills
kerry.mills@canberra.edu.au

✉ Honggang Li
lhgyx@hotmail.com

Mohammad Ishraq Zafar
drishraq@live.com

Charles D. Baird
charles@trudatarx.com

Huahua Jiang
xzjhh72@163.com

[1] Institute of Reproductive Health/Center of Reproductive Medicine, Tongji Medical College, Huazhong University of Science and Technology, 13 Hang Kong Road, Wuhan 430030, China

[2] Reproductive Medicine Center, Fourth Affiliated Hospital Zhejiang University School of Medicine, Yiwu, China

[3] Department of Science and Technology, University of Canberra, Bruce 2617, Canberra, Australia

[4] TruDataRx, White River Junction, Vermont, USA

[5] Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing, China

[6] Wuhan Huake Reproductive Hospital, Wuhan, China

Key Points

Male infertility is a serious and increasing problem worldwide. Advanced surgical procedures have high personal and financial costs, and the availability of treatment in underdeveloped countries remains another source of challenge.

This study overall findings identified that L-carnitine alone or combined with other supplements significantly improved sperm quality leading to improved pregnancy rates. Men with oligozoospermia largely benefited from treatment and had increased pregnancy rates compared with men receiving placebo or no treatment.

For men, even with severe conditions (oligoasthenoteratozoospermia), nutritional therapies effectively improved sperm characteristics, sex hormones, and, most importantly, pregnancy rates.

1 Introduction

Infertility, is defined as the inability of a sexually-potent couple to conceive after a year of regular intercourse without using contraceptive methods—it occurs in 10–15% of couples [1, 2]. Despite the absence of reliable figures on the worldwide rate of infertility [3], it is suggested that fertility issues occur in approximately 60–80 million couples worldwide [4, 5].

Overall, male factor infertility represents 40–50% of total infertility [6], with 7% of all men being affected [7]. It can result from a reduction in sperm concentration (oligospermia), motility (asthenospermia), morphology (teratospermia), or a combination of any or all of these [8]. Male factor infertility is diagnosed when a man has sperm parameters that do not meet the values set by the World Health Organization (WHO) [9]; semen volume or hormonal changes are associated with male infertility to a lesser degree [10]. Indeed, approximately 90% of male factor infertility can be attributed to changes in the total sperm count [11].

The source of male factor infertility can be broadly classified into hypothalamic–hypophyseal tract disorders, testicular diseases, seminal tract disorders, immunological conditions, and psychosomatic conditions [12]. Varicocele is one of the leading correctable causes of male infertility [13], both in general (14.8%) and azoospermic populations (10.9%) [14]. Various modifiable risk factors are identified to impact semen parameters directly. For example, unhealthy dietary habits and elevated body mass index (BMI) are associated with a decline in semen parameters [15], along with tobacco smoking [16], caffeine intake [17], and alcohol intake [18].

In recent years, accumulating evidence suggests that healthy dietary patterns/habits and nutritional modifications are associated with improved sperm quality and other sperm-related parameters, including quantity, concentration, motility, morphology, and DNA fragmentation [19–22]. In this context, various dietary and nutritional interventions have been investigated for their efficacy in improving sperm parameters in infertile men. For example, omega-3 fatty acids combined with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) improve sperm motility [23]. Coenzyme Q10 (CoQ10) has been shown to significantly impact semen parameters in infertile men, with improvement in sperm count, total sperm concentration, sperm motility, and sperm morphology [24–26], even in men with oligospermia and asthenozoospermia [27]. Selenium is an essential element for spermatogenesis [28], and has been reported to improve oligozoospermia and asthenozoospermia [27] through an effect on sperm parameters [25]. Meanwhile, L-carnitine and acetyl-L-carnitine have been shown to have beneficial outcomes on asthenozoospermia [27], resulting in a significant increase in sperm motility and morphology [25]. Moreover, various randomized controlled trials (RCTs) have shown the beneficial effects of supplementation with vitamin C [29, 30], vitamin E [31–33], and vitamin D [34] on pregnancy rates [32] and semen-related parameters, and a recent meta-analysis also found significant improvements in both sperm health and pregnancy rates after antioxidant treatment [35].

Access to in vitro fertilization and other assisted reproductive technologies is not available worldwide, particularly in low- and middle-income countries [36]. Even in comparatively wealthy countries, significant disparities exist in access to infertility treatment [37]. Thus, access to information about safe, effective, and affordable interventions for infertility would be of immense value. A recent meta-analysis summarized the evidence for drug and nutritional interventions for male factor infertility [38]. Our study summarizes and ranks the comparative efficacy of all nutritional interventions in treating male infertility of different origins or causes. Therefore, we performed a comprehensive network meta-analysis to determine the most effective interventions for each subtype of male factor infertility. This analysis gives doctors and other health professionals an evidence-based approach to the affordable and safe initial treatment of male factor infertility.

2 Methods

2.1 Preferred Reporting Items for Systematic Reviews and Meta-analyses Guidelines and Review Registration

This systematic review and network meta-analysis was undertaken in accordance with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network

Meta-analyses of Health Care Interventions [39] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42020159070.

2.2 Review Question [PICOTS: Population (P), Intervention (I), Comparison (C), Outcome (O), Time (T), Study (S)]

The PICOTS for our review were: adult men with subfertility or infertility (**P**), dietary interventions or nutritional supplements (**I**), compare with placebo, no treatment, or other dietary interventions or nutritional supplements (**C**), increase sperm parameters, sperm quality, hormone concentrations, or rates of pregnancy or live births (**O**), for two weeks or longer (**T**) in randomized, controlled trials (**S**)?

2.3 Data Sources and Search Strategy

We designed a comprehensive search strategy (Supplementary Table 1) and modified it for use in PubMed, the Cochrane Library, Scopus, clinicaltrials.gov, and the WHO clinical trials database. We had no restrictions on dates or language. The last search was carried out on 29 August 2022.

2.4 Eligibility Criteria

The criteria for inclusion in the review were: randomized, controlled trials of two weeks or longer in duration in men with subfertility or infertility who used dietary changes or nutritional supplements as an intervention, compared with other interventions, placebo, or no treatment. The studies had to report at least one measure of sperm quality or fecundity. Studies that were not RCTs, did not treat male factor infertility, used drugs instead of nutritional or dietary interventions, had an intervention period shorter than two weeks, carried out in healthy men, and animal models or cell lines, were excluded.

2.5 Study Selection

The search results were uploaded to EPPI-Reviewer Web [40], where duplicates were removed. All abstracts were then assigned to MIZ and KEM for double-blind inclusion and exclusion using the coding assignment function. Disagreements were resolved by consensus. After abstract coding, full texts of the included articles were obtained and were included or excluded using EPPI-Reviewer in a double-blind manner by the same two authors. Disagreements were resolved by consensus.

2.6 Study Quality

The quality of the included studies was determined by MIZ and KEM using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials [41]. Disagreements were resolved by consensus. The risk of bias was assessed in seven areas: (i) random sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) incomplete outcome data (attrition bias), (vi) selective reporting (reporting bias), and (vii) other bias.

In the network meta-analysis, we assessed bias in our model with a network funnel plot using the funnel command of *netmeta* [42].

2.7 Outcomes

The following outcomes were included in our analysis: pregnancy (defined as clinical intrauterine pregnancy, or simply "pregnancy" if not otherwise stated), live births, sperm count (defined as $n \times 10^6$), semen volume (mL), percent of sperm with normal morphology, percent of motile sperm (total motile sperm, unless only forward motility data were given), DNA fragmentation, chromomycin A3 staining, follicular stimulating hormone (FSH), luteinizing hormone (LH), Inhibin B, and testosterone.

2.8 Data Extraction

Study characteristics and pre-specified outcomes of interest were extracted by HJ and checked by KEM. The data were extracted into a series of spreadsheets specifically designed for the analysis. If data were available only within figures, we extracted the data using WebPlotDigitizer [43]. For all studies, the baseline sperm characteristics were compared with the WHO normal values, which were used to categorize the type of infertility. If the men in a study exceeded all WHO normal values but were still infertile, we assigned them as having idiopathic infertility.

2.9 Data Synthesis

2.9.1 Data Conversions

Where data reported outcomes as means and standard errors, the standard errors were converted to standard deviations using the equation:

$$\mathrm{SD} = \mathrm{SEM} \times \sqrt{n-1},$$

where *n* is the number in the study arm, data reported as medians and range or interquartile range were tested for skewness [44] and, if not skewed, were converted to means and standard deviations using the models of Luo et al. [45] and Wan et al. [46], respectively.

2.9.2 Meta-analysis

For meta-analysis of included studies, data were copied into Review Manager 5.4.1 [47]. Continuous outcomes were calculated as mean differences with 95% confidence intervals (CIs) using a random effects, inverse variance model [48]. Dichotomous outcomes were calculated as random effects Mantel–Haenszel risk ratios or odds ratios with 95% CIs. Random effects models were chosen due to differences in the types of infertility, age, and ethnicity of the men and other baseline differences, such as BMI and other comorbidities.

Heterogeneity was calculated using Review Manager 5.4 and was reported as Tau^2, Chi^2, and I^2. Heterogeneity was interpreted using the I^2 statistic. As suggested by the Cochrane Handbook for Systematic Reviews of Interventions [49], we interpreted the I^2 statistic thus: 0 to 40%: might not be important; 30 to 60%: may represent moderate heterogeneity; 50 to 90%: may represent substantial heterogeneity; and 75 to 100%: considerable heterogeneity.

The overall consideration of the importance of the calculated heterogeneity involved the I^2 statistic, along with other information such as the number of studies, the types of included studies, and other factors [49].

2.9.3 Meta-regression

We undertook univariate meta-regression of pregnancy rates using the sperm characteristics (sperm count, sperm morphology, sperm motility, and semen volume) as covariates, given there were at least 10 studies available. We undertook multivariate meta-regression of pregnancy rates using sperm characteristics and type of infertility as covariates. Multivariate meta-regression was undertaken only if 10 studies per covariate were available [49]. We undertook univariate and multivariate meta-regression using OpenMetaAnalyst with a random-effects model [50]. The 10-study limit was to ensure the outcomes could be meaningfully interpreted [49].

2.9.4 Network Meta-analysis

Frequentist network meta-analyses of risk ratios with the function *netmetabin* and mean differences in interventions with the function *netmeta* were performed with the R package *netmeta* [42]. We checked for heterogeneity within comparisons, quantified with the I^2 statistic. The direct and indirect evidence was compared using local and global methods. We used the netsplit command of *netmeta* to detect inconsistency locally by checking for disagreement between direct and indirect estimates. We used the decomp.design command of *netmeta* to detect inconsistency throughout the network, assuming a full design-by-treatment interaction random effects model. Heat plots generated by the netheat command of netmeta are included to visualize hot spots of inconsistency. Sensitivity analyses were performed on all interventions where at least three studies reported the outcome measure. Transitivity was assessed via the geometry of the networks of the four outcomes. Visualizations of the data from these analyses were done using the R packages *netmeta,* and *ggplot2* [51]. League tables were created using the R package *netmeta*. We ranked the interventions in order of most to least efficacious using the surface under the cumulative ranking (SUCRA) curve [52] and visualized these as forest plots and SUCRA curves.

2.9.5 Sensitivity and Subgroup Analyses

We planned subgroup analyses a priori by dietary advice versus provision of the intervention (e.g., foods, supplements, and beverages), the type of dietary intervention or supplement, the age of the participants, the baseline sperm count, the baseline BMI or body weight, the baseline glycemic markers (e.g., fasting blood glucose, diabetes status), baseline inflammatory markers (e.g., C reactive protein [CRP], erythrocyte sedimentation rate, $\alpha-1$ antitrypsin, tumor necrosis factor alpha-receptor type II, etc.), ethnicity, high quality versus low quality studies, and concomitant medication.

Where standard deviations were imputed, sensitivity analysis was done by removing these studies and observing the effect this had on the effect sizes or risk ratios, along with the 95% CIs.

2.9.6 Clinical Relevance

The WHO published reference values for human semen characteristics in 2010 [53]. According to this publication, healthy, fertile men have the following sperm values; semen volume: ≥2 mL; sperm concentration: ≥20 million per mL; motility: ≥50% motile; morphologically normal forms: ≥15%. In infertile men, it has been shown that a motile sperm count of 5 million/mL can significantly increase pregnancy rates, based on the findings of Bostofte et al. [54].

2.10 Presentation and Interpretation of Findings

We presented the findings of our pairwise meta-analysis as forest plots using Review Manager 5.4 [47]. The outcomes

of the meta-analyses and network meta-analyses are presented as GRADE tables [55] using the template for continuous outcomes given in Yepes-Nuñez 2019 [56]. The results are discussed with respect to GRADE evaluations of certainty throughout the results section.

3 Results

3.1 Included Studies

We received 8649 citations, of which 7425 were duplicates. We reviewed the remaining 1224 citations at the title and abstract level using EPPI-Reviewer Web with double-blind coding. This resulted in 112 full texts. These were obtained and submitted to double-blind coding as above. We excluded 43 full texts, leaving 69 included articles with 94 different study arms (Fig. 1).

3.2 Study Characteristics

The studies (Supplementary Table 2) ran for 1–18 months and included as dietary interventions antioxidants, carob, coenzyme Q10, folic acid, L-carnitine, myoinositol, cysteine, fatty acids, herb and mineral supplements, saffron, selenium, spirulina, vitamin C, vitamin D, vitamin E, calcium, zinc

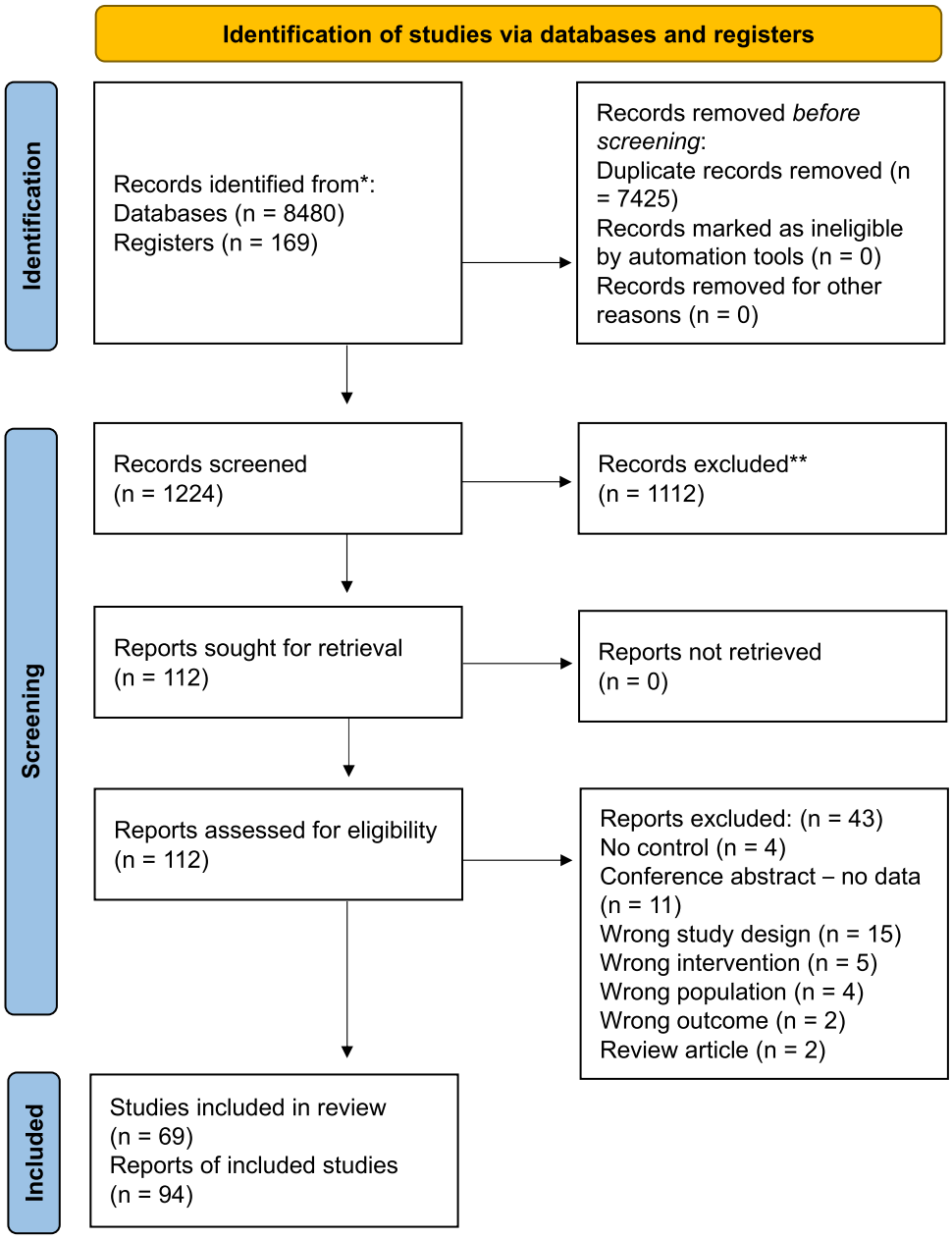


Fig. 1 PRISMA Flow diagram. Of 8649 records identified from databases and registers, 7425 were duplicates. The remaining 1224 records were screened at the title and abstract level, which excluded a further 1112 records. The remaining 112 reports were obtained and subjected to the inclusion and exclusion criteria. Of these, 69 studies including 94 study arms were included in the final review

and micronutrient and other dietary mixed supplements. The vast majority of studies used a placebo as a control, with 10 studies (12 study arms) using no treatment as a control. In terms of active control studies, one study compared two commercial fertility supplements, one compared traditional honey with a herbal extract, one study compared walnuts with a micronutrient supplement, two studies used vitamin E as a control, and three studies used a combination of vitamin E and vitamin C as a control. Study sizes varied widely, from 8 participants to 1185 participants in the intervention groups. Studies were conducted in many countries representing major cultural and ethnic groups. Most studies were published in English, but our analysis included Russian, Mandarin, and Farsi studies. These were translated with the help of native speakers.

The men in the studies were aged 18–61 years and presented with asthenoteratozoospermia, asthenozoospermia, hypogonadotropic hypogonadism, idiopathic infertility (all sperm parameters exceeded the WHO normal thresholds), oligoasthenoteratozoospermia, oligoasthenozoospermia, oligozoospermia, teratozoospermia, varicocele (grades 1–5), and varicocelectomy. Body weight and BMI were only rarely reported, but the mean BMI ranged from 21.5 to 28.0.

3.3 Quality of Included Studies

The quality of the included studies was generally good or unclear (Supplementary Fig. 1). Many studies did not report on the method of randomization or if allocation concealment or outcome assessors were blinded. Most studies did not publish a protocol prior to the trial, and it was thus impossible to determine if all measured outcomes were reported. However, most studies were blinded, at least to participants, and most were not funded by pharmaceutical companies or other industries.

3.4 Quality of the Network

We used the back-calculation method to split the indirect evidence from direct evidence in order to test for local inconsistency within the network. No local inconsistencies were found in any of the networks, which is consistent with our expectations after inspection of the network geometry. Global consistency was tested using a full design-by-treatment interaction model [57]. While the value of the Q statistic is considerably smaller in the morphology and volume networks; significant between-design inconsistency is indicated in the count and motility networks. For the volume and pregnancy networks, which contained only two designs, a between-design Q statistic was not calculated.

Inspection of network heat plots indicates much higher inconsistency under a common (fixed) effects model, supporting our use of random effects. The heat plot for the pregnancy network did not show significant inconsistency (Supplementary Fig. 2). In the sperm count network, the evidence contributed by comparing L-carnitine to placebo (and to a lesser extent, Herbal supplement to placebo and Vitamin E to Herbal supplement) for the estimation of Vitamin E to L-carnitine is inconsistent (Supplementary Fig. 3). In the motility network, the evidence contributed by comparing Vitamin C + Vitamin E to L-carnitine for estimating Vitamin C + Vitamin E to placebo is inconsistent (Supplementary Fig. 4). Inspection of the heat plots for sperm morphology (Supplementary Fig. 5) and semen volume (Supplementary Fig. 6) did not show significant inconsistency.

Treatments were ordered by the number of studies per treatment from fewest to most. The funnel plots for the continuous outcomes: sperm count (Supplementary Fig. 7), sperm motility (Supplementary Fig. 8), sperm morphology (Supplementary Fig. 9), and semen volume (Supplementary Fig. 10) appear symmetrical upon inspection and do not indicate bias. This is supported by non-significant results from Egger's test for regression (0.5951, 0.8586, 0.3230, and 0.5077, respectively) [58]. A funnel plot to test for asymmetry in the pregnancy network was not included, as according to the Cochrane handbook, funnel plots have been extensively studied for odds ratios, but not for risk ratios and risk differences [59].

3.5 Fecundity

Network meta-analysis: The pregnancy rates were reported by 22 studies (28 study arms). The geometry of the network (Fig. 2a,) highlights that most studies used placebo/no intervention as the control. Two studies used Vitamin E plus Vitamin C as a control [60, 61], and one study used Vitamin E alone [25]. The network meta-analysis shows that although all but one intervention numerically increased the chance of pregnancy, only L-carnitine + micronutrients reached statistical significance (Fig. 2b, Supplementary Fig. 11, Supplementary Tables 3–4). The certainty of the evidence was mostly very low; L-carnitine + micronutrients and L-carnitine/L-acetyl carnitine were the only interventions that achieved a moderate rating for certainty.

Meta-analysis: The number of events was low; thus, few interventions reached statistical significance (Fig. 3). Overall, L-carnitine + micronutrients and zinc were the only interventions that significantly increased the pregnancy rate during the study periods (risk ratio [RR] 3.60, 95% CI 1.86, 6.98, $p = 0.0002$; RR 5.39, 95% CI 1.26, 23.04, $p = 0.02$, respectively). However, all intervention groups except zinc + folic acid numerically increased the pregnancy rate. An increase in the number of studies could see one or more of these other interventions become statistically significant.

A different picture emerges when the studies are grouped by type of infertility (Supplementary Fig. 12). The largest

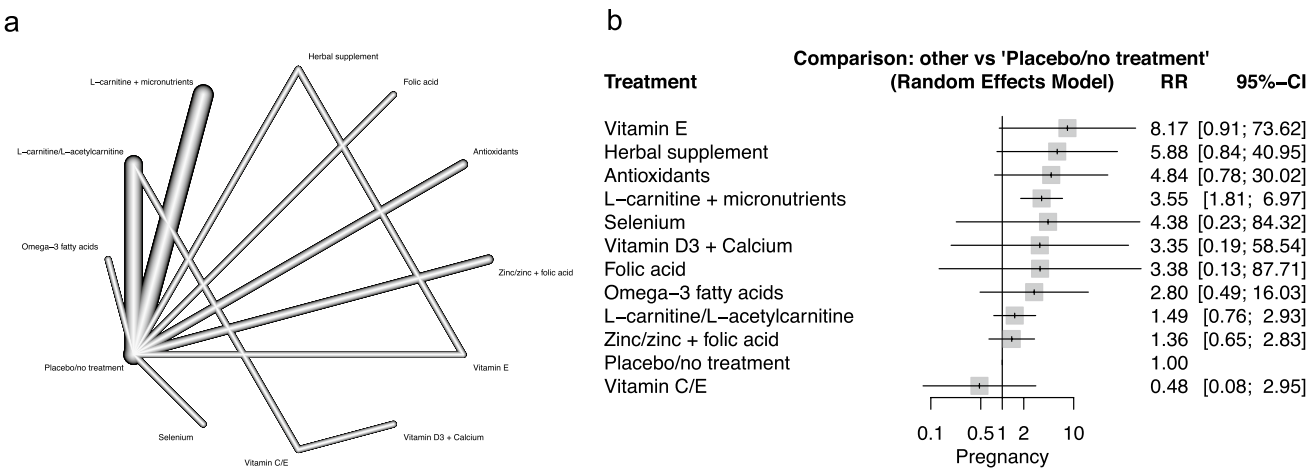


Fig. 2 Network diagram (**a**) and results of the network meta-analysis (**b**) for rate of pregnancy, given as risk ratios with 95% Cis. *CI* confidence intervals, *RR* risk ratio

increase in pregnancy rates compared with placebo/no treatment were seen in men with oligozoospermia (RR: 4.89; 95% CI: 1.48, 16.17; $p = 0.009$). The two studies in this group used zinc [62] and a commercial fertility product containing herbs and minerals (Y virilin) [63]. Other groups that experienced a large increase in the rate of pregnancies were men with oligoasthenozoospermia (RR: 4.20; 95% CI 1.13, 15.58; $p = 0.03$) and asthenoteratozoospermia (RR: 3.53; 95% CI 1.59, 7.86; $p = 0{,}002$).

The rate of live births was reported by only five studies, each using a different intervention (Supplementary Fig. 13, Supplementary Table 5). Although all studies except Schisterman 2020 reported a numerical increase in the rate of live births (with folic acid + zinc, and calcium + vitamin D3 treatments having "high" and "moderate" ratings, respectively, for certainty of the evidence [Supplementary Table 5]) no studies showed a statistically significant increase in the rate of live births compared with placebo/no treatment.

3.6 Sperm Count

Network meta-analysis: The geometry of the network (Fig. 4a) highlights that most studies used placebo/no intervention as the control. Two studies used a fertility supplement as a comparator [64, 65], one study used a combination of vitamin C + vitamin E as a comparator [60], one used a herbal supplement [66], and one study used vitamin E as a comparator [67].

Overall, the network meta-analysis showed that the most effective interventions were the L-carnitine-containing micronutrient and antioxidant supplements (TDS, FDC, Proxeed Plus) (Fig. 5a, Supplementary Fig. 14, Supplementary Tables 6–7). Most of these interventions, however, were graded as very low or low in terms of certainty of evidence. Other treatments that cause a statistically significant increase in sperm count were EPA + DHA, herbal supplements (Manix, Y Virilin, *Withania somnifera*), L-carnitine + L-acetylcarnitine, N-acetyl cysteine, *Nigella sativa* seeds oil, Prelox, selenium, Tulang honey, and vitamin C.

Meta-analysis: Seventy-nine study arms were subjected to pairwise subgroup meta-analysis by type of dietary intervention (Supplementary Fig. 15). The analysis results show that the most effective interventions were herbal/mineral supplements, L-carnitine + micronutrients, antioxidants, and Selenium supplements. The herbal/mineral supplements increased the sperm concentration to a clinically important extent (MD: 14.45; 95% CI: 8.77, 20.14, $p < 0.00001$) [63, 68, 69]. When the studies were limited to men who had WHO-defined oligozoospermia (i.e., oligozoospermia, oligoasthenozoospermia, and oligoasthenoteratozoospermia), two interventions increased sperm count to normal ranges (Supplementary Fig. 16). These were herbal/mineral supplements and L-carnitine + micronutrients.

Analysis of all studies sub-grouped by type of infertility (Supplementary Fig. 17) showed that the type of infertility influenced the results of the dietary interventions. Men who had undergone varicocelectomy and took a nutritional intervention showed the greatest improvement in sperm count over those who had a varicocelectomy but were assigned to placebo or no treatment (MD: 12.50; 95% CI: 8.45, 16.54, $p < 0.00001$). In contrast, men with grade 4 or 5 varicocele and men with hypogonadotropic hypogonadism showed little or no improvement in their sperm count compared with placebo.

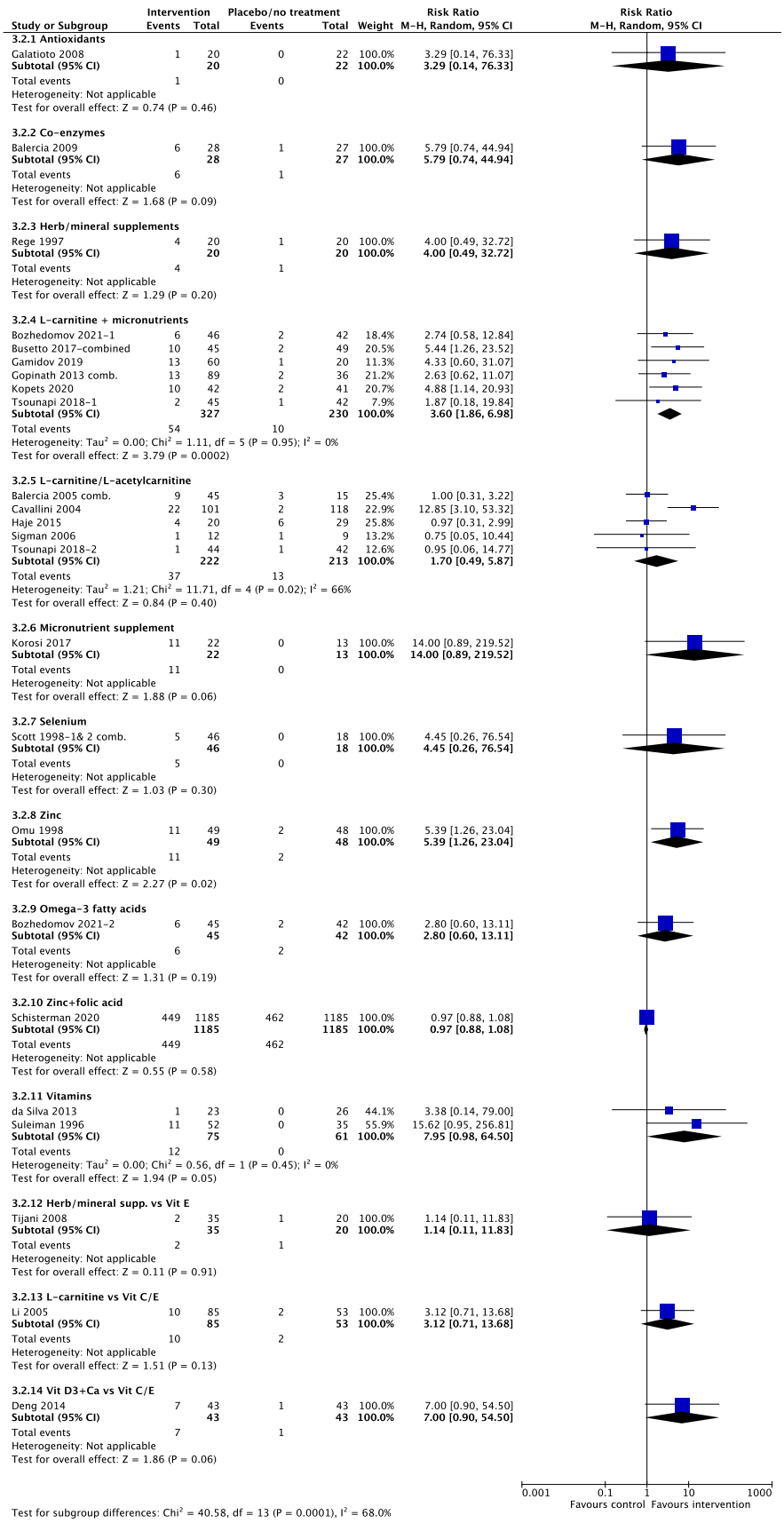


Fig. 3 Subgroup meta-analysis of the risk of pregnancy in the female partners of men receiving a nutritional intervention versus those receiving placebo or no treatment, by type of intervention. Data were meta-analyzed using a Mantel-Haenszel method and a random effects model. Data show risk ratios with 95% confidence intervals (CIs)

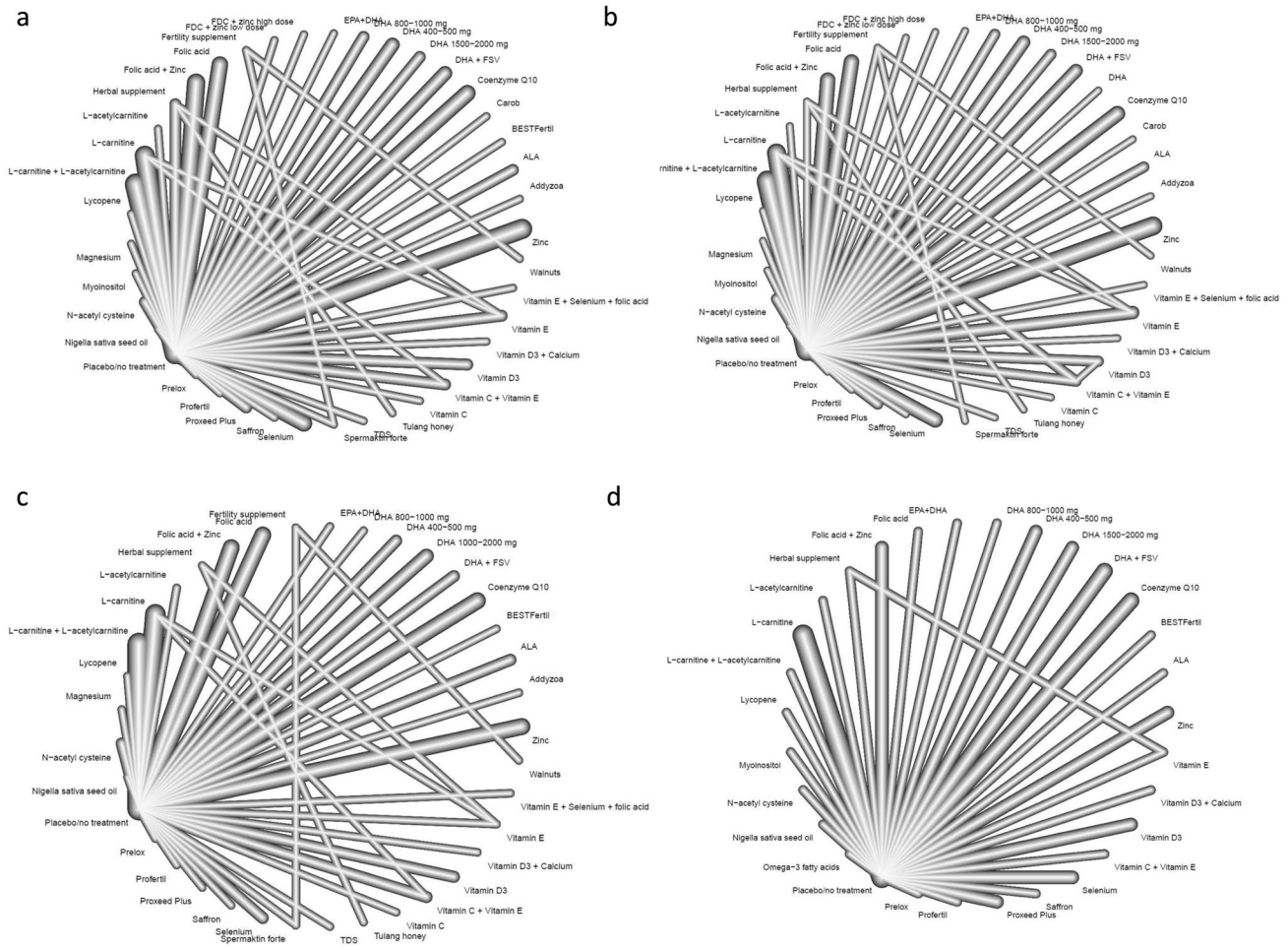


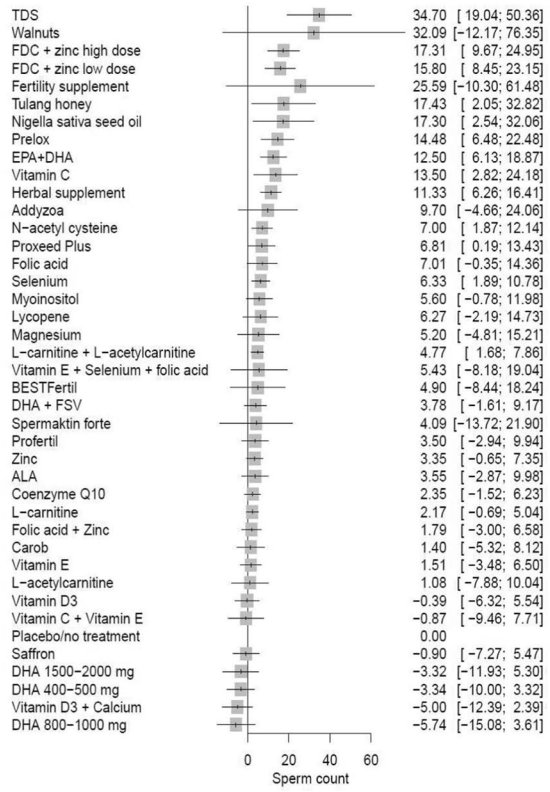
Fig. 4 Network diagrams for sperm count (**a**), sperm motility (**b**), sperm morphology (**c**), and semen volume (**d**) *DHA* docosahexaenoic acid, EPA eicosapentaenoic acid

3.7 Sperm Motility

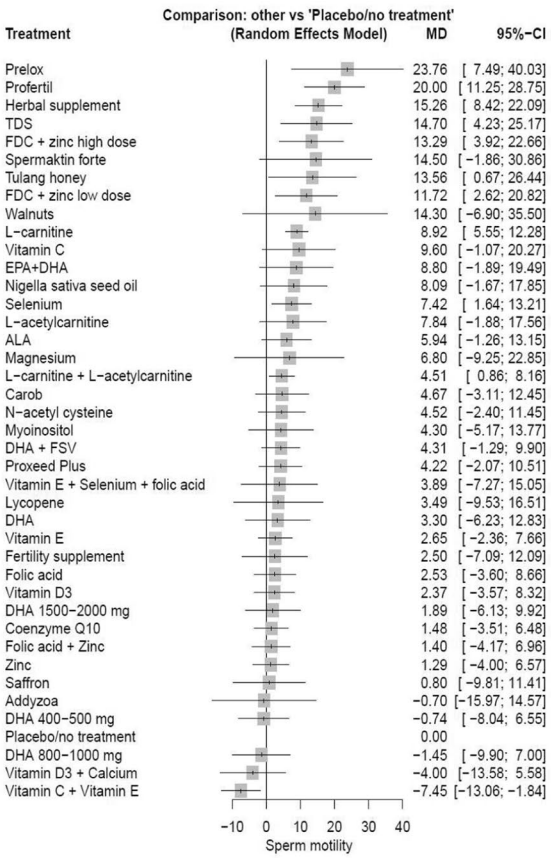
Network meta-analysis: The network for sperm motility was similarly dominated by comparisons with placebo or no treatment (Fig. 4b). The non-placebo controls were fertility supplements [64, 65], a herbal supplement [66], vitamin E [67, 70], and vitamin C + vitamin E [60, 61, 71].L-arginine- and L-carnitine-containing supplements, along with herbal supplements and traditional honey, were the most efficacious treatments for improving sperm motility (Fig. 5b, Supplementary Fig. 18, Supplementary Tables 8–9). These changes were statistically but also clinically significant in several cases. The certainty of the evidence for most interventions was low or very low, given that most were represented by a single study. However, there is a high level of certainty that L-carnitine improves sperm motility (MD 8.92%; 95% CI 5.55% to 12.28%), and a moderate level of certainty that selenium and L-carnitine + L-acetylcarnitine are also effective.

Meta-analysis: Seventy-nine study arms were included in the pairwise analysis of sperm motility by type of dietary intervention (Supplementary Fig. 19). The intervention that resulted in the greatest improvement in motility was L-carnitine + micronutrients (MD: 11.05%; 95% CI 5.68%, 16.41%; $p < 0.0001$). Other interventions that saw statistically significant increases in sperm motility were antioxidants, L-carnitine/L-acetylcarnitine, Selenium supplements, omega-3 fatty acids, and vitamins. When the analysis was limited to men with low sperm motility (i.e., asthenozoospermia, asthenoteratozoospermia, oligoasthenozoospermia, oligoasthenoteratozoospermia) (Supplementary Fig. 20), L-carnitine + micronutrients continued to be the most effective intervention for increasing sperm motility (MD 12.32%; 95% CI 6.77%, 17.87%; $p < 0.0001$). In contrast to the overall analysis, antioxidants were not effective in increasing sperm motility in men with low sperm motility at baseline, and omega-3 fatty acids were slightly less effective than in the overall analysis. L-carnitine/L-acetylcarnitine, selenium,

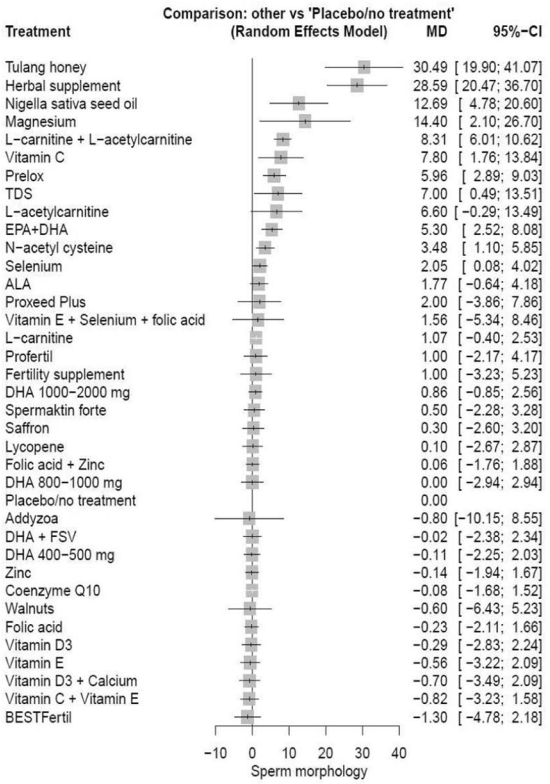
a


Comparison: other vs 'Placebo/no treatment'
Treatment
(Random Effects Model)
MD
95%−CI
TDS 34.70 [19.04; 50.36]
Walnuts 32.09 [−12.17; 76.35]
FDC + zinc high dose 17.31 [9.67; 24.95]
FDC + zinc low dose 15.80 [8.45; 23.15]
Fertility supplement 25.59 [−10.30; 61.48]
Tulang honey 17.43 [2.05; 32.82]
Nigella sativa seed oil 17.30 [2.54; 32.06]
Prelox 14.48 [6.48; 22.48]
EPA+DHA 12.50 [6.13; 18.87]
Vitamin C 13.50 [2.82; 24.18]
Herbal supplement 11.33 [6.26; 16.41]
Addyzoa 9.70 [−4.66; 24.06]
N−acetyl cysteine 7.00 [1.87; 12.14]
Proxeed Plus 6.81 [0.19; 13.43]
Folic acid 7.01 [−0.35; 14.36]
Selenium 6.33 [1.89; 10.78]
Myoinositol 5.60 [−0.78; 11.98]
Lycopene 6.27 [−2.19; 14.73]
Magnesium 5.20 [−4.81; 15.21]
L−carnitine + L−acetylcarnitine 4.77 [1.68; 7.86]
Vitamin E + Selenium + folic acid 5.43 [−8.18; 19.04]
BESTFertil 4.90 [−8.44; 18.24]
DHA + FSV 3.78 [−1.61; 9.17]
Spermaktin forte 4.09 [−13.72; 21.90]
Profertil 3.50 [−2.94; 9.94]
Zinc 3.35 [−0.65; 7.35]
ALA 3.55 [−2.87; 9.98]
Coenzyme Q10 2.35 [−1.52; 6.23]
L−carnitine 2.17 [−0.69; 5.04]
Folic acid + Zinc 1.79 [−3.00; 6.58]
Carob 1.40 [−5.32; 8.12]
Vitamin E 1.51 [−3.48; 6.50]
L−acetylcarnitine 1.08 [−7.88; 10.04]
Vitamin D3 −0.39 [−6.32; 5.54]
Vitamin C + Vitamin E −0.87 [−9.46; 7.71]
Placebo/no treatment 0.00
Saffron −0.90 [−7.27; 5.47]
DHA 1500−2000 mg −3.32 [−11.93; 5.30]
DHA 400−500 mg −3.34 [−10.00; 3.32]
Vitamin D3 + Calcium −5.00 [−12.39; 2.39]
DHA 800−1000 mg −5.74 [−15.08; 3.61]
0 20 40 60
Sperm count

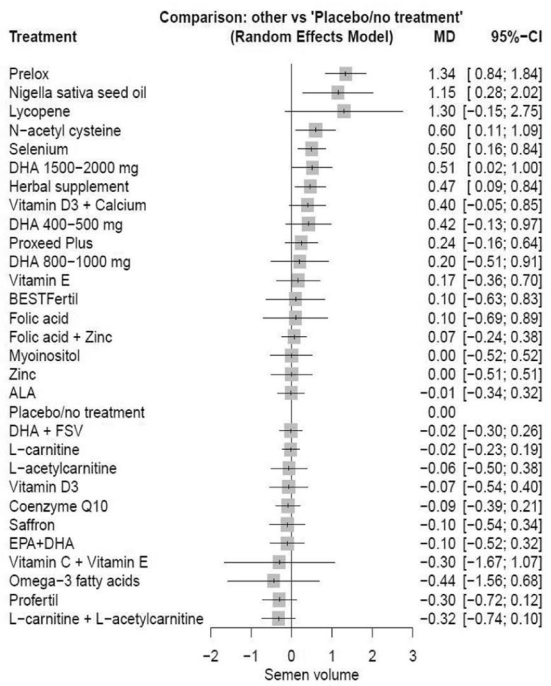
b


Comparison: other vs 'Placebo/no treatment'
Treatment
(Random Effects Model)
MD
95%−CI
Prelox 23.76 [7.49; 40.03]
Profertil 20.00 [11.25; 28.75]
Herbal supplement 15.26 [8.42; 22.09]
TDS 14.70 [4.23; 25.17]
FDC + zinc high dose 13.29 [3.92; 22.66]
Spermaktin forte 14.50 [−1.86; 30.86]
Tulang honey 13.56 [0.67; 26.44]
FDC + zinc low dose 11.72 [2.62; 20.82]
Walnuts 14.30 [−6.90; 35.50]
L−carnitine 8.92 [5.55; 12.28]
Vitamin C 9.60 [−1.07; 20.27]
EPA+DHA 8.80 [−1.89; 19.49]
Nigella sativa seed oil 8.09 [−1.67; 17.85]
Selenium 7.42 [1.64; 13.21]
L−acetylcarnitine 7.84 [−1.88; 17.56]
ALA 5.94 [−1.26; 13.15]
Magnesium 6.80 [−9.25; 22.85]
L−carnitine + L−acetylcarnitine 4.51 [0.86; 8.16]
Carob 4.67 [−3.11; 12.45]
N−acetyl cysteine 4.52 [−2.40; 11.45]
Myoinositol 4.30 [−5.17; 13.77]
DHA + FSV 4.31 [−1.29; 9.90]
Proxeed Plus 4.22 [−2.07; 10.51]
Vitamin E + Selenium + folic acid 3.89 [−7.27; 15.05]
Lycopene 3.49 [−9.53; 16.51]
DHA 3.30 [−6.23; 12.83]
Vitamin E 2.65 [−2.36; 7.66]
Fertility supplement 2.50 [−7.09; 12.09]
Folic acid 2.53 [−3.60; 8.66]
Vitamin D3 2.37 [−3.57; 8.32]
DHA 1500−2000 mg 1.89 [−6.13; 9.92]
Coenzyme Q10 1.48 [−3.51; 6.48]
Folic acid + Zinc 1.40 [−4.17; 6.96]
Zinc 1.29 [−4.00; 6.57]
Saffron 0.80 [−9.81; 11.41]
Addyzoa −0.70 [−15.97; 14.57]
DHA 400−500 mg −0.74 [−8.04; 6.55]
Placebo/no treatment 0.00
DHA 800−1000 mg −1.45 [−9.90; 7.00]
Vitamin D3 + Calcium −4.00 [−13.58; 5.58]
Vitamin C + Vitamin E −7.45 [−13.06; −1.84]
−10 0 10 20 30 40
Sperm motility

c


Comparison: other vs 'Placebo/no treatment'
Treatment
(Random Effects Model)
MD
95%−CI
Tulang honey 30.49 [19.90; 41.07]
Herbal supplement 28.59 [20.47; 36.70]
Nigella sativa seed oil 12.69 [4.78; 20.60]
Magnesium 14.40 [2.10; 26.70]
L−carnitine + L−acetylcarnitine 8.31 [6.01; 10.62]
Vitamin C 7.80 [1.76; 13.84]
Prelox 5.96 [2.89; 9.03]
TDS 7.00 [0.49; 13.51]
L−acetylcarnitine 6.60 [−0.29; 13.49]
EPA+DHA 5.30 [2.52; 8.08]
N−acetyl cysteine 3.48 [1.10; 5.85]
Selenium 2.05 [0.08; 4.02]
ALA 1.77 [−0.64; 4.18]
Proxeed Plus 2.00 [−3.86; 7.86]
Vitamin E + Selenium + folic acid 1.56 [−5.34; 8.46]
L−carnitine 1.07 [−0.40; 2.53]
Profertil 1.00 [−2.17; 4.17]
Fertility supplement 1.00 [−3.23; 5.23]
DHA 1000−2000 mg 0.86 [−0.85; 2.56]
Spermaktin forte 0.50 [−2.28; 3.28]
Saffron 0.30 [−2.60; 3.20]
Lycopene 0.10 [−2.67; 2.87]
Folic acid + Zinc 0.06 [−1.76; 1.88]
DHA 800−1000 mg 0.00 [−2.94; 2.94]
Placebo/no treatment 0.00
Addyzoa −0.80 [−10.15; 8.55]
DHA + FSV −0.02 [−2.38; 2.34]
DHA 400−500 mg −0.11 [−2.25; 2.03]
Zinc −0.14 [−1.94; 1.67]
Coenzyme Q10 −0.08 [−1.68; 1.52]
Walnuts −0.60 [−6.43; 5.23]
Folic acid −0.23 [−2.11; 1.66]
Vitamin D3 −0.29 [−2.83; 2.24]
Vitamin E −0.56 [−3.22; 2.09]
Vitamin D3 + Calcium −0.70 [−3.49; 2.09]
Vitamin C + Vitamin E −0.82 [−3.23; 1.58]
BESTFertil −1.30 [−4.78; 2.18]
−10 0 10 20 30 40
Sperm morphology

d


Comparison: other vs 'Placebo/no treatment'
Treatment
(Random Effects Model)
MD
95%−CI
Prelox 1.34 [0.84; 1.84]
Nigella sativa seed oil 1.15 [0.28; 2.02]
Lycopene 1.30 [−0.15; 2.75]
N−acetyl cysteine 0.60 [0.11; 1.09]
Selenium 0.50 [0.16; 0.84]
DHA 1500−2000 mg 0.51 [0.02; 1.00]
Herbal supplement 0.47 [0.09; 0.84]
Vitamin D3 + Calcium 0.40 [−0.05; 0.85]
DHA 400−500 mg 0.42 [−0.13; 0.97]
Proxeed Plus 0.24 [−0.16; 0.64]
DHA 800−1000 mg 0.20 [−0.51; 0.91]
Vitamin E 0.17 [−0.36; 0.70]
BESTFertil 0.10 [−0.63; 0.83]
Folic acid 0.10 [−0.69; 0.89]
Folic acid + Zinc 0.07 [−0.24; 0.38]
Myoinositol 0.00 [−0.52; 0.52]
Zinc 0.00 [−0.51; 0.51]
ALA −0.01 [−0.34; 0.32]
Placebo/no treatment 0.00
DHA + FSV −0.02 [−0.30; 0.26]
L−carnitine −0.02 [−0.23; 0.19]
L−acetylcarnitine −0.06 [−0.50; 0.38]
Vitamin D3 −0.07 [−0.54; 0.40]
Coenzyme Q10 −0.09 [−0.39; 0.21]
Saffron −0.10 [−0.54; 0.34]
EPA+DHA −0.10 [−0.52; 0.32]
Vitamin C + Vitamin E −0.30 [−1.67; 1.07]
Omega−3 fatty acids −0.44 [−1.56; 0.68]
Profertil −0.30 [−0.72; 0.12]
L−carnitine + L−acetylcarnitine −0.32 [−0.74; 0.10]
−2 −1 0 1 2 3
Semen volume

◂**Fig. 5** Results of the network meta-analyses. Changes in sperm count (**a**), sperm motility (**b**), sperm morphology (**c**), and semen volume (**d**) compared with placebo are given as mean differences with 95% confidence intervals (CIs). *DHA* docosahexaenoic acid, EPA eicosapentaenoic acid

and vitamins increased sperm motility compared with the overall analysis.

When sub-grouped by type of infertility, differences were apparent (Supplementary Fig. 21). Dietary interventions improved the motility of sperm in men with all forms of infertility except varicocele (any grade), hypogonadotropic hypogonadism, and teratozoospermia. The group that saw the greatest improvement in sperm motility compared with placebo or no treatment was men with oligozoospermia.

3.8 Sperm Morphology

Network meta-analysis: The evidence base for change in percent normal sperm morphology (Fig. 4c) was based mostly on comparisons with placebo or no treatment. Active controls included fertility supplements [64, 65], a herbal supplement [66], vitamin E [70, 72], and vitamin C + vitamin E [67]. The greatest changes in normal sperm morphology were seen with traditional honey (Tulang honey) and a herbal supplement (Manix capsules) (Fig. 5c, Supplementary Fig. 22, Supplementary Tables 10–11). However, it should be noted that each of these interventions was represented by a single study, so confidence in these effect sizes is low. L-carnitine + L-acetylcarnitine, EPA+DHA, N-acetyl cysteine, and selenium significantly increased the percent of normal sperm morphology with a moderate degree of certainty.

Meta-analysis: Sixty-four study arms reported on the effects of dietary interventions on sperm morphology (Supplementary Fig. 23). The most robust improvement in percent of sperm with normal morphology was with L-carnitine/L-acetylcarnitine (MD: 4.48%; 95% CI: 2.16%, 6.80%; $p = 0.0002$). Other statistically significant improvements in normal sperm morphology were seen in men taking antioxidants (MD: 3.24, 95% CI 0.86, 5.63, $p < 0.00001$), Selenium (MD: 2.05, 95% CI 1.52, 2.58, $p < 0.00001$), and magnesium (MD: 14.40, 95% CI 2.39, 26.41, $p = 0.02$). None of the other interventions significantly improved sperm morphology compared with placebo or no treatment. An analysis of studies in men with teratozoospermia, increases in the percent of normal sperm was less impressive but significant (Supplementary Fig. 24), interventions like L-carnitine/L-acetylcarnitine (MD: 2.14, 95% CI 1.40, 2.88, $p < 0.00001$), Selenium (MD: 2.05, 95% CI 1.52, 2.58, $p < 0.00001$), and coenzymes (MD: 0.78, 95% CI 0.30, 1.26, $p = 0.001$) were statistically more effective than placebo or no treatment.

When sub-grouped by type of infertility, significant differences emerged (Supplementary Fig. 25). The nutritional therapies, compared with placebo or no treatment, improved the percent of sperm with normal morphology in men asthenoteratozoospermia (MD: 1.12, 95% CI 0.23, 2.02, $p = 0.01$), varicocele grades 1 to 3 ($p < 0.05$), oligozoospermia (MD: 14.40, 95% CI 2.39, 26.41, $p = 0.02$), and varicocelectomy (MD: 4.19, 95% CI 2.31, 6.08, $p < 0.0001$).

3.9 Semen Volume

Network meta-analysis: The geometry of the network shows that placebo/no treatment dominated the comparators. Indeed, only a single study used an active comparator (herbal supplement vs vitamin E) [70] (Fig. 4d). The lack of direct connection makes evaluation of consistency difficult, and as such, the results should be interpreted with caution.

The dietary supplement Prelox (L-arginine and antioxidants) and *Nigella sativa* seed oil were the most effective interventions for increasing semen volume (Fig. 5d, Supplementary Fig. 26, Supplementary Tables 12–13), although each of these interventions was represented by a single study. Other interventions, including N-acetyl cysteine, selenium, DHA 1500–2000 mg, and herbal supplements, were statistically superior to placebo. Interestingly, however, close to half the interventions ranked below placebo for this outcome, suggesting that heterogeneity was high for this outcome.

Meta-analysis: Forty-four study arms were included in the pairwise analysis of semen volume by type of dietary intervention (Supplementary Fig. 27). The greatest increase in semen volume was seen in men taking antioxidants (MD: 0.74 mL; 95% CI 0.39 mL, 1.10 mL; $p < 0.00001$). Other statistically significant increases were seen in men taking herbal/mineral supplements and Selenium supplements. When sub-grouped by type of infertility (Supplementary Fig. 28), increases in semen volume compared with placebo or no treatment were only seen in men with asthenoteratozoospermia (MD: 0.35, 95% CI 0.03, 0.67, $p = 0.03$), grade 2 varicocele (MD: 0.80, 95% CI 0.12, 1.48, $p = 0.02$), and oligozoospermia (MD: 0.45, 95% CI 0.18, 0.72, $p = 0.001$). However, it should be noted that few, if any, studies were undertaken in men with semen volume that did not meet the WHO normal value of 2 mL.

3.10 Sperm DNA and Chromosomal Integrity

Twelve studies (17 study arms) reported DNA fragmentation (Supplementary Fig. 29). Vitamin/mineral combinations were the only interventions that significantly improved DNA fragmentation (MD: 0.13, 95% CI 0.03, 0.23, $p = 0.008$). Two studies (six study arms) reported protamine levels

through chromomycin A_3 staining (Supplementary Fig. 30). The interventions included vitamins (folic acid), minerals (zinc), and vitamin/mineral combinations (zinc + folic acid). The limited data suggest that both folic acid and zinc may be effective in reducing protamine deficiency, as the reductions in chromomycin A_3 staining were similar for zinc for three intervention types.

3.11 Hormones

The concentration of follicle-stimulating hormone (FSH) was reported by 13 studies (16 study arms) (Supplementary Fig. 31). Several interventions reduced FSH to a statistically significant degree; these were antioxidants (MD: −0.70, 95% CI −1.02, −0.38, $p < 0.0001$), coenzymes (MD: −3.30, 95% CI −5.06, −1.53, $p = 0.0002$), L-carnitine ± micronutrients (MD: −2.50, 95% CI −3.97, −1.03, $p = 0.0009$), L-carnitine/L-acetylcarnitine (MD: −1.76, 95% CI −3.06, −0.46, $p = 0.008$), Selenium (MD: −0.85, 95% CI −1.14, −0.55, $p < 0.00001$), and omega-3 fatty acids (MD: −1.20, 95% CI −1.78, −0.62, $p < 0.0001$). Mixed results were found for luteinizing hormone (LH) (Supplementary Fig. 32). Of all the interventions, limited data suggest that L-carnitine + micronutrients (MD: −2.50, 95% CI −3.97, −1,03, $p = 0.0009$), coenzymes (MD: −3.75, 95% CI −4.21, −3.28, $p < 0.00001$), and omega-3 fatty acids (MD: −1.20, 95% CI −1.78, −0.62, $p < 0.0001$) may lower LH concentrations, while other interventions resulted in no difference or an increase in LH. Of the six studies (eight study arms) that reported on inhibin B (Supplementary Fig. 33), the antioxidant N-acetyl cysteine, selenium, and myoinositol increased inhibin B concentrations, but data were limited. Thirteen studies (16 study arms) reported testosterone concentrations (Supplementary Fig. 34). The antioxidant (MD: 2.70, 95% CI 0.63, 4.77, $p = 0.01$), coenzymes (MD: 1.11, 95% CI 0.20, 2.01, $p = 0.02$), L-carnitine + micronutrients (MD: 2.69, 95% CI 2.20, 3.18, $p < 0.00001$), L-carnitine/L-acetylcarnitine (MD: 0.84, 95% CI 0.29, 1.38, $p = 0.003$), and minerals (MD: 2.22, 95% CI 1.31, 3.14, $p < 0.00001$) all significantly increased testosterone concentrations compared with placebo or no treatment.

3.12 Adverse Events

Very few studies reported the rates of adverse events (Supplementary Fig. 35). Of these, only a single study reported adverse events that were statistically significant (Safarinejad 2010). It is, therefore, difficult to draw any conclusions on the comparative safety of the interventions.

3.13 Meta-regression

The correlation between the rate of pregnancy and change in sperm characteristics is given in Table 1. We found that increases in sperm count, normal morphology, and motility, but not semen volume, were significantly correlated with increases in pregnancy. In our data, for each increase in sperm count of 1×10^6, a 6% increase in pregnancy was observed. Similar statistically significant effects were seen with increases in normal morphology (14.7% increase in pregnancy for each% increase in normal morphology) and motility (8.3% increase in pregnancy for each% increase in motility), but not with semen volume.

To determine if this increase in pregnancy differed across types of infertility, we did a multivariate meta-regression by sperm parameter and type of infertility (Supplementary Tables 14–16). The pregnancy rate was not associated with different types of infertility (Supplementary Table 14) when changes in sperm count were accounted for. An increase in sperm count had the same effect on pregnancy outcomes regardless of the cause or severity of infertility. Similar results were seen with percent normal morphology and percent motile sperm (Supplementary Tables 15–16). This suggests that increases in sperm count, normal morphology, and/or motility are reasonable pseudo-endpoints for increases in pregnancy rates.

3.14 Subgroup Meta-analysis and Publication Bias

We intended to undertake subgroup analyses by dietary advice versus provision of the intervention (e.g., foods, supplements, beverages), the type of dietary intervention or supplement, the age of the participants, the baseline BMI

Table 1 Meta-regression on the correlation between changes in sperm parameters and rate of pregnancy

Covariate	Studies	Coefficient	Lower CI	Upper CI	*p* value
Sperm count ($\times 10^6$)	19	0.060	0.034	0.086	**< 0.001**
Sperm motility (%)	19	0.083	0.040	0.125	**< 0.001**
Normal morphology (%)	15	0.147	0.054	0.241	**0.002**
Semen volume (mL)	10	0.828	−1.607	3.263	0.505

Bold values indicate statistical significance ($p < 0.05$)

CI confidence interval

or body weight, the baseline glycemic markers (e.g. fasting blood glucose, diabetes status), baseline inflammatory markers (e.g., C reactive protein (CRP), erythrocyte sedimentation rate, α-1 antitrypsin, and tumor necrosis factor alpha-receptor type II, etc.), ethnicity, high quality versus low quality studies, and concomitant medication. However, insufficient information was available to make these analyses meaningful.

4 Discussion

Our systematic review is the only network meta-analysis on this topic and the first to undertake such a comprehensive analysis, as previous meta-analyses used only observational studies [21], included a mixture of drugs and supplements [38], and did not directly compare interventions [25], or focused on a single nutrient or group of nutrients [23, 24, 35, 73–76].

Although many male factor infertility studies have focused on sperm number, quality, and hormone concentrations, it was previously unclear if baseline sperm quality is a good predictor of an improvement in pregnancies and live births—the outcomes of interest for patients. The existing studies conflict with one another [54, 77–82].

However, it does appear that improvement in sperm characteristics improves pregnancy rates. For example, following antegrade sclerotherapy of internal spermatic veins, improvement in sperm count, motility improved, and pregnancy rates were high (37.4%) [83]. After varicocele repair, mean sperm concentration and motile sperm increased, and pregnancy rates were also high (up to 51.1%) [84]. An RCT of prednisolone found both increased sperm motility and pregnancy [85]. Finally, an RCT of clomiphene citrate in oligospermia men found both an improvement in sperm volume, density and motility, and pregnancy [86]. Thus, although sperm parameters do not correlate well with pregnancy, improvements in sperm number and quality do seem to improve pregnancy rates.

In our analysis, sperm count, motility, and normal morphology were improved in men taking L-carnitine-containing supplements, several traditional foods/supplements, and antioxidants. Semen volume was only improved by seed oils, fertility supplements, selenium, and antioxidants. Thus, nutritional supplementation can and does improve sperm characteristics to both statistically and clinically significant degrees.

In our meta-regression, we found a strong correlation between increases in sperm count, sperm motility and normal morphology, but not semen volume, and associated increases in the rate of pregnancies during the follow-up periods of the studies. Our meta-regression analyses further showed that this association held, regardless of the type of infertility the men suffered from. That is, the increase in sperm characteristics improves the pregnancy rate and shows that each of these characteristics is an appropriate pseudo-endpoint for an increase in pregnancy rates. It also demonstrates that in men with grade 1–3 varicocele, sperm parameters can be improved but not in men with grade 4–5 varicocele. Men with high-grade varicocele and low sperm count should be referred for varicocelectomy.

In order to determine whether other factors, such as hormones or sperm integrity increase pregnancies, many more studies would be required to measure these factors and follow patients over a period of at least 6 months.

4.1 Limitations

Despite including a large number of studies ($n = 69$) with an even larger number of study arms ($n = 94$), we found low confidence in the relative rankings of many of the included interventions. This was in part because of the comprehensive nature of our study; we included men with any kind of infertility and dietary interventions of any kind. Therefore, the number of studies per type of infertility and intervention was small, the studies were sometimes of low quality, and the studies often had few participants. We hope that this network meta-analysis will encourage researchers to conduct targeted, large, high-quality studies to confirm and strengthen our analysis.

4.2 Implications and Conclusion

Our data show that nutritional interventions can improve sperm characteristics, sex hormones, and, most importantly, pregnancy rates for many men with low fertility. Even for men with severe conditions such as oligoasthenoteratozoospermia, nutritional interventions can significantly increase sperm numbers and quality to thresholds known to substantially increase spontaneous pregnancy. Nutritional interventions are widely available, affordable, safe, and effective and can therefore be favored as initial treatment options, reducing the physical, psychological, and financial burden on men and their partners.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-023-01853-0.

Acknowledgements We would like to acknowledge Elena Smertina for translating several articles from Russian into English and Sima Haee for translating articles from Farsi into English. We want to thank the University of Canberra library staff for prompt, thorough, cheerful, and professional assistance. We would like to thank our reviewers for extremely thorough, detailed, and helpful feedback on our manuscript.

Declarations

Author contributors MIZ, KEM, and HL designed the study and defined the inclusion and exclusion criteria; MIZ and KEM designed the study search; MIZ and KEM did abstract and full-text inclusion and exclusion; HJ and KEM extracted data from studies and cross-checked; CDB designed the network meta-analysis approach, undertook all network meta-analysis and sensitivity analyses for the networks; KEM did pairwise meta-analysis and meta-regression; MIZ, KEM, and CDB wrote the manuscript; HL provided critical feedback on the manuscript.

Conflict of interest/competing interest MIZ, KEM, CBD, HJ and HL have no conflicts to declare.

Funding The study was supported by two grants to MI Zafar: the Research Fund for Young International Scientists from the National Natural Science Foundation Fund (Grant number 82150410456) and a research fund from the Postdoctoral Science Foundation, P.R. China (Grant number 2019M662636).

Role of the funder/sponsor The funding bodies are public entities; they had no role in the study conception, design, conduct, or result interpretation and publication of the manuscript.

Data availability All data and network meta-analysis are available at https://github.com/trucharles/fertility. The meta-analyses themselves are available upon request to the authors.

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Code availability The code used in this study is available at https://github.com/trucharles/fertility.

References

1. Cavallini G, Beretta G. Clinical management of male infertility. Geneva: Springer International; 2015.
2. Vander Borght M, Wyns C. Fertility and infertility: definition and epidemiology. Clin Biochem. 2018;62:2–10.
3. Mascarenhas MN, Cheung H, Mathers CD, Stevens GA. Measuring infertility in populations: constructing a standard definition for use with demographic and reproductive health surveys. Popul Health Metr. 2012;10:17.
4. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod Oxf Engl. 2007;22:1506–12.
5. Rutstein SO, Shah IH. Infecundity, infertility, and childlessness in developing countries. 2004. https://dhsprogram.com/publications/publication-cr9-comparative-reports.cfm. Accessed 15 Apr 2022.
6. Agarwal A, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the globe. Reprod Biol Endocrinol RBE. 2015;13:37.
7. Lotti F, Maggi M. Ultrasound of the male genital tract in relation to male reproductive health. Hum Reprod Update. 2015;21:56–83.
8. WHO. WHO Laboratory Manual for the examination of human semen and sperm-cervial mucus interaction. Int J Androl. 1996;19:149–149.
9. Plachot M, Belaisch-Allart J, Mayenga J-M, Chouraqui A, Tesquier L, Serkine AM. Outcome of conventional IVF and ICSI on sibling oocytes in mild male factor infertility. Hum Reprod Oxf Engl. 2002;17:362–9.
10. Harris ID, Fronczak C, Roth L, Meacham RB. Fertility and the aging male. Rev Urol. 2011;13:e184-190.
11. Sabra SMM, Al-Harbi MS. An influential relationship of seminal fluid microbial infections and infertility, Taif Region, KSA. World J Med Sci. 2014;10:32–7.
12. Ghuman N, Ramalingam M. Male infertility. Obstet Gynaecol Reprod Med. 2018;28:7–14.
13. Cozzolino DJ, Lipshultz LI. Varicocele as a progressive lesion: positive effect of varicocele repair. Hum Reprod Update. 2001;7:55–8.
14. Nieschlag E, Behre HM, Nieschlag S, editors. Andrology: Male Reproductive Health and Dysfunction [Internet]. 3rd ed. Berlin Heidelberg: Springer-Verlag; 2010. https://www.springer.com/gp/book/9783540783541. Accessed 29 Sep 2021.
15. Kort HI, Massey JB, Elsner CW, Mitchell-Leef D, Shapiro DB, Witt MA, et al. Impact of body mass index values on sperm quantity and quality. J Androl. 2006;27:450–2.
16. Asare-Anane H, Bannison SB, Ofori EK, Ateko RO, Bawah AT, Amanquah SD, et al. Tobacco smoking is associated with decreased semen quality. Reprod Health. 2016;13:90.
17. Chiu YH, Afeiche MC, Gaskins AJ, Williams PL, Mendiola J, Jørgensen N, et al. Sugar-sweetened beverage intake in relation to semen quality and reproductive hormone levels in young men. Hum Reprod. 2014;29:1575–84.
18. Jensen TK, Swan S, Jørgensen N, Toppari J, Redmon B, Punab M, et al. Alcohol and male reproductive health: a cross-sectional study of 8344 healthy men from Europe and the USA. Hum Reprod Oxf Engl. 2014;29:1801–9.
19. Giahi L, Mohammadmoradi S, Javidan A, Sadeghi MR. Nutritional modifications in male infertility: a systematic review covering 2 decades. Nutr Rev. 2016;74:118–30.
20. Ricci E, Al-Beitawi S, Cipriani S, Alteri A, Chiaffarino F, Candiani M, et al. Dietary habits and semen parameters: a systematic narrative review. Andrology. 2018;6:104–16.
21. Salas-Huetos A, Bulló M, Salas-Salvadó J. Dietary patterns, foods and nutrients in male fertility parameters and fecundability: a systematic review of observational studies. Hum Reprod Update. 2017;23:371–89.
22. Salas-Huetos A, James ER, Aston KI, Jenkins TG, Carrell DT. Diet and sperm quality: nutrients, foods and dietary patterns. Reprod Biol. 2019;19:219–24.
23. Hosseini B, Nourmohamadi M, Hajipour S, Taghizadeh M, Asemi Z, Keshavarz SA, et al. The Effect of omega-3 fatty acids, EPA, and/or DHA on male infertility: a systematic review and meta-analysis. J Diet Suppl. 2019;16:245–56.
24. Lafuente R, González-Comadrán M, Solà I, López G, Brassesco M, Carreras R, et al. Coenzyme Q10 and male infertility: a meta-analysis. J Assist Reprod Genet. 2013;30:1147–56.
25. Salas-Huetos A, Rosique-Esteban N, Becerra-Tomás N, Vizmanos B, Bulló M, Salas-Salvadó J. The effect of nutrients and dietary supplements on sperm quality parameters: a systematic review and meta-analysis of randomized clinical trials. Adv Nutr Bethesda Md. 2018;9:833–48.
26. Salvio G, Cutini M, Ciarloni A, Giovannini L, Perrone M, Balercia G. Coenzyme Q10 and male infertility: a systematic review. Antioxidants. 2021;10:874.
27. Buhling K, Schumacher A, Eulenburg CZ, Laakmann E. Influence of oral vitamin and mineral supplementation on male infertility: a meta-analysis and systematic review. Reprod Biomed Online. 2019;39:269–79.
28. Boitani C, Puglisi R. Selenium, a key element in spermatogenesis and male fertility. Adv Exp Med Biol. 2008;636:65–73.

29. Abel BJ, Carswell G, Elton R, Hargreave TB, Kyle K, Orr S, et al. Randomised trial of clomiphene citrate treatment and vitamin C for male infertility. Br J Urol. 1982;54:780–4.
30. Cyrus A, Kabir A, Goodarzi D, Moghimi M. The effect of adjuvant vitamin C after varicocele surgery on sperm quality and quantity in infertile men: a double-blind placebo controlled clinical trial. Int Braz J Urol Off J Braz Soc Urol. 2015;41:230–8.
31. ElSheikh MG, Hosny MB, Elshenoufy A, Elghamrawi H, Fayad A, Abdelrahman S. Combination of vitamin E and clomiphene citrate in treating patients with idiopathic oligoasthenozoospermia: a prospective, randomized trial. Andrology. 2015;3:864–7.
32. Ghanem H, Shaeer O, El-Segini A. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: a randomized controlled trial. Fertil Steril. 2010;93:2232–5.
33. Kessopoulou E, Powers HJ, Sharma KK, Pearson MJ, Russell JM, Cooke ID, et al. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril. 1995;64:825–31.
34. Blomberg Jensen M, Lawaetz JG, Petersen JH, Juul A, Jørgensen N. Effects of vitamin D supplementation on semen quality, reproductive hormones, and live birth rate: a randomized clinical trial. J Clin Endocrinol Metab. 2018;103:870–81.
35. Agarwal A, Cannarella R, Saleh R, Harraz AM, Kandil H, Salvio G, et al. Impact of antioxidant therapy on natural pregnancy outcomes and semen parameters in infertile men: a systematic review and meta-analysis of randomized controlled trials. World J Mens Health. 2023;41:14–48.
36. Chiware TM, Vermeulen N, Blondeel K, Farquharson R, Kiarie J, Lundin K, et al. IVF and other ART in low- and middle-income countries: a systematic landscape analysis. Hum Reprod Update. 2021;27:213–28.
37. Ekechi C. Addressing inequality in fertility treatment. Lancet. 2021;398:645–6.
38. Omar MI, Pal RP, Kelly BD, Bruins HM, Yuan Y, Diemer T, et al. Benefits of empiric nutritional and medical therapy for semen parameters and pregnancy and live birth rates in couples with idiopathic infertility: a systematic review and meta-analysis. Eur Urol. 2019;75:615–25.
39. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777–84.
40. Thomas J, Graziosi S, Brunton J, Ghouze Z, O'Driscoll P, Bond M, et al. EPPI-Reviewer: advanced software for systematic reviews, maps and evidence synthesis. London: EPPI-Centre, Social Science Research Institute, University College London; 2022.
41. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343: d5928.
42. Rücker G, Krahn U, König J, Efthimiou O, Davies A, Papakonstantinou T, et al. netmeta: Network Meta-Analysis using Frequentist Methods [Internet]. 2022. https://CRAN.R-project.org/package=netmeta. Accessed 9 Sep 2022.
43. Rohatgi, Ankit. WebPlotDigitizer [Internet]. Austin, Texas, USA; 2017. http://arohatgi.info/WebPlotDigitizer
44. Shi J, Luo D, Wan X, Liu Y, Liu J, Bian Z, et al. Detecting the skewness of data from the sample size and the five-number summary. ArXiv201005749 Stat [Internet]. 2020. http://arxiv.org/abs/2010.05749. Accessed 21 Sep 2021.
45. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27:1785–805.
46. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
47. Centre TNC. Review Manager (RevMan). Copenhagen: The Cochrane Collaboration; 2014.
48. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
49. Higgins JP, Greeen S. Cochrane handbook for systematic reviews of interventions. London: The Cochrane Collaboration; 2011.
50. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. J Stat Softw. 2012;49:1–15.
51. Wickham H. ggplot2: Elegant Graphics for Data Analysis [Internet]. Springer, New York; 2016. https://ggplot2.tidyverse.org
52. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163–71.
53. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HWG, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16:231–45.
54. Bostofte E, Serup J, Rebbe H. Relation between sperm count and semen volume, and pregnancies obtained during a twenty-year follow-up period. Int J Androl. 1982;5:267–75.
55. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349: g5630.
56. Yepes-Nuñez JJ, Li S-A, Guyatt G, Jack SM, Brozek JL, Beyene J, et al. Development of the summary of findings table for network meta-analysis. J Clin Epidemiol. 2019;115:1–13.
57. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods. 2012;3:98–110.
58. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
59. Sterne JAC, Egger M, Moher D, editors. 10.4.3.1 Recommendations on testing for funnel plot asymmetry. Cochrane Handb Syst Rev Interv [Internet]. 5.1. Cochrane Collaboration; 2011. https://handbook-5-1.cochrane.org/chapter_10/10_4_3_1_recommendations_on_testing_for_funnel_plot_asymmetry.htm. Accessed 10 Feb 2023.
60. Li Z, Chen G, Shang X, Bai W, Han Y, Chen B, et al. A controlled randomized trial of the use of combined L-carnitine and acetyl-L-carnitine treatment in men with oligoasthenozoospermia. Zhonghua Nan Ke Xue Natl J Androl. 2005;11:761–4.
61. Deng X-L, Li Y-M, Yang X-Y, Huang J-R, Guo S-L, Song L-M. Efficacy and safety of vitamin D in the treatment of idiopathic oligoasthenozoospermia. Zhonghua Nan Ke Xue Natl J Androl. 2014;20:1082–5.
62. Omu AE, Dashti H, Al-Othman S. Treatment of asthenozoospermia with zinc sulphate: andrological, immunological and obstetric outcome. Eur J Obstet Gynecol Reprod Biol. 1998;79:179–84.
63. Rege NN, Date J, Kulkarni V, Prem AR, Punekar SV, Dahanukar SA. Effect of Y virilin on male infertility. J Postgrad Med. 1997;43:64–7.
64. Masterson JM, Kim HH, Robbins WA. Walnuts improve semen quality in infertile men: a randomized control dietary intervention trial. Fertil Steril Elsevier. 2020;114:e23–4.
65. Vinogradov IV, Gabliya MY, Lychagin AS, Moskvichev DV. Comparative study of the efficacy and safety of the vitamin-mineral complex with L-carnitine and the complex of acetyl-L-carnitine,

L-carnitine fumarate, alpha-lipoic acid in the treatment of male infertility. Russ J Hum Reprod. 2020;26:97–103.
66. Ismail SB, Bakar MB, Nik Hussain NH, Norhayati MN, Sulaiman SA, Jaafar H, et al. Comparison on the effects and safety of Tualang Honey and Tribestan in sperm parameters, erectile function, and hormonal profiles among oligospermic males. Evid-Based Complement Altern Med ECAM. 2014;2014: 126138.
67. Ma L, Sun Y. Comparison of L-carnitine vs. Coq10 and vitamin E for idiopathic male infertility: a randomized controlled trial. Eur Rev Med Pharmacol Sci. 2022;26:4698–704.
68. Ambiye VR, Langade D, Dongre S, Aptikar P, Kulkarni M, Dongre A. Clinical evaluation of the spermatogenic activity of the root extract of ashwagandha (Withania somnifera) in oligospermic males: a pilot study. Evid-Based Complement Altern Med ECAM. 2013;2013: 571420.
69. Kumar R, Saxena V, Shamsi MB, Venkatesh S, Dada R. Herbomineral supplementation in men with idiopathic oligoasthenoteratospermia: a double blind randomized placebo-controlled trial. Indian J Urol IJU J Urol Soc India. 2011;27:357–62.
70. Tijani KH, Adegoke K, Oluwole AA, Ogunlewe J. The role of manix in the management of idiopathic oligospermia. A pilot study at the Lagos University Teaching Hospital. Niger Q J Hosp Med. 2008;18:142–4.
71. Li Z, Gu R-H, Liu Y, Xiang Z-Q, Cao X-R, Han Y-F, et al. Curative effect of L-carnitine supplementation in the treatment of male infertility. Acta Univ Med Second Shanghai. 2005;25:292–4.
72. Wang Y, Yang S, Qu C, Huo H, Li W, Li J, et al. L-carnitine: safe and effective for asthenozoospermia. Zhonghua Nan Ke Xue Natl J Androl. 2010;16:420–2.
73. Falsig A-ML, Gleerup CS, Knudsen UB. The influence of omega-3 fatty acids on semen quality markers: a systematic PRISMA review. Andrology. 2019;7:794–803.
74. Irani M, Sadeghi R, Amirian M, Le Lez J, Roudsari RL. The effect of folate and folate plus zinc supplementation on endocrine parameters and sperm characteristics in sub-fertile men: a systematic review and meta-analysis. Urol J. 2017;14:4069–78.
75. Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2019;3: CD007411.
76. Li K, Yang X, Wu T. The effect of antioxidants on sperm quality parameters and pregnancy rates for idiopathic male infertility: a network meta-analysis of randomized controlled trials. Front Endocrinol. 2022. https://doi.org/10.3389/fendo.2022.810242.
77. Findeklee S, Radosa JC, Radosa MP, Hammadeh ME. Correlation between total sperm count and sperm motility and pregnancy rate in couples undergoing intrauterine insemination. Sci Rep. 2020;10:7555.
78. Buck Louis GM, Sundaram R, Schisterman EF, Sweeney A, Lynch CD, Kim S, et al. Semen quality and time to pregnancy: the Longitudinal Investigation of Fertility and the Environment Study. Fertil Steril. 2014;101:453–62.
79. Slama R, Eustache F, Ducot B, Jensen TK, Jørgensen N, Horte A, et al. Time to pregnancy and semen parameters: a cross-sectional study among fertile couples from four European cities. Hum Reprod Oxf Engl. 2002;17:503–15.
80. Lemmens L, Kos S, Beijer C, Brinkman JW, van der Horst FAL, van den Hoven L, et al. Predictive value of sperm morphology and progressively motile sperm count for pregnancy outcomes in intrauterine insemination. Fertil Steril. 2016;105:1462–8.
81. Sripada S, Townend J, Campbell D, Murdoch L, Mathers E, Bhattacharya S. Relationship between semen parameters and spontaneous pregnancy. Fertil Steril. 2010;94:624–30.
82. Gubert PG, Pudwell J, Van Vugt D, Reid RL, Velez MP. Number of motile spermatozoa inseminated and pregnancy outcomes in intrauterine insemination. Fertil Res Pract. 2019;5:10.
83. Galfano A, Novara G, Iafrate M, De Marco V, Cosentino M, D'Elia C, et al. Improvement of seminal parameters and pregnancy rates after antegrade sclerotherapy of internal spermatic veins. Fertil Steril. 2009;91:1085–9.
84. Yazdani M, Hadi M, Abbasi H, Nourimahdavi K, Khalighinejad P, Mirsattari A, et al. Efficacy of varicocele repair in different age groups. Urology. 2015;86:273–5.
85. Taiyeb AM, Ridha-Albarzanchi MT, Taiyeb SM, Kanan ZA, Alatrakchi SK, Kjelland ME, et al. Improvement in pregnancy outcomes in couples with immunologically male infertility undergoing prednisolone treatment and conventional in vitro fertilization preceded by sperm penetration assay: a randomized controlled trial. Endocrine. 2017;58:448–57.
86. Mandal A, Chattopadhyay S, Sasmal C, Maiti TK, Bhattacharyya S. Effects of clomiphene citrate on seminal parameters in idiopathic oligospermia: a single blinded prospective randomized controlled trial. Int J Reprod Contracept Obstet Gynecol. 2019;9:94–8.