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Systematic Review Article

Adherence to the Mediterranean Diet for a Better Sperm Quality: A Comprehensive Systematic Review and Meta-Analysis

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ABSTRACT

The aim of this study is to investigate whether a higher adherence to the Mediterranean Diet (MD) can enhance reproductive indicators in infertile men. A comprehensive review and meta-analysis were conducted to assess whether increased adherence to the MD can enhance reproductive indicators in infertile men. An extensive search was conducted for pertinent studies in PubMed, Medline, and Google Scholar. The search included relevant publications published in the last 10 years from 2015. The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) 2020 instrument was used to evaluate the studies. The study's quality was evaluated using the Newcastle-Ottawa Scale (NOS). The data were analyzed and evaluated using RevMan version 5.4.1. The data on sperm volume were not statistically significant. The meta-analysis indicated an odds ratio of 1.06 for low semen volume (<1.5 mL) associated with low adherence to the MD (I^2=12%; 95% CI:0.59–1.93, p=0.84). Furthermore, the analysis revealed a 2.86-fold increase in the probability of achieving higher sperm concentration (>15 × 106/mL) in individuals who adhered to the MD (I^2=33%; 95% CI:1.58–5.18, p=0.0005). The meta-analysis further suggests that adherence to the MD is associated with a 2.54-fold increase in the likelihood of improving sperm count (>39 × 106/ejaculate) (I^2=48%; OR=2.54; 95% CI:1.32–4.90, p=0.005). The meta-analysis on sperm motility demonstrated that individuals who adhere strictly to the MD are more likely to exhibit normal motility (>40%) (I^2=0%; OR=4.64; 95% CI:2.41–8.95, p<0.00001). The meta-analysis further revealed a 2.66-fold increased likelihood of better sperm morphology (>4%) (I^2=0%; OR=2.66; 95% CI:1.39–5.10, p=0.003) in individuals adhering to the MD. The present systematic review with meta-analysis indicates that higher adherence to the MD is associated with improved sperm quality parameters (sperm count, sperm concentration, sperm motility, and sperm morphology).

INTRODUCTION

Infertility is defined as the inability to conceive after one year of active attempts to do so without the use of contraception. This condition affects approximately 10% of couples worldwide, and it is recognized as a public health concern. The contribution of males to infertility cases ranges from 40% to 60%, a proportion that rivals the contribution of females. Sperm quality serves as an indicator of health, with male infertility being associated with an increased incidence of chronic illnesses and mortality. Oxidative stress has been identified as a primary contributing factor to male infertility, accounting for approximately 80% of cases. This is attributed to its role in inducing alterations in sperm quality and the process of gametogenesis (Del Giudice

et al. 2020; Ferramosca & Zara 2022; de Ligny *et al.* 2022).

Based on its etiology, male infertility can be classified into four primary categories. The predominant etiology of decreased spermatogenesis, accounting for 70–80% of cases, is basic testicular dysfunction. The second category, which includes 10 to 20% of cases in men with a normal sperm assay, is attributed to idiopathic conditions (Alesi *et al.* 2022). The third category, accounting for 5–15% of cases, consists of endocrine and systemic illnesses manifesting as hypogonadotropic hypogonadism. The fourth category, accounting for 2–5% of cases, is characterized by impaired sperm motility (Jungwirth *et al.* 2012; Piera-Jordan *et al.* 2024; Punab *et al.* 2017).

The prevailing etiology of male infertility is typically attributed to chronic inflammation and oxidative stress. Adopting healthy behaviors, such as consuming a diet abundant in antioxidants, may potentially mitigate these factors. The Mediterranean Diet (MD), a dietary pattern with a strong scientific basis, has been extensively studied due to its well-documented beneficial effects on human health (Mohammadifard *et al.* 2022; Pizzol *et al.* 2021). In 2010, UNESCO designated the MD a "Intangible Cultural Heritage of Humanity", signifying its global recognition. The dietary patterns of populations residing in the proximity to the Mediterranean Sea serve as the foundation for the MD. The diet emphasizes the consumption of fresh, seasonal fruits and vegetables, legumes, olive oil, nuts, and whole grains. It also includes moderate consumption of animal products such as eggs, dairy, poultry, and fish, while limiting the intake of red and processed meat. The Mediterranean diet is notable for its high content of unsaturated fatty acids, complex carbohydrates, fiber, antioxidants, and anti-inflammatory elements (Di Tucci *et al.* 2021; Pecora *et al.* 2023; Salas-Huetos *et al.* 2018).

Research has identified a correlation between the MD and improved health, with a focus on the investigation of its ingredients and their capacity to enhance fertility (Petre *et al.* 2023; Rahimlou *et al.* 2022). A high adherence to the MD has been identified as a factor that may contribute to successful reproductive outcomes in infertile men. However, this hypothesis remains a subject of debate. The present study constitutes a comprehensive review and meta-analysis, the objective of which is to investigate the potential of enhanced reproductive indicators in infertile men, as a result of greater adherence to the MD.

METHODS

Design, location, and time

This study adhered to the 2020 standards of The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The design requirements were established based on the following fundamental framework steps: 1) Scoping; 2) Planning; 3) Searching; 4) Screening; 5) Eligibility; and 6) Interpretation.

The analysis exclusively included cohort studies that focused on infertile men of reproductive age. The Food Frequency Questionnaire (FFQ), a tool used in these studies, was designed to comprehensively assess the intake of all primary food categories comprising the MD. These food categories include legumes, fish, whole grain foods, soybeans, and olive oil. Exclusion criteria encompassed studies involving animals, cases of sterility, and trials that replicated the MD with supplements. The decision to utilize cohort studies was made to a more precise and insightful comparison. Exposition is defined as the process of measuring an individual's level of adherence to the MD. This is achieved by calculating their FFQ scores. The comparator exhibited a different behavioral profile from the MD (Muffone *et al.* 2023).

Sampling

A methodical search was conducted across multiple databases, namely PubMed, Medline, Embase, Cinahl, and Central, to comprehensively appraise the extant literature. The search was limited to publications from the past 10 years, specifically those published in 2015 and subsequent years. The PRISMA 2020 guidelines were used to guide the performance and explanation of the meta-analysis. The evaluation of adherence to the MD was based on scores specifically designed for this purpose. An FFQ was employed to determine the score, with higher scores allocated to the food groups that are characteristic of the MD. As the score increases, so does the level of adherence. The categorization of results into terciles or quartiles signifies low, moderate, or high adherence to the diet (Muffone *et al.* 2023).

Data collection

The relevant publications were determined by employing precise keywords that were tailored to each search engine's parameters. The search query incorporated the keyword "Mediterranean diet" along with the terms "male infertility" or "sperm quality parameters."

Data analysis

Two independent reviewers employed the Newcastle-Ottawa Scale (NOS), a quality assessment instrument for non-randomized control trials, to evaluate the selected papers for bias. The NOS was developed through a collaborative effort between the Universities of Newcastle, Australia and Ottawa, Canada. In instances of disagreement, the opinion of the two reviewers was sought. The approach to this specific observational study has been previously assessed in the context of categorized systematic reviews (Norris *et al.* 2021). The quality assessment tool comprises nine questions. The articles were divided into three groups based on their quality: 0–2 (poor), 3–5 (fair), and 6–9 (good/high) (Figure 2) (Moskalewicz & Oremus 2020).

The results were then meta-analyzed using the Cochrane Review Manager (RevMan) 5.4.1 software. The rationale behind this choice was to uphold uniform standards, establish correlations between the results, and assess the strength of the evidence. The outcome analyses were compared by computing the pooled Odds Ratios (ORs) and 95% Confidence Intervals (CIs). The degree of adherence to the Mediterranean diet was evaluated using a binary approach that distinguished between high and low adherence. The heterogeneity of the data was assessed using I^2 statistic, with values less than 25% indicating low heterogeneity, values between 25% and 75% indicating intermediate heterogeneity, and values greater than 75% indicating high heterogeneity. A $p<0.10$ was considered indicative of a low degree of heterogeneity. Due to the limited number of publications included, the meta-analysis did not incorporate funnel charts.

RESULTS AND DISCUSSION

The initial search encompassed a total of 292 studies, including 73 sourced from PubMed, 59 from Medline, 63 from Embase, 53 from Cinahl, and 44 from Central. Following a review of the titles and abstracts of the initial 292 studies, 250 duplicate records were eliminated, and 30 more were omitted based on adherence to the specified inclusion and exclusion criteria (Figure 1). After a thorough examination of the remaining 12 articles, only three satisfied the criteria for full reading. Following a review of the nine excluded publications, it was deterined that four of them failed to meet the requisite methodology. Furthermore, three of these publications were of a review nature, while two were incomplete conference proceedings.

The quality of sperm is determined by a number of factors, including volume, concentration, motility, motility progression, morphology, counting, and the presence of abnormalities in the semen. The technical parameters used in all of the studies encompassed in this analysis were consistent and adhered to the guidelines stipulated by the World Health Organization (WHO) in 2010. This uniformity in methodology enabled a more meaningful and accurate comparison of the studies (Muffone *et al.* 2023).

The three included studies examined semen volume. Ejaculate volume less than 1.5 mL is considered abnormal and is associated with infertility. There were no statistically significant differences in volume results. The meta-analysis revealed an Odds Ratio (OR) of 1.06 for low semen volume (<1.5 mL) among individuals adhering to the MD with low frequentcy (I^2=12%; 95% CI:0.59–1.93, p=0.84).

A statistically significant association was identified between oligospermia, defined as sperm concentration less than 15 × 106 mL, and non-adherence to the MD in the studies by Karayiannis *et al.* 2017, Ricci *et al.* 2019 and Salae *et al.* The meta-analysis yielded an OR of 2.86, indicating that individuals who do not adhere strictly to the Mediterranean diet are 2.86 times more prone to develop oligospermia (I^2=33%; 95% CI:1.58–5.18, p=0.0005).

A sperm count greater than 39 × 106 mL/sample is considered normal and is a crucial determinant of fertility (Punab *et al.* 2017). The meta-analysis revealed a robust correlation between adherence to the Mediterranean diet and an enhancement in sperm count, with a 2.54-fold increased probability of improvement (>39 × 106/ejaculate) (I^2=48%; OR=2.54, 95% CI:1.32–4.90, p=0.005).

It is noteworthy that achieving an optimal level of motility is contingent upon the capability of movement in at least 40% of the sample. This

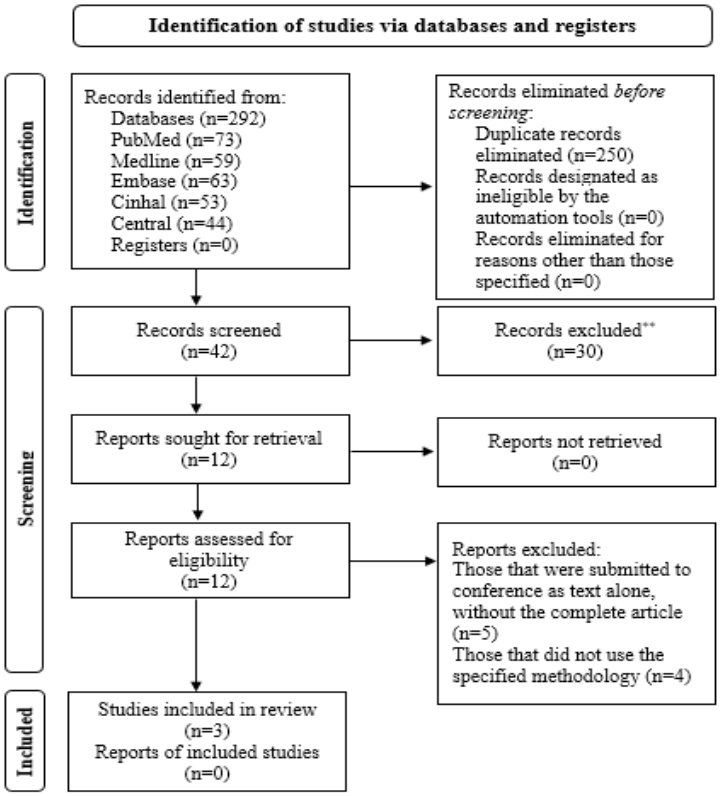

Figure 1. PRISMA 2020 flow diagram for systematic reviews

criterion was assessed by both Karayiannis *et al.* 2017 and Salas-Huetos *et al.* 2019. The meta-analysis revealed that there was a statistically significant relationship between high adherence to a Mediterranean diet and a higher likelihood of having normal motility, with a percentage greater than 40% (I^2=0%; OR=4.64, 95% CI:2.41–8.95, p<0.00001).

Table 1. Newcastle-Ottawa Scale (NOS) for the quality assessment of non-randomized controlled trial studies

Domain		Karayiannis *et al.* 2017	Ricci *et al.* 2019	Salas-Huetos *et al.* 2019
Selection (maximum four stars)	Representativeness of the exposed	*	*	*
	Selection of the non-exposed cohort	-	*	-
	Ascertainment of exposure	-	*	*
	Absence of any outcomes of interest at the onset of the study	8	*	*
Comparability (maximum of two stars)	Comparability of cohorts on the basis	*	*	*
	Design analysis	*	*	*
Outcomes (maximum of three stars)	Assessment of outcome	*	-	-
	Sufficiently prolonged follow-up for outcomes	*	*	*
	Adequacy of follow-up	*	*	*
	Score	7	8	7

Table 2. Study outcome

Reference	Adherence to MD	No	Volume		Consentration		Counting		Motility		Morphology	
			Volume Semen (mL) (95 % CI)	<1.5 mL (n)	<15 x 106/ mL (95 % CI)	<15 x 106/ mL (n)	Sperm Counting x 106/mL	<39 x 106/ mL (n)	<40% (95 % CI)	<40% (n)	%	<40% (n)
Karayiannis *et al.* 2017	HA	66	2.1 (1.9−2.3)	8	37.9 (31.4−44.4)	11	82.1 (64.7−99.5)	15	42.6 (37.6−47.5)	21	47 (71.2)	19
	MA	86	2.2 (2.0−2.3)	11	37.1 (31.5−42.6)	18	86.6 (71.8−101.4)	27	40.7 (36.5−44.9)	30	62 (74.7)	28
	LA	73	2 (1.7−2.2)	15	30.5 (24.3−36.7)	36	63.8 (47.2−80.4)	42	32.1 (27.4−36.8)	50	66 (86.8)	38
	p		0.403		<0.001		<0.001		<0.001	<0.001	0.023	
Ricci *et al.* 2019	HA	92	2.7 (1.5−4.0)	20	35 (15.0−63.0)	22	80.5 (38.2−138.6)	23				
	MA	131	2.5 (1.7−3.3)	23	32 (12.0−74.0)	37	84.0 (25.9−162.8)	39				
	LA	86	2.8 (1.7−3.8)	16	31 (6.4−65.6)	33	68.4 (16.8−159.1)	34				
	p		0.59		0.03		0.03					
Salas-Huetos *et al.* 2019	HA	27	3.3	4	25.2 (16.1−35.6)	5	76.7 (30.8−139.5)	6	73.2 (64.7−82.7)	2	6.3 (5.0−8.0)	2
	MA	49	3.0	8	23 (10.0−38.1)	19	65.0 (24.8−126.0)	19	64.4 (43.8−72.7)	7	6.5 (5.6−7.9)	5
	LA	30	2.8	3	27.6 (9.1−53.7)	11	79.0 (43.5−101.0)	9	54.5 (38.8−72.4)	8	6.4 (4.4−8.0)	5
	p		0.731		0.175		0.321		0.127	0.127	0.515	

MD: Mediterranean Diet; HA: High Adherence; MA; Moderate Adherence; LA: Low Adherence; CI: Confidence Interval; mL: Milliliter; n: The sample size; Significant value at p<0.10 based on binary approach analysis

Oxidative stress has been demonstrated to induce DNA damage, which is associated with changes in morphology. According to the Kriger index, these changes are considered normal if they exceed 4%, and indicate a tendency towards infertility if they fall below this threshold. An assessment of morphology was conducted by Karayiannis *et al.* 2017 and Salas Huetos *et al.* The meta-analysis yielded findings that support the hypothesis that a strict adherence to the MD is associated with a 2.66-fold increase in the likelihood of improving morphology (>4%) (I^2=0%; OR= 2.66; 95% CI:1.39–5.10, p=0.03).

The studies examining sperm in men who strictly adhere the MD reveal several notable findings. First, men who adhere strictly to the MD have been shown to have higher sperm counts (>39 x 106 per ejaculate). Second, these men have been obsserved to have higher sperm concentrations (>15 x 106 per mL). Third, the sperm motility of men following the MD has been found to be faster, with a greater than 40% motility rate. Finally, the sperm shape of these men has been demonstrated to be better (more than 4%). Salas-Huetos *et al.* conducted a randomized clinical trial to investigate the effects of incorporating oilseeds, a component of the MD, into the dietary regimen of infertile men with a Western dietary profile. The study's findings indicated that the inclusion of oilseeds resulted in a notable improvement in sperm quality.

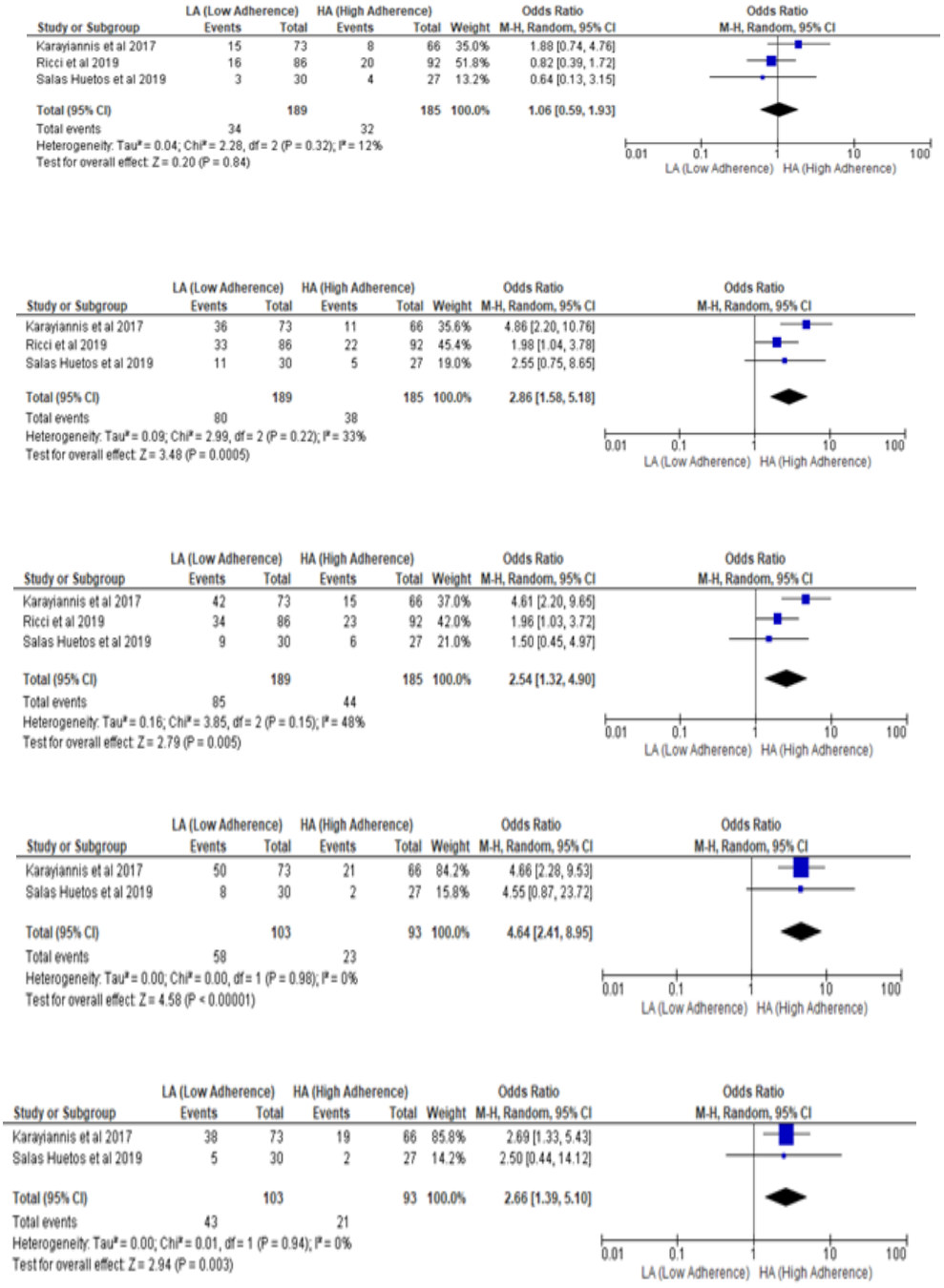

Figure 3. Meta-analysis of sperm quality parameters: A) Sperm volume; B) Sperm concentration; C) Sperm count; D) Sperm motility; E)Sperm morphology

A cross-sectional study found a positive correlation between increased intake of b-carotene and improved sperm motility, as well as between lycopene intake and better sperm morphology (Di Tucci *et al.* 2021; Ghyasvand *et al.* 2015) . Due to its abundance in tomatoes an other key Mediterranean food sources, lycopene aligns with the dietary patterns characteristics of the MD. The diet emphasizes the consumption of foods high in lycopene due to its numerous

health benefits, including its potential to protect the heart, reduce inflammation, and possibly even prevent cancer. The Mediterranean diet, characterized by a focus on plant-based foods and healthy fats, naturally provides a framework for the incorporation of lycopene into a well-rounded, nutrient-dense dietary pattern (Petre *et al.* 2023). The Mediterranean diet is notable for its inclusion of both lycopene and other nutrients (Salas-Huetos *et al.* 2019). The present study examined the precise function of particular antioxidants in the quality of semen. Antioxidants have been the focus of research due to their potential to enhance sperm quality, with several studies suggesting a positive effect. Oxidative stress, defined as an imbalance between antioxidants or free radicals in the body, has been demonstrated to influence sperm quality parameters such as concentration, motility, morphology, and DNA integrity. Free radicals have been shown to impair sperm cells, potentially compromising their motility, DNA integrity, and overall functionality. Antioxidants, on the other hand, counteract free radicals, thereby safeguarding sperm from harm (Li *et al.* 2019).

Suliga and Głuszek (2019) conducted a study that found a positive correlation between improved sperm concentration and motility and a nutritious diet characterized by higher consumption of fruits, vegetables, whole grains, fish, and low-fat dairy products. Nevertheless, debate persists regarding the consumption of nonorganic fruits and vegetables, given their antioxidant content and potential xenobiotic contamination (Suliga & Głuszek 2019). These findings support the established link between inflammation and oxidative stress, as well as alterations in sperm and gametogenesis. The peroxidation of lipids in sperm membranes is a contributing factor to this phenomenon, leading to a decline in vital antioxidant enzymes such as glutathione and catalase within the sperm (Corsetti *et al.* 2023). Furthermore, a breakdown of essential proteins necessary for sperm maintenance ensues, rendering it impossible to repair this damage. Ultimately, this cascade of events exerts an indirect influence on the release of sexual hormones by the hypothalamus (Gaskins *et al.* 2019).

Research has identified that enhancing male fertility necessitates the incorporation of additional food groups rich in antioxidants and the supplementation of anti-inflammatory nutrients such as omega-3 fatty acids, lycopene, and b-carotene (Palani *et al.* 2024). Contrary to previous findings, Danielewicz *et al.* (2018) observed a decline in semen quality associated with the Western diet. However, they observed no improvement in quality with a "pro-health" diet, which is characterized by an increased consumption of antioxidants derived from fruits and vegetables. The presence of xenobiotic contamination may provide a plausible explanation for these findings (Danielewicz *et al.* 2018).

A number of biases were identified in the systematic review that are associated with the characteristics of the selected studies. Fertility clinics are the optimal venues for conducting the majority of studies in this field. The term "sample calculation" refers to the process of performing a mathematical computation using a representative subset of data. The availability of individuals seeking this treatment in clinics and their willingness to participate are also limited and dependent on the feasibility of the treatment. The evaluation of dietary intake in individuals who have already commenced treatment is only feasible through the utilization of a FFQ. The reliance on self-reported dietary data introduces potential inaccuracies due to memory lapses, particularly when the study spans a period frame of more than 6 months. Another constraint pertains to the various methods of assessing the MD, which can lead to discrepancies in comparisons and pose challenges in establishing a direct link between diet and fertility markers. It is important to acknowledge that numerous confounding factors also play a role in this matter. A notable shortcoming in the surveys was the impracticality of evaluators concealing the MD's identity in a prospective cohort investigation.

This systematic review was conducted using a rigorous methodology, adhering to strict protocols at every stage to ensure the accuracy of the results. It addressed an unresolved scientific inquiry by conducting a comprehensive search of studies on this topic across all databases. The selected articles were reviewed, and their inclusion or exclusion was justified. Two researchers separately extracted the data from the articles and subsequently compared them. Following the confirmation of the validity of all relevant methods, including a dual review process, the biases were examined using a specific protocol for evaluating observational studies. The meta-analysis incorporated potential

outcomes. A notable strength of this study lies in its examination of High Adherence (HA) to the Mediterranean diet versus Low Adherence (LA) as determined by FFQ scores. The findings indicated that HA can enhance sperm quality. The search revealed a paucity of research examining the effects of the Mediterranean diet on male fertility using FFQ scoring. This systematic review is not without limitations; the number of studies included in the quantitative synthesis was only 3 studies, which impacts the number of populations and population characteristics.

CONCLUSION

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The Mediterranean diet has been demonstrated to exert an influence on the quality of semen in men experiencing infertility. Adherence to healthy diets, such as the Mediterranean diet, has been shown to have a positive impact on male reproductive health. Research has demonstrated that consuming foods that are high in omega-3 fatty acids, antioxidants, and anti-inflammatory agents can improve semen quality. These nutrients can help reduce oxidative stress and protect sperm from its harmful effect. Consequently, it is recommended that couples planning pregnancy receive dietary counseling to facilitate the adoption of healthy eating habits, which have the potential to mitigate infertility issues. Further research is necessary to elucidate the connections between diet and semen quality. This study offers invaluable insights into the promotion of health and the prevention of diseases by targeting men's dietary patterns during their reproductive years.

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AM was responsible for searching and reviewing the literature one by one after obtaining the relevant literature and for preparing the research manuscript, including the abstract, introduction, research methods, and research citations. The role of ZTA entailed the extraction of pertinent data and the subsequent structuring of the research results, discussion, and conclusion.

DECLARATION OF CONFLICT OF INTERESTS

The authors declared that there are no conflicts of interest. This work does not receive any funding from external entities.

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