

Manuscript Details

Manuscript number	REPPIO_2019_186_R1
Title	Diet and sperm quality: nutrients, foods and dietary patterns
Short title	Diet and sperm quality
Article type	Review Article

Abstract

Human semen quality has declined worldwide in the last 40 years, by some accounts as much as 50-60%, causing serious concerns and implications for human fertility. Even though it has been shown to be a worldwide problem, this decrease is more pronounced in the developed and industrialized countries, pointing to changes in modifiable lifestyle factors (e.g. unhealthy diets, lifestyles, and pollution) as the main causes. The studies investigating the relation between diet and semen quality can be classified into three groups; studies assessing the association between semen quality and 1) nutrients, dietary supplements and antioxidants, 2) food, and 3) dietary patterns. The present narrative review provides a wide-ranging vision of the positive associations and effects of diet on sperm quality. Although the picture of the relationship between diet and sperm quality and fertility is far from complete, a number of broad conclusions have emerged. First, increased intake of selenium and zinc, omega-3 (ω -3) fatty acids, CoenzymeQ10 (CoQ10) and carnitine supplements have been positively related to sperm quality. In terms of food groups, vegetables, fruits, nuts and whole cereals, all rich in fiber and antioxidants, and fish, seafood, shellfish, poultry, and low-fat dairy products have been positively associated with sperm quality. Finally, adherence to healthy dietary patterns are positively associated with sperm concentration and sperm motility.

Keywords	Nutrients; supplements; foods; dietary patterns; sperm quality
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Suggested reviewers	Nerea Becerra Tomás, Bárbara Vizmanos, Marc Yeste, Lluís BassasArnau

Submission Files Included in this PDF

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Answers to editor and reviewers_vdef.docx [Response to Reviewers]

Changes Salas-Huetos et al. 2019_Diet and sperm quality_vdef.docx [Manuscript File]

Figure 1_def.pptx [Figure]

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July 2019

Prof. Nafis Rahman

Editor-in-Chief of Reproductive Biology

Re: Manuscript Number: Manuscript # ID REPBIO_2019_186

Dear Prof. Nafis Rahman,

Thank you for your response to our manuscript.

Please find enclosed our manuscript entitled “**Diet and sperm quality: nutrients, foods and dietary patterns**”, which we would like to be accepted for publication in **REPRODUCTIVE BIOLOGY**.

In submitting this revision, we have taken into account all of the reviewers’ criticisms and the editor suggestions. Our responses are itemised on the accompanying sheets and discuss the changes we have made to the revised text.

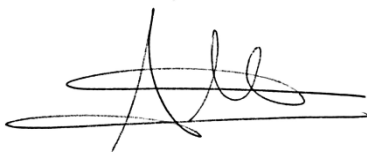
We hope that the new manuscript is now suitable for publication in **REPRODUCTIVE BIOLOGY**.

I certify,

1. That the corresponding author and all of the authors have read and approved the final submitted manuscript
2. That no portion of the work has been or is currently under consideration for publication elsewhere.
3. That no portions of the manuscript other than the abstract has been published or posted on the Internet.

Looking forward to hearing from you,

Yours sincerely,



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July 2019

Prof. Nafis Rahman
Editor-in-Chief of Reproductive Biology

Dear Prof. Nafis Rahman,

Enclosed please find the revised manuscript # ID REPBIO_2019_186 entitled “Diet and sperm quality: nutrients, foods and dietary patterns” which we would like to be reconsidered for publication in *Reproductive Biology*.

A list of detailed answers to the editor and the reviewers has been included below. We thank all of them for their helpful and thoughtful critique of our manuscript.

Reviewer #1

The authors present an important updated narrative review to summarize the existing evidence regarding diet and sperm quality. There are several issues that need to be addressed:

We thank the reviewer for his/her comments and the overall appreciation of our narrative review.

1. It is a very comprehensive and well-done review. However, you would need to explain how you are adding something new to the body of literature already written on this topic.

We have included a new paragraph discussing the new information that provides this review (lines 73-78).

2. It is important to expand in the introduction section why this review focuses on diet and sperm quality. Authors have stated that among the causes of the decline in the sperm quality, pollution, psychological stress, smoking, alcohol consumption, pesticides in food, and unhealthy diets are the main reasons, but they do not explain the rationale of focusing this review only in diet. Maybe it would be interesting to delete the subheading “Diet and sperm quality”, and add the information of this section to the introduction.

As suggested by the reviewer we have merged both sections and included two new paragraphs explaining the rationale of the present manuscript (lines 66-70 and 73-78).

3. Lines 145-158: authors must be cautious. They say: “we can draw the conclusion that the effect of specific supplements or antioxidants on semen quality are generally well-defined”. However, they also state that the safety of the supplement used has not been tested and the studies conducted so far have a limited sample size. I suggest rewriting the sentence avoiding these solid conclusions.

We have modified this sentence in the manuscript (lines 147-149).

4. Lines 181-188: the heading of this section is Cereals. However, authors mainly focused on fiber. Readers may expect to read here information about cereals as a food group (rice, pasta, bread etc.). I guess authors only included information about fiber

because there is a lack of studies in this topic. However, it would be important to point out the gap of knowledge in this area (if actually this is the case).

Requested information has been included in the manuscript (line 181 and 188-191).

5. *Lines 182-183: please add references for the studies that have assessed the association between fiber consumption and fertility.*

As suggested, we have included two references (“Mendiola J, Torres-Cantero AM, Vioque J, Moreno-Grau JM, Ten J, Roca M, et al. A low intake of antioxidant nutrients is associated with poor semen quality in patients attending fertility clinics. *Fertil Steril* 2010;93:1128–33. doi:10.1016/j.fertnstert.2008.10.075.” and “Eslamian G, Amirjannati N, B R, Sadeghi M, Hekmatdoost A. Nutrient patterns and asthenozoospermia: A case-control study. *Andrologia* 2016:In Press. doi:10.1111/and.12624.”) (line 183).

6. *Lines 189-196: A recently published paper (Joint Analysis of Metabolite Markers of Fish Intake and Persistent Organic Pollutants in Relation to Type 2 Diabetes Risk in Swedish Adults) suggest that fatty fish consumption may protect against type 2 diabetes after removing the counteractive effects of coexposure to persistent organic pollutants. As in the introduction section it has been explained that pollution is one of the main causes of semen quality decline, it would be interesting to explain here also the potential negative effects of fish consumption on sperm quality taking into account the high presence of pollutants in this food group (as has been done in the case of poultry regarding the use of antibiotics).*

As suggested, we have included a new paragraph with this information (lines 198-201).

7. *Line 227: please remove “the” from “identified a the reduction in sperm DNA”*

We have removed “the” from line 232 in the manuscript.

8. *Lines 229-231: Again, taking into account the design of the published studies, authors need to be cautious. They cannot affirm that some associations between specific foods and male semen quality are well-defined. Moreover, evidence is scarce and sometimes controversial.*

We have modified this sentence in the manuscript (lines 233-235).

9. *Please, change review for narrative review through the manuscript.*

Thanks, done as suggested (lines 36, 74, 294, and 297).

Reviewer #2

This is a very interesting, thoughtful and well written review that tackles a relevant subject: the effects of diet upon men’s sperm quality. This is crucial, since western lifestyle appears to be linked to a reduction of spermiogram parameters. I do not have major comments on the content/scientific approach of the Manuscript, because the take-home message is clear, but just one minor suggestion:

We thank the reviewer for the overall appreciation of our manuscript.

L106 Suggestion: change ‘scavenging’ to ‘destroying’?

As suggested by the reviewer we have changed this word (line 110).

Associate Editor

Besides answering to point by point to above-mentioned issues from REVs, I would request

- to have a bit more of expert comments in the Review Ms (revised one), if possible, as that is what the readers want to read from a review paper.

As suggested, we have included a new paragraph with this information (lines 300-308).

- the Revised Ms would greatly profit from a refreshing by a native language speaker "scientist".

We have revised the English of the new manuscript.

We do hope that all the modifications we have made to the manuscript will make it possible for the paper to be accepted and published in *Reproductive Biology*.

We are looking forward to receiving the editorial decision concerning the new submitted article.

Yours sincerely,

Dr. Albert Salas-Huetos

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1 **Type of Manuscript: Mini-Review**

2 **Title**

3 Diet and sperm quality: nutrients, foods and dietary patterns

4 **Running title**

5 Diet and sperm quality

6
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28 **ABSTRACT**

29 Human semen quality has declined worldwide in the last 40 years, by some accounts as
30 much as 50-60%, causing serious concerns and implications for human fertility. Even though
31 it has been shown to be a worldwide problem, this decrease is more pronounced in
32 developed and industrialized countries, pointing to changes in modifiable lifestyle factors
33 (e.g. unhealthy diets, lifestyles, and pollution) as the main causes. Studies investigating the
34 relation between diet and semen quality can be classified into three groups; studies
35 assessing the association between semen quality and 1) nutrients, dietary supplements and
36 antioxidants, 2) food, and 3) dietary patterns. The present **narrative review** provides a wide-
37 ranging vision of the positive associations and effects of diet on sperm quality. Although the
38 picture of the relationship between diet and sperm quality and fertility is far from complete,
39 a number of broad conclusions have emerged. First, increased intake of selenium and zinc,
40 omega-3 (ω -3) fatty acids, CoenzymeQ10 (CoQ10) and carnitine supplements have been
41 positively related to sperm quality. In terms of food groups, vegetables, fruits, nuts and whole
42 cereals, all rich in fiber and antioxidants, and fish, seafood, shellfish, poultry, and low-fat
43 dairy products have been positively associated with sperm quality. Finally, adherence to
44 healthy dietary patterns is positively associated with sperm concentration and sperm motility.

45

46 **Key words**

47 Nutrients; supplements; foods; dietary patterns; sperm quality

48 INTRODUCTION

49 Infertility affects about 15% of the world's population (~60-70 million couples) and male
50 factors are responsible for 40–50% of these cases. A recent meta-analysis including 185
51 studies and more than 42,000 men without known fertility problems, reported that human
52 semen quality (specifically sperm concentration and sperm count parameters) has declined
53 by approximately 50-60% worldwide in the last 40 years, causing serious concerns about
54 the future of human fertility [1]. Even though it has been shown to be a worldwide problem,
55 this decrease is more evident in particular geographic regions of the world, chiefly in
56 developed and industrialized countries [2], suggesting that the etiology may largely involve
57 modifiable lifestyle factors. There are multiple possible causes of this decline, but pollution,
58 psychological stress, smoking, alcohol consumption, pesticides in food, and unhealthy diets
59 are hypothesized as principal potential causes.

60 **Populations** in developed and developing countries are increasingly consuming higher
61 proportions of unhealthy foods, resulting in diets that are rich in fat from animal-origin, sugar,
62 salt, and calories with little nutritional value (e.g. Western-style diet) [3]. A Western-style diet
63 has been recognized as the major contributor to metabolic disturbances and the
64 development of obesity-related diseases including type 2 diabetes, hypertension and
65 cardiovascular diseases, among others [4].

66 **Due to the worldwide reduction of sperm quality and the increase in consumption of**
67 **unhealthy diets, this field of study has received more attention. In fact, in the last decade,**
68 **several observational studies, and a few randomized clinical trials (RCT), were published to**
69 **investigate possible associations between diet and sperm quality. Studies investigating this**
70 **association or relationship** can be classified into three groups: studies assessing the effects
71 or associations between semen quality and 1) nutrients, dietary supplements and
72 antioxidants, 2) foods, and 3) dietary patterns.

73 Previously published reviews have only focused on some of the types of study designs or
74 classifications previously listed. The aim of the present narrative review is to shed light on
75 the whole body of published literature, regardless of the type of study design or
76 classifications (because dietary patterns, foods, and nutrients are inexorability linked), to
77 provide a wide-ranging vision of the potential positive associations or effects of diet with
78 sperm quality, and to discuss the strengths and limitations of the published literature.

79 **DIET AND SPERM QUALITY**

80 **1.1. Nutrients, supplements and antioxidants**

81 **RCTs** have provided evidence-based data that link some dietary supplements and
82 antioxidants with semen quality. In terms of antioxidants, a very recent Cochrane systematic
83 review of RCTs conducted in infertile males concluded that there is low-quality evidence
84 from small trials suggesting that antioxidant supplementation in subfertile males may
85 improve live birth rates for couples attending fertility clinics [5]. However, the evidence for
86 the effects on sperm quality appear stronger. Salas-Huetos and collaborators analyzed 28
87 articles (involving 2,900 participants) and finally meta-analyzed 15 providing the most wide-
88 ranging analysis to date of the potential effects of not only antioxidants, but also different
89 nutrients and supplements on sperm quality parameters [6]. The study revealed a significant
90 beneficial effect on sperm concentration from supplementation with selenium (Se), zinc (Zn)
91 (these two as the main antioxidant supplements), omega 3 (ω -3) fatty acids, and
92 CoenzymeQ10 (CoQ10). In addition, supplementation with ω -3 fatty acids and CoQ10 has
93 shown beneficial effects on total sperm count, and supplementation with Se, Zn, ω -3 fatty
94 acids, CoQ10, and carnitines, on sperm total motility. Sperm progressive motility was
95 increased only after supplementation with carnitines; and sperm morphology after
96 supplementation with Se, ω -3 fatty acids, CoQ10, and carnitines. However, most of the
97 studies were of short duration and have been conducted with few participants.

98 *1.1.1. Selenium*

99 Selenium is an essential trace nutrient for mammals. Animal studies have shown that Se
100 deficiency is related to reproductive problems, and that a very high amount of Se intake has
101 been associated with impaired semen quality [7]. However, most of the studies in humans
102 revealed a beneficial effect of this antioxidant on semen parameters [6]. It is worth noting
103 that oxidative stress (OS) has been identified as one of the main mediators of male infertility
104 because spermatozoa are particularly susceptible to OS. Oxidative stress occurs when there
105 is an imbalance between the production of reactive oxygen species (ROS) and the ability to
106 neutralize these toxic products. To prevent oxidative damage or stress, the body has
107 developed an antioxidant defense mechanism that is not always fully functional. For that
108 reason, some researchers focused their RCTs on antioxidant supplementation. In the case
109 of Se, the effects seem to be mediated by increasing glutathione peroxidase-1 activity,
110 **scavenging** hydrogen peroxide molecules and reducing ROS production in sperm [8].

111 *1.1.2. Zinc*

112 Another interesting antioxidant in the context of fertility is Zn. Zinc is an essential mineral,
113 typically included in prenatal and postnatal diets to help development in humans. Zn
114 deficiencies are considered a major cause of morbidity and mortality in young children [9].
115 Specifically in sperm, Zn acts as a membrane-stabilizing source by inhibiting membrane-
116 bound oxidative enzymes such as NAD(P) oxidase [10], increasing sperm concentration and
117 motility [6]. Zn is also required for correct sperm DNA condensation/descondensation. Some
118 studies suggest that chromatin stability of the ejaculated human spermatozoon is Zn-
119 regulated and that Zn controls the formation of disulfide bridges. Low content of sperm
120 chromatin zinc has been related with some cases of male infertility [11].

121 *1.1.3. ω -3 fatty acids*

122 Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs) with anti-inflammatory and
123 antioxidant properties, especially when substituting ω -6 fatty acids, reducing the risk of
124 coronary heart attack and cardiovascular disease events [12]. There are three main ω -3
125 fatty acids involved in human physiology and metabolism: α -linolenic acid (ALA), primarily
126 found in plant oils, and docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA),
127 mainly found in marine oils. Interestingly, mammals are unable to synthesize the essential
128 ALA. Generally, ω -3 fatty acids not only possess beneficial effects on semen parameters [6]
129 and studies have also confirmed that the addition of ω -3 fatty acids to the diet of pregnant
130 women has a positive effect on development of the fetus. In the case of ω -3 fatty acids,
131 studies suggest that they act by modifying the cell membrane composition through their
132 incorporation into the spermatozoa cell membrane, helping functionality of the cell [13].

133 1.1.4. *CoQ10*

134 Coenzyme Q10, also known as ubiquinone, is also an antioxidant molecule with a central
135 role in the electron transport chain and participates in aerobic cellular respiration. This
136 coenzyme has three redox states and can inhibit organic peroxide formation in seminal fluid,
137 reducing sperm OS and increasing the sperm quality [6]. Some researchers tried to discover
138 the effects of CoQ10 on couples' fecundability, but no improvements were found in
139 pregnancy or live birth rates [14].

140 1.1.5. *Carnitines*

141 Carnitines, such as L-acetyl carnitine (LAC) and L-carnitine (LC), are involved in metabolism
142 in most mammals. In the human body, carnitines act as a transporter of long-chain fatty
143 acids into the mitochondria providing energy for use by spermatozoa [15]. This is the primary
144 mechanism of action that can positively affect sperm motility [6]. Recently, carnitines were
145 also described as regulators of the oxidative and metabolic status of the female reproductive
146 system, and capable of improving female fertility [16].

147 Taking into account all of the published literature, evidence suggests that dietary
148 supplementation with certain supplements or antioxidants can beneficially modulate sperm
149 quality parameters and affect male fertility, although more clinical trials are warranted in the
150 future to better establish the clinical efficacy of these supplements and the ideal doses that
151 can be recommended to increase fertility without long-term adverse effects. This is
152 important, because in the last two decades ART clinics have commonly used mixtures of
153 commercially available antioxidants and supplements to treat patients. Unfortunately, the
154 safety of these dietary supplements and antioxidants has not been tested, and the dangers
155 for the user population are mostly unknown. Furthermore, recent studies reported that abuse
156 in the administration of antioxidants may instead lead to increased oxidative stress induced
157 by the “antioxidant paradox” which may ultimately trigger infertility phenotypes [16].

158 It is also worth mentioning that the results of the most recent systematic reviews and meta-
159 analysis [5,6] must be interpreted with caution due to the limited sample size of the included
160 studies and the substantial observed inter-study heterogeneity.

161

162 **1.2. Foods**

163 In the case of foods, data are primarily from observational studies. Results from 35 studies,
164 involving 12,672 participants, were systematically reviewed two years ago [17]. The review
165 showed that the consumption of vegetables, fruits and nuts (rich antioxidants food), whole
166 grain and cereals rich in fiber, fish, seafood and shellfish, poultry, and low-fat dairy products
167 may improve sperm quality. However, diets rich in processed meat, soy foods, potatoes,
168 full-fat dairy products, coffee, alcohol and sugar-sweetened beverages and sweets have
169 adverse effects on sperm quality.

170 *1.2.1. Vegetables and fruits*

171 Vegetables and fruits are antioxidant-rich foods, and as mentioned above, the use of
172 antioxidants can act as sperm ROS regulators reducing sperm DNA damage and increasing
173 sperm motility and vitality. High consumption of fruits and vegetables is also related to an
174 increased intake of folate which may have positive effects on sperm quality. In fact, Young
175 and collaborators reported that men with high folate intake had a lower risk of having sperm
176 aneuploidy [18], suggesting folate as an important player in spermatogenesis. Animal
177 studies revealed that folate-deficient diets could result in an alteration of sperm DNA
178 methylation at genes implicated in development and some metabolic processes. Moreover,
179 they have also demonstrated that compared with folate sufficient males, mice receiving a
180 folate deficient diet displayed negative pregnancy outcomes [19].

181 **1.2.2. Cereals and fiber**

182 Cereals are the main source of dietary fiber in most countries. Very few studies have
183 demonstrated a direct effect of fiber on **fertility [20,21]**, however, fiber consumption could
184 reduce plasma estrogen levels [22]. This is important, because high estrogen levels could
185 disrupt endocrine homeostasis, which is essential for normal spermatogenesis. It is worth
186 mentioning that nowadays breakfast cereals are routinely fortified with some antioxidants
187 and vitamins mentioned previously that are associated with better semen quality
188 parameters. **Only one study showed that consumption of cereals (as a food group: rice,**
189 **pasta, bread, maize, etc.) together with vegetables, were positively related not only with**
190 **sperm quality but also with implantation rates [23]. Therefore it is important to point out the**
191 **gap of knowledge in this area.**

192 **1.2.3. Fish, seafood and shellfish**

193 Fish, seafood and shellfish are ω -3 fatty acid-rich foods. As mentioned previously, ω -3 fatty
194 acids have potent anti-inflammatory and antioxidant properties, especially when substituting
195 ω -6 fatty acids. This is important because humans are unable to synthesize ω -3 fatty acids

196 in vivo. In fact, the most relevant study published to date, showed that the consumption of
197 fish has a positive impact on sperm counts and morphology. The substitution of processed
198 red meat with fish was particularly beneficial in terms of sperm quality [24]. However, these
199 beneficial effects can be negatively affected by the high concentration of some
200 environmentally-persistent organic pollutants in the fish, as well as mercury (Hg) and other
201 neuro-toxic elements, as demonstrated in a recent type 2 diabetes outcome study [25].

202 1.2.4. Poultry

203 Poultry consumption is interesting because an increased intake of poultry has been
204 associated with a significantly lower risk of asthenozoospermia [26]. Another study reported
205 a positive association between poultry consumption and fertilization rates [27]. Intriguingly,
206 none of the authors were able to explain any potential biological mechanisms that could
207 explain these results. However, as mentioned before, these positive results must be
208 cautiously interpreted due to the difference in the use of antibiotics in different
209 countries/regions in poultry and other animals. The use of antibiotics could be a confounding
210 factor and possibly responsible for the inconsistencies seen in results between poultry
211 studies.

212 1.2.5. Low-fat dairy products and skimmed milk

213 The effect of dairy product consumption on sperm quality and fertility is highly controversial.
214 Full-fat dairy, total dairy products and cheese have been negatively associated with sperm
215 quality parameters, however, low-fat dairy products and skimmed milk have been related to
216 improved semen parameters (mainly in terms of spermatozoa concentration and motility)
217 [28]. Low-fat and skimmed milk consumption have been associated with increased
218 circulating levels of insulin, probably through increasing the levels of insulin-like growth
219 factor 1 (IGF-1), and animal studies indicated that subcutaneous insulin administration may
220 increase sperm motility and concentration [29].

221 **1.2.6. Nuts**

222 Nuts merit special attention because they are the only food that has been tested by two
223 RCT's [30,31]. Nuts are a nutrient-dense food rich in unsaturated fatty acids, fiber, minerals,
224 tocopherols, phytosterols, and polyphenols that beneficially impact heart health. After the
225 administration of 75 g/d of walnuts (that are rich in ALA) for 12 weeks, Robbins *et al.* reported
226 improvements in sperm vitality, motility, and morphology. The authors related the
227 improvements in semen parameters in parallel with increases in blood serum ω -6 fatty acids
228 and ALA ω -3 fatty acids [31]. However, more recently, Salas-Huetos and collaborators
229 reported that the inclusion of a mix of nuts (almonds, hazelnuts and walnuts) in a Western-
230 style diet (for 14 weeks) significantly improved not only the vitality, motility, and morphology,
231 but also the total sperm count. The authors also tried to explain the mechanisms of these
232 beneficial effects and **identified a reduction** in sperm DNA fragmentation [30].

233 Taking into account the number of observational studies published in the literature, **we can**
234 **suggest that male adherence to specific healthy foods can improve semen quality and**
235 **fecundability rates.** Unfortunately, with only observational studies we cannot infer causality,
236 and results must be cautiously interpreted. Only RCTs give the highest level of evidence in
237 order to establish recommendations, and RCTs are scarce and in some cases conducted in
238 small numbers of subjects. Only in the case of nut consumption has a clear positive effect
239 on sperm quality been strongly demonstrated, although large RCTs with infertile men are
240 warranted in the future to further confirm the beneficial effect of nut consumption on this
241 condition.

242

243 **1.3. Dietary patterns**

244 A recent meta-analysis of 6 studies involving more than 8,200 participants concluded that,
245 compared to participants in the highest adherence to a healthy dietary patterns, those in the

246 lowest category of adherence, had significantly lower sperm concentration. In the same
247 meta-analysis, no significant associations with other semen quality parameters were found
248 [32].

249 *1.3.1. Health-conscious dietary pattern*

250 Fruits, vegetables, fish, legumes, and whole grains are the main foods consumed in a health-
251 conscious dietary pattern. The only study testing this dietary pattern was conducted by
252 Vujkovic et al. [33], and demonstrated that men consuming the health-conscious diet had
253 lower sperm DNA damage when compared with those consuming a ‘traditional Dutch’
254 dietary pattern (rich in meat, potatoes and whole grains, and low in sugar drinks and
255 sweets). However, sperm concentrations were higher in men who strongly adhered to the
256 ‘traditional Dutch’ dietary pattern, revealing some controversial findings that have to be
257 investigated.

258 *1.3.2. Prudent dietary pattern*

259 Some studies have tested the Prudent diet characterized by a high consumption of fruits,
260 vegetables, fish, legumes, poultry, and whole grains [34–36]. In general, the studies
261 comparing adherence to this Prudent diet with adherence the Western-style dietary pattern
262 found not only a positive association with higher sperm concentrations, but also with
263 decreased frequencies of sperm disomy.

264 *1.3.3. Mediterranean dietary pattern*

265 The Mediterranean diet (MD) is characterized by a high consumption of olive oil, nuts, fruits,
266 vegetables, legumes, and whole cereals, along with a moderate consumption of fish, poultry
267 and wine. The MD pattern has been considered one of the healthiest dietary patterns and
268 has been associated with extensive benefits on human health [37]. Cutillas-Tolín and
269 collaborators were the first describing potential beneficial effects of the MD on total sperm

270 count [38]. Recently, using a cross-sectional study, adherence to the MD was also positively
271 associated with sperm motility [39].

272 Results in this last section of the present article must be cautiously interpreted due to the
273 nature of the design of the published studies. All are observational, and therefore no
274 causation can be determined. The strongest limitation of these published articles is the
275 difficulty in excluding some associated factors of the individuals that consume a healthy diet
276 (generally these individuals are more active, with a minimum intake of alcohol and tobacco
277 and limited fast food consumption). Given the growing number of studies analyzing the
278 associations between dietary patterns and semen parameters, now is time to test the effect
279 of healthy dietary patterns on semen and/or fertility rates using well-designed multicenter
280 RCTs involving a large number of participants. However, to draw strong conclusions the
281 resulting RCTs must take into account large lists of lifestyle factors, such as physical activity,
282 areas where the people live (air pollution), alcohol consumption, and smoking, among
283 others.

284

285 **CONCLUSIONS**

286 Although the picture of the relationship between diet and men's sperm quality and fertility is
287 far from complete, a number of broad associations have emerged. First, increased intake of
288 selenium and zinc, ω -3 fatty acids, CoQ10 and carnitine supplements have been positively
289 related to sperm quality. In terms of food groups, vegetables, fruits, nuts and whole cereals,
290 all rich in fiber and antioxidants, as well as fish, seafood and shellfish, poultry, and low-fat
291 dairy products have been positively associated to sperm quality. Finally, adherence to
292 healthy dietary patterns is positively associated with sperm concentration and sperm motility
293 (**Figure 1 and Table 1**).

294 The present narrative review provides some evidences of the associations between diet and
295 the risk of impaired fertility, suggesting that male adherence to healthy diets can improve
296 semen quality and possibly fecundability rates. While the associations and effects
297 summarized in the present narrative review are incomplete and, in some cases,
298 controversial, the available data are intriguing and warrant further exploration with large
299 prospective cohort studies and well-designed RCTs.

300 In the absence of this information, the only recommendation that can currently be made to
301 the general male population is to adhere to a healthy dietary pattern rich in plant-based
302 foods such a vegetarian diet, the Dietary Approach to Stop Hypertension (DASH) diet or the
303 Mediterranean diet. In the future it is essential to study specific dietary supplements to
304 improve not only the quality of the semen, but also to verify that this translates into an
305 improvement in the fecundity of those men with different types of infertility. Finally, more
306 studies are also warranted to try to clarify the mechanisms through which diet can improve
307 fertility. This can help in the future in improving the current dietary recommendations for
308 populations where fertility is in constant decline.

309 **AUTHOR'S ROLES**

310 A.S-H.: Initiated the idea of the review, designed the review, collected and selected the data,
311 wrote the manuscript and had a primary responsibility for final content. E.R.J., K.I.A., T.G.J.,
312 D.T.C.: Critically revised the manuscript. All the authors approved the final manuscript.

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321 The authors report no financial or commercial conflicts of interest.

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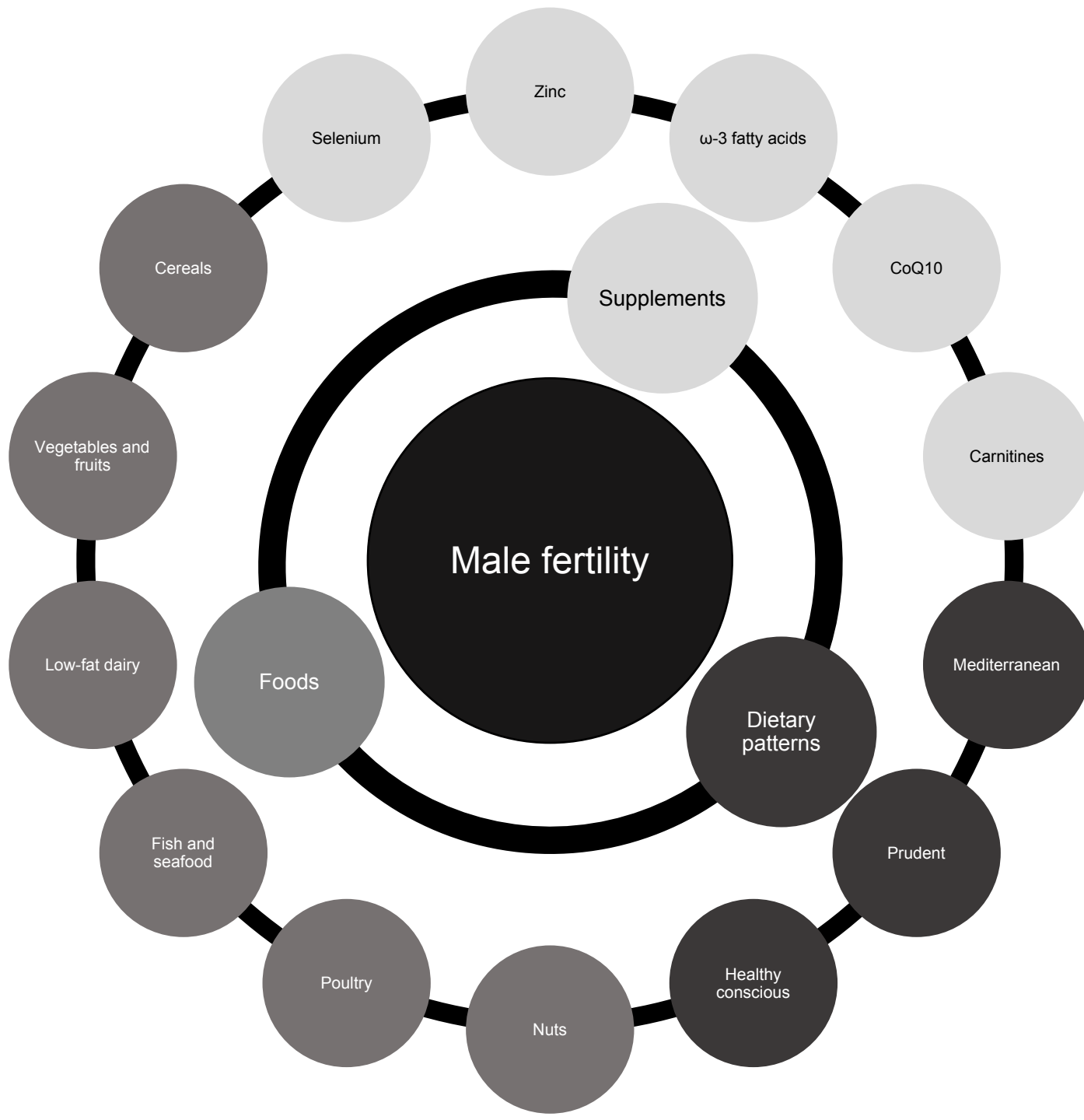
445

446 **Table 1.** Most studied supplements (and antioxidants), foods and dietary patterns that
 447 positively affect (or are associated with) sperm quality, main benefits, evidence level and
 448 primary references.

Variables	Main benefits: associations (from observational studies) or effects (from RCT)	Problems in the evidence	Main references
Antioxidants			
Selenium	Beneficial effect on sperm concentration, total sperm motility and morphology	RCTs of low-quality and small population	[5,6]
Zinc	Beneficial effect on sperm concentration and total sperm motility	RCTs of low-quality and small population	[5,6]
Other supplements			
ω-3 fatty acids	Beneficial effect on sperm count and concentration, total motility and normal morphology	RCTs of low-quality and small population	[6]
CoQ10	Beneficial effect on sperm count and concentration, total motility and normal morphology	RCTs of low-quality and small population	[6]
Carnitines	Beneficial effect on sperm progressive and total motility and normal morphology	RCTs of low-quality and small population	[6]
Foods			
Vegetables and fruits	Positively associated with sperm motility	No RCTs to date	[17]
Cereals	Positively associated with sperm motility	No RCTs to date	[17]
Fish, shellfish and seafood	Positively associated with total sperm count, concentration and morphology	No RCTs to date	[17]
Poultry	Positively associated with sperm motility	No RCTs to date	[17]
Low-fat dairy and skimmed milk	Positively associated with sperm concentration and motility	No RCTs to date	[17]
Nuts	Beneficial effect on sperm count, vitality, total and progressive motility and normal morphology	RCTs of small population	[30,31]
Dietary patterns			
Health conscious	Positively associated with sperm concentration and lower sperm DNA damage	No RCTs to date	[17,32]
Prudent	Positively associated with sperm concentration and decreased frequencies of sperm disomy	No RCTs to date	[17,32]
Mediterranean	Positively associated with sperm concentration and sperm motility	No RCTs to date	[17,32,39]

450 **FIGURE CAPTIONS**

451 **Figure 1.** Supplement intake, food consumption and dietary pattern adherence that may
452 improve male factor fertility.







Conflict of Interest and Authorship Conformation Form

Article Title: **Diet and sperm quality: nutrients, foods and dietary patterns**

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