Type of Manuscript: Systematic Review

TITLE

Dietary patterns, foods and nutrients in male fertility parameters and fecundability: a systematic review of observational studies

Running title

Diet and male fertility: a systematic review

Authors

Albert Salas-Huetos, Ph.D., [a,b]; Mònica Bulló, Ph.D., [a,b]; and Jordi Salas-Salvadó, M.D, Ph.D., [a,b,*]

Affiliations

[a] Human Nutrition Unit, Biochemistry and Biotechnology Department, Faculty of Medicine and Health Sciences, University Hospital of Sant Joan de Reus, IISPV, Universitat Rovira i Virgili, Reus, Spain.

[b] CIBER Physiopathology of Obesity and Nutrition (CIBERobn), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.

*** Corresponding author**

Jordi Salas-Salvadó

Human Nutrition Unit, Faculty of Medicine and Health Sciences, Universitat Rovira i Virgili, St/ Sant Llorenç 21, 43201 Reus, Spain.

Tel: (+34) 977 75 93 12

Fax: (+34) 977 75 93 22

E-mail: jordi.salas@urv.cat

TABLE OF CONTENTS

ABSTRACT

Background

Infertility is a global public health issue, affecting 15% of all reproductive age couples. Male factors, including decreased semen quality, are responsible for approximately 25% of these cases. The dietary pattern, the components of the diet and nutrients have been studied as possible determinants of sperm function and/or fertility.

Objective and rationale

Previous systematic reviews have been made of the few heterogeneous ~~and~~ low-quality randomized clinical trials conducted in small samples of participants and investigating the effect of specific nutrients and nutritional supplements on male infertility. However, as yet there has been no systematic review of observational studies.

Search methods

A comprehensive systematic review was made of the published literature, from the earliest available online indexing year to November 2016, in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We have included cross-sectional, case-control, and prospective and retrospective studies in which fertile/infertile men were well-defined (men with sperm disorders, sperm DNA damage, varicocele or idiopathic infertility). The primary outcomes were semen quality or fecundability. With the data extracted, we evaluated and scored the quality of the studies selected. We excluded randomized clinical trials, animal studies, review articles and low quality studies.

Outcomes

A total of 1,944 articles were identified, of which 35 were selected for qualitative analysis. Generally, the results indicated that diets rich in some nutrients such as omega-3 fatty acids, some antioxidants (vitamin E, vitamin C, β-carotene, selenium, zinc, cryptoxanthin and lycopene), other vitamins (vitamin D and folate), and low in saturated fatty acids and trans fatty acids were inversely associated with low semen quality parameters. Fish, shellfish and seafood, poultry, cereals, vegetables and fruits, low-fat dairy and skimmed milk were positively related with several sperm quality parameters. However, diets rich in processed meat, soy foods, potatoes, full-fat dairy and total dairy products, cheese, coffee, alcohol, sugar-sweetened beverages and sweets have been detrimentally associated with the quality of semen in some studies. As far as fecundability is concerned, a high intake of alcohol, caffeine, and red meat and processed meat by males has a negative influence on the chance of pregnancy or fertilization rates in their partners.

Wider implications

Male adherence to a healthy diet could improve semen quality and fecundability rates. Since observational studies may prove associations but not ~~demonstrate~~ causation, the associations summarized in the present review need to be confirmed with large prospective cohort studies and especially with well-designed randomized controlled clinical trials.

Systematic review registration

PROSPERO 2016: CRD42016039410. Available ~~from~~ at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016039410.

Keywords

Diet, nutrition, nutrients, food, male infertility, sperm parameters, fecundability

INTRODUCTION

Infertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. In recent decades infertility has become a global public health issue and a major clinical concern, affecting 15% of all reproductive age couples. It has been estimated that 70 million couples worldwide experience subfertility or infertility (Boivin *et al.*, 2007). Male factors, including decreased semen quality, are responsible for approximately 25% of cases of infertility (Evers, 2002; Sharlip *et al.*, 2002) and, in the United States, the prevalence of men seeking help for fertility is estimated at 3.3–4.7 million (Anderson *et al.*, 2009).

Some studies suggest that human semen quality has declined in some geographic regions of the world (Mendiola *et al.*, 2013; Merzenich *et al.*, 2010). Currently the etiology of suboptimal semen quality is poorly understood, and many physiological, environmental~~,~~ and genetic factors, including oxidative stress, have been implicated (Jungwirth *et al.*, 2012; WHO, 2010).

Environmental factors such as air pollution, smoking, stress, chemicals and other toxic agents in the diet have all been considered as possibly responsible for the decrease in semen quality observed in developed countries (Carlsen *et al.*, 1992; Merzenich *et al.*, 2010). And in terms of the diet, since the 1980s several components and nutrients have been considered as ~~the~~ possible determinants of sperm function, fertility or normal function of the reproductive system ~~from the 80's~~ (Abbasi *et al.*, 1979).

Accumulating evidence from in vitro and animal studies indicates that male obesity and some components of the diet may play a pivotal role in modulating spermatogenesis, sperm maturation and fertilizing ability. For example, male obesity has been related to impaired reproductivity because of its effect on the molecular and physical structure of sperm (Mitchell *et al.*, 2011; Palmer, Bakos, Fullston, *et al.*, 2012; Palmer, Bakos, Owens, *et al.*, 2012). In addition, several foods and some components of the diet that have been associated to an increased risk of obesity, insulin resistance and diabetes have also been related to low sperm quality or function in animal models. For example, diets rich in calories (Rato *et al.*, 2014), trans fatty acids, saturated fats (Ng *et al.*, 2010) or cholesterol (Morgan *et al.*, 2014) have been associated to testicular disruption, impairments in spermatogenesis potentially affecting male fertility and the offspring.

Likewise, several cross-sectional, case-control, retrospective and prospective observational studies, some of which were conducted in large samples of individuals, have assessed the associations between diet and semen quality and/or fecundability, with controversial results.

In spite of this, there are many assisted reproductive clinics that recommend simple lifestyle changes such as increases in physical activity, cognitive behavioral therapy and yoga to reduce stress, give advice on how to reduce alcohol and caffeine intake or provide lists of dietary recommendations (Collins and Rossi, 2015) in order to improve semen quality and fertility chances. Nonetheless, reality shows how important it is to have a better understanding of the effect of lifestyle and diet on male fertility before useful recommendations can be made.

~~: e.g. L-carnitine, zinc, folic acid and vitamin C, vitamin B12 and vitamin E . However, the role of nutritional supplements in men and women undergoing assisted reproductive technology (ART) is controversial, and the results of some studies should be interpreted with caution. Nonetheless, reality shows how important it is to have a better understanding of the effect of diet and supplements on male fertility.~~

Recently, a review was published of randomized clinical trials (RCTs) investigating the effect of specific nutrients and nutritional supplements on male infertility (Giahi *et al.*, 2016). In total 12~~23~~ heterogeneous and low-quality RCTs, conducted in small samples of participants, investigating the effect of specific nutrients and nutritional supplements on male infertility were systematically reviewed. Oral complexes of selenium; selenium plus vitamin A; vitamin C; vitamin E; L-carnitine plus L-acetylcarnitine; beta-carotene, alpha-tocopherol and arachidonic acid; coenzyme Q10; clomiphene citrate plus vitamin E; eicoseptanoic plus docohexanoid acid; and ubiquinol were used in an attempt to improve such classical sperm quality parameters as sperm concentration, motility and morphology, or sperm DNA fragmentation (SDF). Only a few studies using supplements of carnitine, coenzyme Q10 and selenium have demonstrated some beneficial effects on sperm parameters although they have been unable to give clear explanations about the potential underlying mechanisms. Therefore, the authors of this review concluded that studies have reported contradictory evidence on the role ~~of~~ that dietary compounds play in male infertility and that large, well-designed RCTs are warranted in the future to better establish recommendations.

In spite of the lack of evidence about the role diet plays in sperm parameters and the effectiveness of supplements to combat male infertility, there has been an invasion of integrative dietary products in the last two decades in some assisted reproductive clinics. Unfortunately, the safety of these dietary supplements has not been tested, and the dangers for the user population are unknown.

~~Likewise, several cross-sectional, case-control, retrospective and prospective observational studies, some of which were conducted in large samples of individuals, have assessed the associations between diet and semen quality and/or fecundity, with controversial results.~~

In an attempt to ~~get~~ provide a wide-ranging vision of ~~this~~ the field and extend the conclusions of the aforementioned review, the aim of the present analysis was to systematically review all those observational studies investigating the relationships of diet, food and nutrient consumption with sperm quality and male fecundability.

METHODS

Protocol and registration

The protocol of the present study has been registered (PROSPERO 2016: CRD42016039410) in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO), an international database for the prospective registration of systematic reviews in health and social care.

~~Data sources and literature search~~Information sources

We conducted a systematic search of the literature published in the MEDLINE-Pubmed database (http://www.ncbi.nlm.nih.gov/pubmed) and a hand searched reference list~~s~~, from the earliest available online indexing year until November 2016, in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati *et al.*, 2009).

The search used a combination of terms as both Medical Subject Headings (MeSH) and keywords. The search strategy used male infertility-related keywords and words related with nutrition and diet: fertility OR infertility OR male fertility OR male infertility OR sperm dysfunction OR sperm dysfunctions OR sperm DNA damage OR varicocele OR asthenozoospermia OR oligozoospermia OR oligoasthenozoospermia OR oligoasthenoteratozoospermia OR teratozoospermia AND mediterranean diet OR diet OR nutrients OR food OR nuts OR vitamin C OR vitamin E OR zinc OR antioxidants OR vitamins OR cereals OR meat OR vegetables OR fruit OR fish OR legumes OR milk OR yogurt OR cheese OR seeds OR eggs OR dairy product OR micronutrient OR macronutrient OR alcohol OR alcohol consumption OR selenium OR fatty acids OR sugar. We applied the following inclusion filters: Classical Article, Clinical Study, Comparative Study, Congresses Dataset, English Abstract, Evaluation Studies, Introductory Journal Article, Journal Article, Letter, Meta-Analysis, Multicenter Study, Observational Study, Abstract, Humans, Male, and English.

~~Study selection and eligibility~~Eligibility criteria, search and study selection

The titles and abstracts of all the articles were screened for eligibility by three researchers, ~~for eligibility:~~ who were specialists in male (in)fertility and ~~specialists in~~ nutrition. We ~~have~~ included case-control, cross-sectional, and observational prospective and retrospective studies in which fertile/infertile men were well-defined (men with sperm disorders, sperm DNA damage, varicocele or idiopathic infertility). In addition, the primary outcomes were semen quality (volume, motility, morphology, and sperm count or concentration, sperm DNA damage or chromatin integrity, sperm aneuploidies and hormonal level) or fecundability (fertilization rate, pregnancy rate, or miscarriage rate). We excluded RCT studies, animal studies, review articles, and low quality studies (see the quality assessment section). After the primary screening (evaluation of the scope of the study), and ~~evaluating~~ once quality and compliance with all the inclusion/exclusion criteria ~~and quality assessment~~had been evaluated, the full text of the selected articles was obtained.

Data extraction

We extracted the following information from each study: author/s, year of publication, journal, title of the article, location of the study, cohort name (if appropriate), age, infertility problem, number of patients or participants (sample size), study design, exposure (nutrient, food, food group or dietary pattern), primary outcomes, and major findings or principal conclusion. After the data had been extracted, it was checked by the researchers for discrepancies to minimize the possibility of errors.

Quality assessment

Using all the data extracted, we evaluated and scored the quality of the studies selected on a six-point scale (Hayden *et al.*, 2006). The quality scores were assessed in parallel by the three authors, and discrepancies were re-evaluated together. With this system, we assessed the quality of individual studies using the following criteria (1 point per criterion): 1) study participation (the study sample represents the key characteristics of the population of interest sufficiently well to limit potential bias to the results); 2) study attrition (loss to follow-up is not associated with key characteristics); 3) prognostic factor measurement (the prognostic factor of interest is measured in study participants in such a way that potential bias is limited); 4) confounding measurement and account (the outcome of interest is measured in study participants in such a way that potential bias is limited); 5) outcome measurement (important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest); and 6) analysis (the statistical analysis is appropriate for the design of the study, and limit~~s~~~~ing~~ the potential for invalid results). Studies with a score between 0 and 3 points were considered to be of low quality, while >3 to 6 were considered to be of high quality.

~~Systematic review registration~~

~~The protocol of the present study has been registered (PROSPERO 2016: CRD42016039410) in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO), an international database for the prospective registration of systematic reviews in health and social care.~~

RESULTS

~~Identification and selection of the articles~~

We identified 1,940 articles after a primary search by MEDLINE-Pubmed and four by other sources (**Figure I**). By analyzing the abstracts (n=1,944), we screened and excluded 1,811 for reasons of the scope of the study. A total of 133 articles were collected as full texts ~~for the assessment of~~ so that the inclusion/exclusion criteria and quality could be assessed: 92 articles were excluded because they did not meet the inclusion/exclusion criteria and six articles because they were not given the minimum quality assessment score. After applying all the eligibility parameters, 35 articles were included for qualitative analysis.

Summary of selected studies and design

The articles included subjects from 18 countries: Argentine, Brazil, Canada, Denmark, Estonia, Finland, France, Germany, Greece, Iran, Italy, Lithuania, Netherlands, Norway, Poland, Spain, Sweden, and USA. The age of the participants ranged between 18 and 80 years old. ~~The studies included comprised~~ There were 11 cross-sectional studies (n=21 articles), six case-control studies (n=8 articles), three prospective studies and three retrospective studies.

Primary outcomes of interest

Of the 35 articles included, 31 (n=12,672 participants) evaluated the effect of dietary patterns and food intake on sperm parameters and quality (**Table I A-D**) (Afeiche *et al.*, 2013; Afeiche, Bridges, *et al.*, 2014; Afeiche, Gaskins, *et al.*, 2014; Afeiche, Williams, *et al.*, 2014; Anifandis *et al.*, 2014; Attaman *et al.*, 2012; Braga *et al.*, 2012; Chavarro *et al.*, 2008, 2014; Chiu *et al.*, 2014; Cutillas-Tolin *et al.*, 2015; Eskenazi *et al.*, 2005; Eslamian *et al.*, 2012, 2015, 2016; Gaskins *et al.*, 2012; Goverde *et al.*, 1995; Jensen *et al.*, 2013, 2014; de Jong *et al.*, 2014; Karayiannis *et al.*, 2016; Mendiola *et al.*, 2009, 2010; Mínguez-Alarcón *et al.*, 2012; Schmid *et al.*, 2012; Serra-Majem *et al.*, 2003; Silver *et al.*, 2005; Stutz *et al.*, 2004; Vujkovic *et al.*, 2009; Young *et al.*, 2008; Zareba *et al.*, 2013), and five (n=13,125 participants) on fecundability (**Table II**) (Braga *et al.*, 2012; Curtis *et al.*, 1997; Florack *et al.*, 1994; Olsen *et al.*, 1997; Xia *et al.*, 2015). It should be pointed out that the Braga *et al.,* 2012 study is included in the two primary outcome groups: sperm parameters, and fecundability of ~~their~~ partners.

Sperm parameters

Only one retrospective study was included in this systematic review (**Table I-A**) (Stutz *et al.*, 2004). It found non-significant associations between alcohol consumption and plasma testosterone concentrations or seminal parameters in 34 healthy participants from Argentina.

Case-control studies are shown in **Table I-B** (Eslamian *et al.*, 2012, 2015, 2016; Goverde *et al.*, 1995; de Jong *et al.*, 2014; Mendiola *et al.*, 2009, 2010; Serra-Majem *et al.*, 2003).

Two of them focused on analyzing the relationship between alcohol consumption and semen quality and their conclusions are controversial. Goverde et al. studied 47 cases and 68 controls with poor semen quality attending an infertility clinic, and showed that men who drank alcohol

every day had a lower percentage of normal sperm morphology than men who did not drink alcohol (Goverde *et al.*, 1995). In contrast, de Jong and collaborators did not find an association between alcohol consumption and such sperm parameters as volume, sperm count, motility and morphology in 42 infertile cases with asthenozoospermia and 121 fertile male controls (de Jong *et al.*, 2014).

A large case-control study based on 405 males with poor semen quality and 379 fertile controls investigated the possible association of cyclamate, cyclohexylamine and other artificial sweeteners with male infertility.~~,~~ The conclusion~~ding~~ was that the ingestion of these sweeteners was not related to sperm quality (Serra-Majem *et al.*, 2003).

Several studies have evaluated the relationship between food groups and fertility. One of these is Mendiola *et al.,* who analyzed infertile cases with poor semen quality and fertile controls (30 cases and 31 controls). They showed that, compared to the controls, infertile cases presented a lower consumption of skimmed milk, shellfish, tomatoes~~,~~ and lettuce; and they consumed more yogurt, meat products and potatoes (Mendiola *et al.*, 2009). In another article using the same population the authors also show that infertile cases presented significantly lower intakes of carbohydrates, fiber, folate, vitamin C, and lycopene; and higher intakes of proteins and total fat (Mendiola *et al.*, 2010).

The associations between the consumption of different food groups and the risk of having different idiopathic asthenozoospermia infertility were also evaluated in 72 asthenozoospermic cases and 169 normozoospermic controls from Iran. Individuals with asthenozoospermia were observed to ~~have a lower consumption of~~consume less fruit~~s~~ and vegetables (especially oranges, tomatoes and dark green vegetables), poultry, skimmed milk and sea food than controls. Nonetheless, an increased intake of processed meats, dairy products and sweets was associated with a significantly higher risk of asthenozoospermia (Eslamian *et al.*, 2012).

More recent studies ~~of~~ by the same group, but with 235 normozoospermic controls and 107 asthenozoospermic cases, concluded that a high intake of saturated fatty acids (SFAs), trans-fatty acids (TFAs), and palmitic and stearic fatty acids ~~were~~ was positively related to the odds of having asthenozoospermia. They also found inverse and dose-dependent associations between the intake of omega-3 polyunsaturated fatty acids (PUFAs) and docosahexaenoic acid and the risk of having asthenozoospermia (Eslamian *et al.*, 2015). In another published report, a high intake of vitamin E, vitamin D, vitamin C, zinc, folate, total fiber, selenium and PUFAs was significantly associated with a lower risk of asthenozoospermia (Eslamian *et al.*, 2016).

Table I-C summarizes the cross-sectional studies (Afeiche *et al.*, 2013; Afeiche, Bridges, *et al.*, 2014; Afeiche, Gaskins, *et al.*, 2014; Afeiche, Williams, *et al.*, 2014; Anifandis *et al.*, 2014; Attaman *et al.*, 2012; Chavarro *et al.*, 2008, 2014; Chiu *et al.*, 2014; Cutillas-Tolin *et al.*, 2015; Eskenazi *et al.*, 2005; Gaskins *et al.*, 2012; Jensen *et al.*, 2013, 2014; Karayiannis *et al.*, 2016; Mínguez-Alarcón *et al.*, 2012; Schmid *et al.*, 2012; Silver *et al.*, 2005; Vujkovic *et al.*, 2009; Young *et al.*, 2008; Zareba *et al.*, 2013).

Two studies focused on alcohol consumption and semen quality, the SDF index and serum reproductive hormones (Anifandis *et al.*, 2014; Jensen *et al.*, 2014). While one of these studies, conducted in 8,344 healthy participants, found that a moderate alcohol intake was not adversely associated with semen quality, but was associated with higher levels of serum testosterone (Jensen *et al.*, 2014), the other (n=207 potentially infertile participants) associated total alcohol consumption ~~was associated~~ with lower sperm volume and higher SDF. This same study found that the combination of cigarette and alcohol consumption was associated with higher SDF (Anifandis *et al.*, 2014).

The Age and Genetic Effects in Sperm (AGES) study, conducted in healthy participants, focused on three different factors, which were reported in three different articles: (i) sperm quality (volume, motility, number of spermatozoa and concentration), (ii) sperm chromatin integrity, and, (iii) sperm aneuploidy. A positive relationship was demonstrated between vitamin C intake and total sperm count, concentration, and total progressive motility; vitamin E intake, and progressive motility or total progressively motile sperm count; and β-carotene intake, and sperm concentration and progressive motility. However, folate and zinc intake were not associated with several parameters of semen quality (Eskenazi *et al.*, 2005). Furthermore, a high antioxidant intake was not related to improved sperm chromatin structure and, therefore, ~~with~~ to fertility problems in 87 healthy men (Silver *et al.*, 2005). Finally, compared to those with low intake, men with high folate intake had lower overall frequencies of several types of sperm aneuploidy (for chromosomes X, Y and 21) (Young *et al.*, 2008).

Only one article, conducted in 80 healthy participants, primarily focused on sperm DNA damage. Compared to those in the reference quartile, men in the top quartile of vitamin C intake had less SDF, with similar findings for vitamin E, folate, and zinc (but not β-carotene). Also, older men (>44 years) in the top quartile of vitamin C intake had less SDF than older men in the reference quartile of intake, with similar findings for vitamin E and zinc. However, younger men (<44 years) did not benefit from higher intakes of the micronutrients surveyed (Schmid *et al.*, 2012).

Two articles conducted in the same population (99 male partners of subfertile couples from the Massachusetts General Hospital Fertility Center who presented for semen analyses) focused on the association between soy rich isoflavone food, fat intake, and semen quality parameters. A higher intake of soy foods was associated with lower sperm concentration (Chavarro *et al.*, 2008), and total fat intake was negatively related to total sperm count and sperm concentration (Chavarro *et al.*, 2008). These associations appeared to be driven primarily by intake of saturated fat. Conversely, intake of omega-3 PUFAs was positively related to normal sperm morphology (Attaman *et al.*, 2012).

The association between food consumption and sperm parameters was also studied by the same group of researchers in another sample of partners of couples presenting for semen analyses (n=155). Low-fat dairy intake, particularly low-fat milk, was related to higher sperm concentration and progressive motility, whereas cheese consumption was related to lower

sperm concentrations, but only among past or current smokers (Afeiche, Bridges, *et al.*, 2014). In addition, processed meat consumption was negatively associated with sperm morphology, whereas fish consumption was positively related to total sperm count and morphology (Afeiche, Gaskins, *et al.*, 2014).

Using data from the Rochester Young Men's Study (RYMS), a cross-sectional study conducted in 189 healthy young men ~~carried out during~~in 2009-2010, five articles were published (Afeiche *et al.*, 2013; Afeiche, Williams, *et al.*, 2014; Chiu *et al.*, 2014; Gaskins *et al.*, 2012; Zareba *et al.*, 2013). When participants were categorized by factor analysis, ~~those following a~~the 'Prudent' diet (characterized by a high intake of fish, chicken, fruit, vegetables, legumes and whole grains) was significantly associated with higher progressive sperm motility (but not with sperm concentration and morphology) while the 'Western' diet (characterized by high intake of red and processed meat, refined grains, pizza, snacks, high-energy drinks and sweets) was not ~~the 'Prudent' dietary pattern was significantly associated with higher progressive sperm motility but not with sperm concentration and morphology~~ (Gaskins *et al.*, 2012). As far as dietary antioxidants are concerned, lycopene intake was related to better sperm morphology, whereas a high intake of vitamin C from food sources alone was associated with a lower sperm concentration and sperm count (Zareba *et al.*, 2013). Three articles ~~of~~ from the RYMS analyzed which foods were related to sperm parameters and reproductive hormone levels. The intake of full-fat dairy products was inversely related to sperm motility and morphology, and these associations were driven primarily by the intake of cheese and were independent of overall dietary patterns. However, non-significant associations were reported between dairy food consumption and hormone levels (Afeiche *et al.*, 2013). As far as the consumption of beverages is concerned, men in the highest quartile of sugar-sweetened beverages showed lower sperm motility than those in the reference quartile. However, no association between sugar-sweetened beverages and other semen quality parameters or reproductive hormone levels were described (Chiu *et al.*, 2014). Finally, intake of processed red meat was inversely related to total sperm count and total progressive motile sperm count (Afeiche, Williams, *et al.*, 2014).

In the Murcia Young Men's cross-sectional Study (MYMS) carried out on about 200 healthy Spanish university students (18–23 years old), a positive association was observed between the dietary intake of several antioxidant nutrients (cryptoxanthin, vitamin C, lycopene and β-carotene) and total motile sperm count. Moreover, semen volume increased in those individuals with a high intake of vitamin C, lycopene and β-carotene (Mínguez-Alarcón *et al.*, 2012). Cutillas-Tolín and collaborators show that traditional Mediterranean diets (characterized by high intakes of vegetables, fruits and seafood) may have a positive impact on male reproductive potential because this pattern was positively associated with total sperm count, although a 'Western' pattern was positively related to the percentage of morphologically normal sperm (Cutillas-Tolin *et al.*, 2015). The same authors reported that dietary cholesterol was inversely related to ejaculate volume after adjusting for potential confounders, whereas the intake of TFAs was inversely related to total sperm count (Chavarro *et al.*, 2014).

One of the largest cross-sectional studies examining the association between dietary fat intake and semen quality was conducted in 701 healthy young ~~healthy~~ Danish men. Compared to those in the bottom quartile, men in the top quartile of energy intake as SFAs showed lower sperm concentrations and lower total sperm counts. In the same study, the percentage of normal morphology spermatozoa was lower among men consuming a high percentage of energy from monounsaturated fatty acids (MUFAs), whereas semen volume was higher among men with a high intake of n-3 fatty acids (Jensen *et al.*, 2013).

~~Vujkovic *et al.*,~~ iIn the FOod, Lifestyle and Fertility Outcome study (FOLFO-study) conducted in 161 healthy Dutch men, Vujkovic *et al.* ~~conducted in 161 healthy Dutch men~~ compared two dietary patterns. When participants were categorized by factor analysis, ~~those following a~~the 'Health Conscious' diet (high intakes of fruits, vegetables, fish and whole grains) was significantly associated with less SDF ~~or a~~but the 'Traditional Dutch' diet (high intakes of meat, potatoes and whole grains and low intakes of beverages and sweets), ~~the 'Health Conscious' dietary pattern was significantly associated with less SDF but also, the 'Traditional Dutch' diet~~ was positively correlated with sperm concentration. (Vujkovic *et al.*, 2009).

Recently, adherence to the Mediterranean diet was positively associated with higher sperm concentration, total sperm count and sperm motility in a cross-sectional study in 225 men (26-55 years old) from couples attending a fertility clinic (Karayiannis *et al.*, 2016).

In the only prospective study conducted to date (**Table I-D**), 250 male participants whose partners had undergone intracytoplasmic sperm injection (ICSI) cycles were analyzed. In this study, the sperm concentration was negatively associated with the frequency of cereal consumption and the number of meals per day. In addition, sperm motility was negatively associated with alcohol and coffee consumption, and positively associated with the consumption of cereals and fruits (Braga *et al.*, 2012).

The quality scores of the articles related to the sperm parameters included in this review are modest (case-control studies, mean=5.06/6, cross-sectional studies, mean=5.27/6 and prospective and retrospective studies=4.5/6).

Fecundability

Table II shows retrospective and prospective studies analyzing the association between male food consumption and fecundability. The two retrospective studies included in this review (Curtis *et al.*, 1997; Olsen *et al.*, 1997) (**Table II**) are both large and focus on the frequency of alcohol consumption. In the study by Curtis *et al.* of 2,607 healthy partners of farmers (2,593 men), individuals who were heavy tea drinkers (regardless of caffeine content) had decreased fecundability. However no association was reported between alcohol consumption and fecundability (Curtis *et al.*, 1997). The largest multicentric study conducted by Olsen et al., in 6,630 theoretically healthy couples (6,279 men) from the general population and 4,035 couples (3,603 men) from a pregnancy register population, non-significant associations were detected between alcohol consumption and fecundability (Olsen *et al.*, 1997).

The three prospective studies (Braga *et al.*, 2012; Florack *et al.*, 1994; Xia *et al.*, 2015) (**Table II**) are small studies that analyze between 141 and 259 male partners of women attending an infertility clinic. Florack *et al.* show that male partners with a consumption of ≥10 alcoholic drinks/week had a higher probability of fecundity, whereas heavy consumers of caffeine (≥ 7 cups/day) had a lower probability (Florack *et al.*, 1994). The other two prospective studies aimed to assess the influence on fecundability of food consumption by men (250 and 141 male partners whose couples had undergone ART cycles, respectively). In the Braga et al. study, alcohol consumption had a negative influence on the fertilization rate, whereas the consumption of red meat had a negative impact on the implantation rate and on the chance of pregnancy (Braga *et al.*, 2012). In Xia's study, poultry intake was positively associated with fertilization rates, whereas processed meat intake was negatively associated with fertilization rates among couples undergoing conventional *in-vitro* fertilization (IVF) (Xia *et al.*, 2015).

The quality scores of the articles related to the fecundability studies included in this review are also modest (mean=4.7/6).

DISCUSSION

The present review of epidemiological-observational studies provides the most comprehensive analysis to date of the associations between diet or nutrient intake and the risk of infertility. It suggests that diet modifications may be useful in modulating male fertility and fecundability.

As far as sperm quality is concerned, the results of this systematic review indicated that healthy diets (i.e. the Mediterranean diet) rich in such nutrients as omega-3 fatty acids, some antioxidants and vitamins, and low in SFAs and TFAs are inversely associated with low semen quality parameters. In terms of food groups, fish, shellfish and seafood, poultry, cereals, vegetables and fruits, and low-fat dairy products have been positively related to sperm quality. However, diets rich in processed meat, soy foods, potatoes, full-fat dairy products, coffee, alcohol, and sugar-sweetened beverages and sweets have been inversely associated with the quality of semen in some studies (**Figure II**).

The few studies relating male nutrient or food intake and fecundability also suggest that diets rich in red meat, processed meat, tea and caffeine are associated with a lower rate of fecundability. This association is only controversial in the case of alcohol (**Figure III**).

The potential biological mechanisms linking diet with sperm function and fertility are largely unknown and require further study ~~in the future~~. Below we show some of the mechanisms deserving attention in relation to the consumption of some foods.

Fruits, vegetables and cereals

Fruits and vegetables are rich in water, antioxidant vitamins (especially vitamin C, vitamin A, β-carotene and polyphenols, but also other phytochemicals), some minerals with antioxidant properties (potassium and magnesium), folate and fiber.

There is a direct association between antioxidant status and the production of reactive oxygen species (ROS) in spermatozoa (Ross *et al.*, 2010). In addition, high concentrations of ROS negatively affect sperm DNA and, consequently, sperm motility, vitality and concentration, but also miscarriage and developmental abnormalities in the offspring (Aitken, 2016; Aitken *et al.*, 2016; Saleh *et al.*, 2003; Tremellen, 2008). Antioxidants are considered to be “scavengers” of ROS and their use has been studied as a treatment to reverse the adverse impact of high ROS concentrations on semen parameters (Ross *et al.*, 2010). In fact most of the clinical trials conducted in humans have demonstrated, with relatively little scientific evidence, some possible benefits of several types of antioxidants on sperm quality (Ghanem *et al.*, 2010; Scott *et al.*, 1998). Antioxidants have also shown some promise in treating idiopathic oxidative stress in spermatozoa (Gharagozloo and Aitken, 2011; Showell *et al.*, 2014). However, these results should be replicated in the future before solid recommendations can be made.

As has been reported, men with a high folate intake had lower frequencies of several types of sperm aneuploidy (Young *et al.*, 2008), which suggests that this vitamin could be important in spermatogenesis. Folate, which is mainly present in green leafy vegetables, is essential for

DNA maintenance, transfer RNA and protein synthesis (Molloy, 2012). Because DNA synthesis is an essential part of spermatogenesis, folate is probably important to the process. In fact, in an RCT, the total normal sperm count increased after combined sulfate and folic acid treatment in both subfertile and fertile men (Wong *et al.*, 2002).

In addition, fruits, vegetables, legumes and whole cereals are the principal sources of fiber. Some studies have demonstrated that fiber consumption reduced plasma estrogen levels by binding directly to unconjugated estrogens (Goldin *et al.*, 1982), and low plasma estrogen levels in males are essential for normal fertility (Amarnath *et al.*, 2016).

Soy foods

The principal hypothesis for the negative effect of soy foods on male fertility was the phytoestrogen concentration. Phytoestrogens have shown deleterious effects on the male endocrine system (Santti *et al.*, 1998) with potential effects on fertility. Nevertheless, the question of whether phytoestrogens are beneficial or harmful to human health remains unresolved. Animal studies have suggested that exposure to phytoestrogens in the developmental period is not advisable because they may disrupt the endocrine system (McMichael-Phillips *et al.*, 1998). However, the only RCT study testing the effect of consuming soy foods in humans has demonstrated no effect on serum gonadotropin and sex hormone levels, or on semen quality (Mitchell *et al.*, 2001).

Potatoes

Potatoes primarily contain starches with a high glycemic index and glycemic load properties (Atkinson *et al.*, 2008). A high glycemic and insulinemic response to food has been associated with oxidative stress (Hu *et al.*, 2006) which, as mentioned above, has an important effect on semen quality (Ross *et al.*, 2010). In addition, a diet with a high glycemic index and high glycemic load has been associated with an increased risk of inflammation (Kristo *et al.*, 2013) and type 2 diabetes (Muraki *et al.*, 2016). In fact, the frequency of potato consumption has recently been positively related to an increased risk of diabetes development (Dong *et al.*, 2011), and this ~~have~~ has a detrimental effect on semen parameters (Ding *et al.*, 2015). Because glucose metabolism is important to spermatogenesis, an excess of potatoes and other high starch glycemic food can have detrimental effects on sperm parameters through their effect on the glucose metabolism. Indeed, hyperglycemia has been shown to affect sperm motility and fertilization in mature sperm (Miki, 2007).

Fish, shellfish and seafood

The possible benefits of fish, seafood and shellfish on sperm parameters ~~would~~ may be the result of their high omega-3 PUFA content. Ecosapentanoic acid (EPA) and docosahexaenoic acid (DHA) are essential fatty acids that play an important role in the anti-inflammatory and antioxidant properties of such enzymes as superoxide dismutase. A significant positive correlation has been reported between DHA sperm concentrations and sperm motility (Gulaya *et al.*, 2001). Because seminal plasma is recognized as one of the most powerful antioxidant

fluids, it is not surprising that any defects it may have are often associated with oxidative stress through and increment of in ROS, followeding by a SDF, , yielding which leads to male infertility (Wathes *et al.*, 2007). In fact, the only RCT conducted in infertile men with idiopathic oligoasthenoteratozoospermia, and lower levels of EPA and DHA in spermatozoa has demonstrated that omega-3 PUFA supplementation has beneficial effects on some semen quality parameters (Safarinejad, 2011).

Therefore, it is plausible that increased fish intake or fish oil supplementation may result in improved parameters of semen quality.

Dairy products

The possible effect of dairy foods on male fertility is highly controversial. In short, full-fat dairy and total dairy products and cheese have been negatively associated with sperm quality parameters. Total low-fat dairy and skimmed milk, however, have been related to better classical semen indices (Afeiche *et al.*, 2013; Afeiche, Bridges, *et al.*, 2014). Commercial milk is a mixture of milk from cows in different stages of pregnancy and non-pregnant cows, with approximately 75% coming from pregnant cows (Ganmaa *et al.*, 2001, 2004). Naturally occurring estrogens of placental origin are present in the milk of pregnant cows. As mentioned above, estrogens, derived from dairy (or other food sources), could contribute to a decrease in sperm production (Afeiche *et al.*, 2013; Amarnath *et al.*, 2016). In theory all dairy products should have the same effect, although in this case low-fat dairy products do not. On the other hand, low-fat and skimmed milk consumption is associated with higher circulating levels of insulin-like growth factor 1 (IGF-1) and insulin (Afeiche, Bridges, *et al.*, 2014). Results from animal studies also indicate that insulin has the potential to increase sperm motility and concentration in rats (Huang *et al.*, 2016), and also to rescue spermatogenesis in type 1 diabetic mice (Schoeller, Albanna, *et al.*, 2012). The consumption of these types of milk has also been associated with higher peripheral concentrations of IGF-1 in free living populations and increases in IGF-1 levels in feeding trials (Bonjour *et al.*, 2012; Hoppe *et al.*, 2005). Given that spermatogenesis is a process of active cell division requiring insulin, and that IGF-1 can bind and activate Leydig cell insulin receptors regulating Sertoli cell proliferation, the relations observed between low-fat dairy products and higher sperm concentration and motility may represent a biological effect in humans (Afeiche, Bridges, *et al.*, 2014). In this case, the IGF-1 levels may have a more important role than hormone homeostasis in humans.

Meat and processed meat

Meat and processed meat are rich in protein, but also in xenobiotics, mainly xenoestrogens (XEs) and in some cases anabolic steroids (Swan *et al.*, 2007). The use of these compounds in the food industry increases the total level of XEs and sex steroids in processed foods, such as meat, the intake of which contributes significantly to daily exposures. XEs are highly lipophilic substances that can accumulate in fat-rich foods like meat, which have estrogenic effects and are suspected to be partially responsible for the decline in semen quality. In an RCT, synthetic estrogens such as polychlorinated biphenyls and phthalate esters (widely used industrial

compounds) showed ~~potential hazards related to the~~ deleterious ~~terioration of~~ effects of some semen parameters in infertile men with unknown etiology (Rozati *et al.*, 2002).

Meat, full-fat dairy products and butter are the principal sources of SFAs. Although improvements in sperm parameters are a response to PUFA omega-3 sources, in human spermatozoa, elevated SFA concentrations and low omega-3 PUFA levels ~~were~~ are related to decreased fertility parameters (Esmaeili *et al.*, 2015). In animal studies, some dietary saturated fatty acids ~~did~~ do not affect sperm quality parameters (Blesbois *et al.*, 1997; Esmaeili *et al.*, 2014; Fair *et al.*, 2014; Samadian *et al.*, 2010). However, several studies in humans ~~showed~~ have shown ~~that~~ higher levels of palmitic acid or stearic acid in spermatozoa ~~were higher~~ in infertile men (Aksoy *et al.*, 2006; Zalata *et al.*, 1998).

Meat and dairy products are also the principal source of natural TFAs. However, in our diet, TFAs mainly come from processed foods such as bakery products, fast foods and snacks, which are made with shortening, margarine or oils that contain partially hydrogenated oils and fats. In rodents, a high intake of TFAs leads to a number of adverse male reproductive outcomes including decreased serum testosterone levels~~,~~ and, in extreme cases, arrest of spermatogenesis and testicular degeneration with ~~a~~ consequences such as low sperm count or motility (Hanis *et al.*, 1989; Veaute *et al.*, 2007). However, studies need to be made on the effect of TFA intake on humans.

Coffee, tea and alcohol

In the present review, adult caffeine intake did not show a clear association with semen quality, but high caffeine intake was associated with higher plasma levels of testosterone (Ramlau-Hansen *et al.*, 2008). Several studies have found a positive association between the consumption of caffeine (from coffee, tea or caffeinated beverages) and subfecundity in women (Hassan and Killick, 2004; Jensen *et al.*, 1998). In males, the principal hypothesis is that elevated testosterone levels could disrupt the endocrine system and have a detrimental effect on sperm production (Diamanti-Kandarakis *et al.*, 2009).

~~**Alcohol**~~

Some epidemiological studies have examined the relationship between alcohol consumption and reproductive function. Most of them ~~have been~~were conducted in small selected populations of infertile men with contradictory results (Vignera *et al.*, 2013). A recent review of 15 cross-sectional studies has shown a detrimental effect of alcohol consumption on semen volume and morphology, mainly in daily, not occasional, consumers. This suggests that a moderate consumption of alcohol should not adversely affect semen quality parameters (Ricci *et al.*, 2016). A positive association between excess alcohol intake and some semen quality parameters has also been observed in some, but not all, cross-sectional and case-control studies. However, in relation to sperm parameters, the only prospective study included in our review that assesses alcohol has reported an inverse association between alcohol consumption

and sperm concentration and motility. In relation to fecundability, prospective studies show contradictory results.

Alcohol has been experimentally shown to have a deleterious effect at all levels of the male reproductive system. It interferes with the regulation of the hypothalamic-pituitary-testicular axis, impairing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion, decreasing testosterone levels, and disrupting endocrine homeostasis (Maneesh *et al.*, 2006; Muthusami and Chinnaswamy, 2005). Likewise, the ratio between free estradiol and free testosterone has been modified by alcohol intake (Hansen *et al.*, 2012) and spermatogenetic arrest, and the Sertoli-cell-only syndrome has been found to be more frequently associated with high alcohol consumption (Pajarinen and Karhunen, 1994).

~~Curiously, alcohol consumption was associated with a deterioration in sperm parameters which may be partially reversible when alcohol consumption is discontinued (Vignera et al., 2013).~~

Sweets and sugar-sweetened beverages

Numerous studies have shown that sugar-sweetened beverages are associated with weight gain and incidence of obesity (Ebbeling *et al.*, 2012; Forshee *et al.*, 2008; Khan and Sievenpiper, 2016; Malik *et al.*, 2013; Te Morenga *et al.*, 2013; de Ruyter *et al.*, 2012), metabolic syndrome (Ferreira-Pêgo *et al.*, 2016; Malik *et al.*, 2010), and type 2 diabetes (Greenwood *et al.*, 2014; Imamura *et al.*, 2015; Wang *et al.*, 2015). All of these disorders can increase insulin resistance (Stanhope *et al.*, 2009) which could negatively influence semen quality via increased oxidative stress (Park *et al.*, 2009). In addition, sperm cells contain receptors for glucose which are required for sperm motility and post ejaculation maturation, both necessary for successful conception (Williams and Ford, 2001). Moreover, glucose and insulin can also disrupt the hypothalamic-pituitary-testicular axis and, therefore, sperm production (Schoeller, Albanna, *et al.*, 2012; Schoeller, Schon, *et al.*, 2012). Alternatively, sweets and sugar-sweetened beverages contain many contaminants (for example, bisphenol A and phthalates) that have leached from plastic containers and which may have a negative influence on sperm quality (Jurewicz *et al.*, 2013). The ~~existing~~ literature on this topic in humans is scarce. However, a recent study in rodents found that sugary drinks negatively impact male fertility (Ruff *et al.*, 2013).

Limitations and strengths

Several limitations of our study should be acknowledged. Although broad search terms were used, and reference lists were hand searched, we may not have identified all publications. In addition, our search strategy was limited to MEDLINE-Pubmed database, and not EMBASE or other databases. However, the main scientific journals are indexed in MEDLINE-Pubmed database. Misclassification of the studies, publication bias and quality score attrition should also be acknowledged as ~~a~~ potential limitations and, to avoid this, three authors independently reviewed all the qualitative studies included. However, the major limitation of the study is that the review was based on epidemiological observational design studies, which limits the ability to

636 determine causality between food and nutrient intake, and parameters of semen quality and
637 fecundability.

638 Moreover, some intrinsic limitations of the studies included in this review should be mentioned.
639 First, populations were heterogeneous between the studies. For instance, the subfertile
640 populations have different phenotypes (asthenozoospermic participants or individuals with poor
641 semen quality). In addition, the control populations were diverse and were taken from different
642 environments (general population, university students, farmers, etc.) which can potentially
643 influence the findings. Second, other potential confounders such as health status, weight, age,
644 medication use, energy intake, physical activity and abstinence time may influence the reported
645 associations. Some of these factors were considered as confounders in some studies, but not
646 all.

647 Notwithstanding these limitations, this review is the most up to date and exhaustive review of
648 observational studies carried out with a quality validated protocol, a tailored checklist and
649 methodologically rigorous quality control points. Future studies are needed to confirm our
650 conclusions.
651

CONCLUSIONS

The present systematic review of observational studies provides the most comprehensive analysis to date of the associations between diet or nutrient intake and the risk of infertility. It suggests that male adherence to a healthy diet can improve semen quality and fecundability rates. Since observational studies can prove associations but not demonstrate causation, the associations summarized in the present review need to be confirmed with large prospective cohort studies of high quality, and especially with well-designed RCTs.

AUTHOR'S ROLES

A.S-H.: Designed the review, collected and selected the data, assessed the articles and wrote the manuscript. M.B.: Assessed the articles, and critically reviewed the article for important intellectual content. J.S-S.: Initiated the idea of the review, designed the review, assessed the articles, contributed to the drafting and critically reviewed the article for important intellectual content. The authors approved the final manuscript.

ACKNOWLEDGEMENTS

CIBERobn is an initiative of the Instituto de Salud Carlos III.

FUNDING

There was no external source of funding for this work.

DECLARATION OF INTEREST

The authors report no financial or commercial conflicts of interest.

REFERENCES

Abbasi A, Prasad A, Rabbani P. Experimental zinc deficiency in man: effect on spermatogenesis. *Trans Assoc Am Physicians* 1979;**92**:292–302.

Afeiche M, Bridges N, Williams P, Gaskins A, Tanrikut C, Petrozza J, Hauser R, Chavarro J. Dairy intake and semen quality among men attending a fertility clinic. *Fertil Steril* 2014;**101**:1280–1287.

Afeiche M, Gaskins A, Williams P, Toth T, Wright D, Tanrikut C, Hauser R, Chavarro J. Processed Meat Intake Is Unfavorably and Fish Intake Favorably Associated with Semen Quality Indicators among Men Attending. *J Nutr* 2014;**144**:1091–1098.

Afeiche M, Williams PL, Mendiola J, Gaskins A, Jørgensen N, Swan SH, Chavarro JE. Dairy food intake in relation to semen quality and reproductive hormone levels among physically active young men. *Hum Reprod* 2013;**28**:2265–75.

Afeiche MC, Williams PL, Gaskins AJ, Mendiola J, Jørgensen N, Swan SH, Chavarro JE. Meat intake and reproductive parameters among young men. *Epidemiology* 2014;**25**:323–30.

Aitken RJ. Oxidative stress and the etiology of male infertility. *J Assist Reprod Genet* 2016:1–2.

Aitken RJ, Gibb Z, Baker MA, Drevet J, Gharagozloo P. Causes and consequences of oxidative stress in spermatozoa. *Reprod Fertil Dev* 2016;**28**:1–10.

Aksoy Y, Aksoy H, Altinkaynak K, Aydin HR, Ozkan A. Sperm fatty acid composition in subfertile men. *Prostaglandins, Leukot Essent Fat Acids* 2006;**75**:75–9.

Amarnath R, Jesse NM, Jacob R. The role of estrogen modulators in male hypogonadism and infertility. *Rev Urol* 2016;**18**:66–72.

Anderson JE, Farr SL, Jamieson DJ, Warner L, Macaluso M. Infertility services reported by men in the United States: national survey data. *Fertil Steril* 2009;**91**:2466–70.

Anifandis G, Bounartzi T, Messini CI, Dafopoulos K, Sotiriou S, Messinis IE. The impact of cigarette smoking and alcohol consumption on sperm parameters and sperm DNA fragmentation (SDF) measured by Halosperm. *Arch Gynecol Obstet* 2014;**290**:777–782.

Atkinson F, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* 2008;**31**:2281–2283.

Attaman JA, Toth TL, Furtado J, Campos H, Hauser R, Chavarro JE. Dietary fat and semen quality among men attending a fertility clinic. *Hum Reprod* 2012;**27**:1466–1474.

Blesbois E, Lessire M, Grasseau I, Hallouis JM, Hermier D. Effect of dietary fat on the fatty acid composition and fertilizing ability of fowl semen. *Biol Reprod* 1997;**56**:1216–20.

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* 2007;**22**:1506–1512.

Bonjour J-P, Benoit V, Rousseau B, Souberbielle J-C. Consumption of vitamin D-and calcium-fortified soft white cheese lowers the biochemical marker of bone resorption TRAP 5b in postmenopausal women at moderate risk of osteoporosis fracture. *J Nutr* 2012;**142**:698–703.

Braga DPDAF, Halpern G, Figueira RDCS, Setti AS, Iaconelli A, Borges E, Figueira S, Sc M, Braga DPDAF, Halpern G, *et al.* Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. *Fertil Steril* 2012;**97**:53–59.

Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. *Br Med J* 1992;**305**:609–613.

Chavarro JE, Toth TL, Sadio SM, Hauser R. Soy food and isoflavone intake in relation to semen quality parameters among men from an infertility clinic. *Hum Reprod* 2008;**23**:2584–2590.

Chavarro JJE, Mínguez-Alarcón L, Mendiola J, Cutillas-Tolín A, López-Espín JJ, Torres-Cantero AAM. Trans fatty acid intake is inversely related to total sperm count in young healthy men. *Hum Reprod* 2014;**29**:429–40.

Chiu YH, Afeiche MC, Gaskins AJ, Williams PL, Mendiola J, Jorgensen N, Swan SH, Chavarro JE. Sugar-sweetened beverage intake in relation to semen quality and reproductive hormone levels in young men. *Hum Reprod* 2014;**29**:1575–1584.

Collins GG, Rossi B V. The impact of lifestyle modifications, diet, and vitamin supplementation on natural fertility. *Fertil Res Pract* 2015;**1**:11.

Curtis KM, Savitz D a, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. *Am J Epidemiol* 1997;**146**:32–41.

Cutillas-Tolin A, Minguez-Alarcon L, Mendiola J, Lopez-Espin JJ, Jorgensen N, Navarrete-Munoz EM, Torres-Cantero AM, Chavarro JE. Mediterranean and western dietary patterns

735 are related to markers of testicular function among healthy men. *Hum Reprod*
736 2015;**30**:2945–2955.
737 Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller
738 RT, Gore AC. Endocrine-disrupting chemicals: an Endocrine Society Scientific Statement.
739 *Endocr Rev* 2009;**30**:293–342.
740 Ding G-L, Liu Y, Liu M-E, Pan J-X, Guo M-X, Sheng J-Z, Huang H-F. The effects of diabetes on
741 male fertility and epigenetic regulation during spermatogenesis. *Asian J Androl* 2015:948–
742 953.
743 Dong J-Y, Zhang L, Zhang Y-H, Qin L-Q. Dietary glycaemic index and glycaemic load in relation
744 to the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Br J Nutr*
745 2011;**106**:1649–1654.
746 Ebbeling C, Feldmen H, Chomitz V, Antonelli T, Gortmaker S, Osganian S, Ludwig D. A
747 randomized trial of sugar-sweetened beverages and adolescent body weight. *N Engl J*
748 *Med* 2012;**367**:1407–1416.
749 Eskenazi B, Kidd SA, Marks AR, Sloter E, Block G, Wyrobek AJ. Antioxidant intake is
750 associated with semen quality in healthy men. *Hum Reprod* 2005;**20**:1006–1012.
751 Eslamian G, Amirjannati N, B R, Sadeghi M, Hekmatdoost A. Nutrient patterns and
752 asthenozoospermia: a case – control study. *Andrologia* 2016:In Press.
753 Eslamian G, Amirjannati N, Rashidkhani B, Sadeghi M-RR, Hekmatdoost A. Intake of food
754 groups and idiopathic asthenozoospermia: A case-control study. *Hum Reprod*
755 2012;**27**:3328–3336.
756 Eslamian G, Amirjannati N, Rashidkhani B, Sadeghi MR, Baghestani AR, Hekmatdoost A.
757 Dietary fatty acid intakes and asthenozoospermia: A case-control study. *Fertil Steril*
758 2015;**103**:190–198.
759 Esmaeili V, Shahverdi a H, Moghadasian MH, Alizadeh a R. Dietary fatty acids affect semen
760 quality: a review. *Andrology* 2015;**3**:450–461.
761 Esmaeili V, Shahverdi AH, Alizadeh AR, Alipour H, Chehrazi M. Saturated, omega-6 and
762 omega-3 dietary fatty acid effects on the characteristics of fresh, frozen-thawed semen
763 and blood parameters in rams. *Andrologia* 2014;**46**:42–49.
764 Evers JLH. Female subfertility. *Lancet* 2002;**360**:151–9.
765 Fair S, Doyle D, Diskin M, Hennessy A, Kenny D. The effect of dietary n-3 polyunsaturated fatty
766 acids supplementation of rams on semen quality and subsequent quality of liquid stored
767 semen. *Theriogenology* 2014;**81**:210–9.
768 Ferreira-Pêgo C, Babio N, Bes-Rastrollo M, Corella D, Estruch R, Ros E, Fitó M, Serra-Majem
769 L, Arós F, Fiol M, *et al.* Frequent consumption of sugar-and artificially sweetened
770 severages and natural and bottled fruit juices is associated with an increased risk of
771 metabolic syndrome in a Mediterranean population at high cardiovascular disease risk. *J*
772 *Nutr* 2016;**146**:1528–1536.
773 Florack EI, Zielhuis GA, Rolland R. Cigarette smoking, alcohol consumption, and caffeine intake
774 and fecundability. *Prev Med (Baltim)* 1994;**23**:175–180.
775 Forshee RA, Anderson PA, Storey ML. Sugar-sweetened beverages and body mass index in
776 children and adolescents: A meta-analysis. *Am J Clin Nutr* 2008;**87**:1662–1671.
777 Ganmaa D, Qin L, Wang P. A two-generation reproduction study to assess the effects of cows ’
778 milk on reproductive development in male and. *Fertil Steril* 2004;**82**:1106–1114.
779 Ganmaa D, Wang PY, Qin LQ, Hoshi K, Sato A. Is milk responsible for male reproductive
780 disorders? *Med Hypotheses* 2001;**57**:510–514.
781 Gaskins AJ, Colaci DS, Mendiola J, Swan SH, Chavarro JE. Dietary patterns and semen quality
782 in young men. *Hum Reprod* 2012;**27**:2899–2907.
783 Ghanem H, Shaeer O, El-Segini A. Combination clomiphene citrate and antioxidant therapy for
784 idiopathic male infertility: A randomized controlled trial. *Fertil Steril* 2010;**93**:2232–2235.
785 Gharagozloo P, Aitken RJ. The role of sperm oxidative stress in male infertility and the
786 significance of oral antioxidant therapy. *Hum Reprod* 2011;**26**:1628–1640.
787 Giahi L, Mohammadmoradi S, Javidan A, Sadeghi MR. Nutritional modifications in male
788 infertility: A systematic review covering 2 decades. *Nutr Rev* 2016;**74**:118–130.
789 Goldin B, Adlercreutz H, Gorbach S, Warram J, Dwyer J, Swenson L, Woods M. Estrogen
790 excretion patterns and plasma levels in vegetarian and omnivorous women. *N Engl J Med*
791 1982;**307**:1542–1547.
792 Goverde HJ, Dekker HS, Janssen HJ, Bastiaans B a, Rolland R, Zielhuis G a. Semen quality
793 and frequency of smoking and alcohol consumption--an explorative study. *Int J Fertil*
794 *Menopausal Stud* 1995;**40**:135–138.

795 Greenwood DC, Threapleton DE, Evans CEL, Cleghorn CL, Nykjaer C, Woodhead C, Burley
796 VJ. Association between sugar-sweetened and artificially sweetened soft drinks and type 2
797 diabetes: systematic review and dose-response meta-analysis of prospective studies. *Br J*
798 *Nutr* 2014;**112**:725–34.
799 Gulaya NM, Margitich VM, Govseeva NM, Klimashevsky VM, Gorpynchenko II, Boyko MI.
800 Phospholipid composition of human sperm and seminal plasma in relation to sperm
801 fertility. *Arch Androl* 2001;**46**:169–175.
802 Hanis T, Zidek V, Sachova J, Klir P, Deyl Z. Effects of dietary trans-fatty acids on reproductive
803 performance of Wistar rats. *Br J Nutr* 1989;**61**:519–529.
804 Hansen ML, Thulstrup AM, Bonde JP, Olsen J, Håkonsen LB, Ramlau-Hansen CH. Does last
805 week's alcohol intake affect semen quality or reproductive hormones? A cross-sectional
806 study among healthy young Danish men. *Reprod Toxicol* 2012;**34**:457–462.
807 Hassan MAM, Killick SR. Negative lifestyle is associated with a significant reduction in
808 fecundity. *Fertil Steril* 2004;**81**:384–392.
809 Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic
810 reviews. *Ann Intern Med* 2006;**144**:427–437.
811 Hoppe C, Molgaard C, Vaag A, Barkholt V, Michaelsen KF. High intakes of milk, but not meat,
812 increase serum IGF-1 and IGFBP-3 in 8-year-old boys. *Eur J Clin Nutr* 2005;**59**:393–398.
813 Hu Y, Block G, Norkus EP, Morrow JD, Dietrich M, Hudes M. Relations of glycemic index and
814 glycemic load with plasma oxidative. *Am J Clin Nutr* 2006;**84**:70–76.
815 Huang P, Zhou Z, Shi F, Shao G, Wang R, Wang J, Wang K, Ding W. Effects of the IGF-
816 1/PTEN/Akt/FoxO signaling pathway on male reproduction in rats subjected to water
817 immersion and restraint stress. *Mol Med Rep* 2016:5116–5124.
818 Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG.
819 Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit
820 juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of
821 population attributable fraction. *BMJ* 2015;**351**:h3576.
822 Jensen TK, Heitmann BL, Jensen MB, Halldorsson TI, Andersson AM, Skakkebæk NE,
823 Joensen UN, Lauritsen MP, Christiansen P, Dalgard C, *et al.* High dietary intake of
824 saturated fat is associated with reduced semen quality among 701 young Danish men
825 from the general population. *Am J Clin Nutr* 2013;**97**:411–418.
826 Jensen TK, Henriksen TB, Hjollund NHI, Scheike T, Kolstad H, Giwercman A, Ernst E, Bonde
827 JP, Skakkebæk NE, Olsen J. Caffeine intake and fecundability: A follow-up study among
828 430 Danish couples planning their first pregnancy. *Reprod Toxicol* 1998;**12**:289–295.
829 Jensen TK, Swan S, Jorgensen N, Toppari J, Redmon B, Punab M, Drobnis EZ, Haugen TB,
830 Zilaitiene B, Sparks AE, *et al.* Alcohol and male reproductive health: A cross-sectional
831 study of 8344 healthy men from Europe and the USA. *Hum Reprod* 2014;**29**:1801–1809.
832 de Jong AME, Menkveld R, Lens JW, Nienhuis SE, Rhemrev JPT. Effect of alcohol intake and
833 cigarette smoking on sperm parameters and pregnancy. *Andrologia* 2014;**46**:112–117.
834 Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G, Krausz C. European
835 association of urology guidelines on male infertility: The 2012 update. *Eur Urol*
836 2012;**62**:324–332.
837 Jurewicz J, Radwan M, Sobala W, Ligocka D, Radwan P, Bochenek M, Hawuła W, Jakubowski
838 L, Hanke W. Human urinary phthalate metabolites level and main semen parameters,
839 sperm chromatin structure, sperm aneuploidy and reproductive hormones. *Reprod Toxicol*
840 2013;**42**:232–241.
841 Karayiannis D, Kontogianni MD, Mendorou C, Douka L, Mastrominas M, Yiannakouris N.
842 Association between adherence to the Mediterranean diet and semen quality parameters
843 in male partners of couples attempting fertility. *Hum Reprod* 2016:In Press.
844 Khan TA, Sievenpiper JL. Controversies about sugars: results from systematic reviews and
845 meta-analyses on obesity, cardiometabolic disease and diabetes. *Eur J Nutr* 2016.
846 Kristo AS, Matthan NR, Lichtenstein AH. Effect of diets differing in glycemic index and glycemic
847 load on cardiovascular risk factors: Review of randomized controlled-feeding trials.
848 *Nutrients* 2013;**5**:1071–1080.
849 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Goetzsche PC, Ioannidis JP, Clarke M, Devereaux
850 P, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and
851 meta-analyses of studies that evaluate health care interventions: explanation and
852 elaboration. *J Clin Epidemiol* 2009;**62**:e1-34.
853 Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children
854 and adults: a systematic review and meta-analysis. *Am Jounral Clin Nutr* 2013;**98**:1084–

855 102.
856 Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages
857 and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*
858 2010;**33**:2477–81.
859 Maneesh M, Dutta S, Chakrabarti A. Alcohol abuse-duration dependent decrease in plasma
860 testosterone and antioxidants in males. *Indian J Physiol Pharmacol* 2006;**50**:291–296.
861 McMichael-Phillips DF, Harding C, Morton M, Roberts SA, Howell A, Potten CS, Bundred NJ.
862 Effects of soy-protein supplementation on epithelial proliferation in the histologically
863 normal human breast. *Am J Clin Nutr* 1998;**68**:1431S–1435S.
864 Mendiola J, Jørgensen N, Mínguez-Alarcón L, Sarabia-Cos L, López-Espín JJ, Vivero-Salmerón
865 G, Ruiz-Ruiz KJ, Fernández MF, Olea N, Swan SH, *et al.* Sperm counts may have
866 declined in young university students in Southern Spain. *Andrology* 2013;**1**:408–413.
867 Mendiola J, Torres-Cantero AM, Moreno-Grau JM, Ten J, Roca M, Moreno-Grau S, Bernabeu
868 R. Food intake and its relationship with semen quality: a case-control study. *Fertil Steril*
869 2009;**91**:812–818.
870 Mendiola J, Torres-Cantero AM, Vioque J, Moreno-Grau JM, Ten J, Roca M, Moreno-Grau S,
871 Bernabeu R, Ph D. A low intake of antioxidant nutrients is associated with poor semen
872 quality in patients attending fertility clinics. *Fertil Steril* 2010;**93**:1128–1133.
873 Merzenich H, Zeeb H, Blettner M. Decreasing sperm quality: a global problem? *BMC Public*
874 *Health* 2010;**10**:1–5.
875 Miki K. Energy metabolism and sperm function. *Soc Reprod Fertil Suppl* 2007;**65**:309–325.
876 Mínguez-Alarcón L, Mendiola J, López-Espín J, Sarabia-Cos L, Vivero-Salmerón G, Vioque J,
877 Navarrete-Muñoz E, Torres-Cantero A. Dietary intake of antioxidant nutrients is associated
878 with semen quality in young university students. *Hum Reprod* 2012;**27**:2807–2814.
879 Mitchell J, Cawood E, Kinniburgh D, Provan A, Collins A, Irvine D. Effect of a phytoestrogen
880 food supplement on reproductive health in normal males. *Clin Sci (Lond)* 2001;**100**:613–
881 618.
882 Mitchell M, Bakos HW, Lane M. Paternal diet-induced obesity impairs embryo development and
883 implantation in the mouse. *Fertil Steril* 2011;**95**:1349–1353.
884 Molloy AM. Genetic Aspects of Folate Metabolism. In: *Water Soluble Vitamins*.Vol 18. Springer
885 Netherlands, 2012, 105–130.
886 Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and
887 meta-analyses of randomised controlled trials and cohort studies. *BMJ* 2013;**346**:e7492.
888 Morgan DH, Ghribi O, Hui L, Geiger JD, Chen X. Cholesterol-enriched diet disrupts the blood-
889 testis barrier in rabbits. *Am J Physiol Endocrinol Metab* 2014;**307**:1125–1130.
890 Muraki I, Rimm EB, Willett WC, Manson JE, Hu FB, Sun Q. Potato consumption and risk of type
891 2 diabetes: Results from three prospective cohort studies. *Diabetes Care* 2016;**39**:376–
892 384.
893 Muthusami KR, Chinnaswamy P. Effect of chronic alcoholism on male fertility. *Fertil Steril*
894 2005;**84**:919–924.
895 Ng S-F, Lin RCY, Laybutt DR, Barres R, Owens J a, Morris MJ. Chronic high-fat diet in fathers
896 programs β-cell dysfunction in female rat offspring. *Nature* 2010;**467**:963–966.
897 Olsen J, Bolumar F, Boldsen J, Bisanti L, Group S. Does moderate alcohol intake reduce
898 fecundability? A European multicenter study on infertility and subfecundity. European
899 Study Group on Infertility and Subfecundity. *Alcohol Clin Exp Res* 1997;**21**:206–212.
900 Pajarinen JT, Karhunen P. Spermatogenic arrest and “Sertoli cell-only” syndrome- common
901 alcohol-induced disorders of the human testis. *Int J Androl* 1994;**17**:292–299.
902 Palmer NO, Bakos HW, Fullston T, Lane M. Impact of obesity on male fertility, sperm function
903 and molecular composition. *Spermatogenesis* 2012;**2**:253–263.
904 Palmer NO, Bakos HW, Owens J a, Setchell BP, Lane M. Diet and exercise in an obese mouse
905 fed a high fat diet improves metabolic health and reverses perturbed sperm function. *Am J*
906 *Physiol Endocrinol Metab* 2012;**3002**:768–780.
907 Park K, Gross M, Lee D-H, Holvoet P, Himes JH, Shikany J., Jacobs JDR. Oxidative stress and
908 insulin resistance: The coronary artery risk development in young adults study. *Diabetes*
909 *Care* 2009;**32**:1302–1307.
910 Ramlau-Hansen CH, Thulstrup AM, Bonde JP, Olsen J, Bech BH. Semen quality according to
911 prenatal coffee and present caffeine exposure: Two decades of follow-up of a pregnancy
912 cohort. *Hum Reprod* 2008;**23**:2799–2805.
913 Rato L, Alves MG, Cavaco JE, Oliveira PF. High-energy diets: A threat for male fertility? *Obes*
914 *Rev* 2014;**15**:996–1007.

915 Ricci E, Al Beitawi S, Cipriani S, Candiani M, Chiaffarino F, Viganò P, Noli S, Parazzini F.
916 Semen quality and alcohol intake: a systematic review and meta-analysis. *Reprod Biomed*
917 *Online* 2016;**34**:38–47.
918 Ross C, Morriss A, Khairy M, Khalaf Y, Braude P, Coomarasamy A, El-Toukhy T. A systematic
919 review of the effect of oral antioxidants on male infertility. *Reprod Biomed Online*
920 2010;**20**:711–23.
921 Rozati R, Reddy PP, Reddanna P, Mujtaba R. Role of environmental estrogens in the
922 deterioration of male factor fertility. *Fertil Steril* 2002;**78**:1187–1194.
923 Ruff JS, Suchy AK, Hugentobler SA, Sosa MM, Schwartz BL, Morrison LC, Gieng SH,
924 Shigenaga MK, Potts WK. Human-relevant levels of added sugar consumption increase
925 female mortality and lower male fitness in mice. *Nat Commun* 2013;**4**:2245.
926 de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened
927 beverages and body weight in children. *N Engl J Med* 2012;**367**:1397–1406.
928 Safarinejad MR. Effect of omega-3 polyunsaturated fatty acid supplementation on semen profile
929 and enzymatic anti-oxidant capacity of seminal plasma in infertile men with idiopathic
930 oligoasthenoteratospermia: A double-blind, placebo-controlled, randomised study.
931 *Andrologia* 2011;**43**:38–47.
932 Saleh RA, Agarwal A, Nada EA, El-Tonsy MH, Sharma RK, Meyer A, Nelson DR, Thomas AJ.
933 Negative effects of increased sperm DNA damage in relation to seminal oxidative stress in
934 men with idiopathic and male factor infertility. *Fertil Steril* 2003;**79**:1597–1605.
935 Samadian F, Towhidi A, Rezayazdi K, Bahreini M. Effects of dietary n-3 fatty acids on
936 characteristics and lipid composition of ovine sperm. *Animal* 2010;**4**:2017–22.
937 Santti R, Mäkelä S, Strauss L, Korkman J, Kostian M. Phytoestrogens: potential endocrine
938 disruptors in males. *Toxicol Ind Health* 1998;**14**:223–237.
939 Schmid TE, Ph D, Eskenazi B, Ph D, Marchetti F, Ph D, Young S, Suzanne Y, Weldon W,
940 Baumgartner A, *et al.* Micronutrients intake is association with improved sperm DNA
941 quality in older men. *Fertil Steril* 2012;**98**:1130–1137.
942 Schoeller EL, Albanna G, Frolova AI, Moley KH. Insulin rescues impaired spermatogenesis via
943 the hypothalamic-pituitary- gonadal axis in Akita diabetic mice and restores male fertility.
944 *Diabetes* 2012;**61**:1869–1878.
945 Schoeller EL, Schon S, Moley KH. The effects of type 1 diabetes on the hypothalamic, pituitary
946 and testes axis. *Cell Tissue Res* 2012;**349**:839–847.
947 Scott R, MacPherson A, Yates R, Hussain B, Dixon J. The effect of oral selenium
948 supplementation on human sperm motility. *Br J Urol* 1998;**82**:76–80.
949 Serra-Majem L, Bassas L, García-Glosas R, Ribas L, Inglés C, Casals I, Saavedra P, Renwick
950 a G. Cyclamate intake and cyclohexylamine excretion are not related to male fertility in
951 humans. *Food Addit Contam* 2003;**20**:1097–104.
952 Sharlip ID, Jarow JP, Belker AM, Lipshultz LI, Sigman M, Thomas AJ, Schlegel PN, Howards
953 SS, Nehra A, Damewood MD, *et al.* Best practice policies for male infertility. *Fertil Steril*
954 2002;**77**:873–882.
955 Showell M, Mackenzie-Proctor R, Brown J, Yazdani A, Stankiewicz M, Hart R. Antioxidants for
956 male subfertility. *Cochrane Database Syst Rev Antioxidants* 2014;**1**.
957 Silver EW, Eskenazi B, Evenson DP, Block G, Young S, Wyrobek AJ. Effect of Antioxidant
958 Intake on Sperm Chromatin Stability in Healthy Nonsmoking Men. *J Androl* 2005;**26**:550–
959 556.
960 Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL,
961 Dyachenko A, Zhang W, *et al.* Consuming fructose-sweetened, not glucose-sweetened,
962 beverages increase visceral adiposity and lipids and decrease insulin sensitivity in
963 overweight/obese men. *J Clin Invest* 2009;**1334**:1322–1334.
964 Stutz G, Zamudio J, Santillán ME, Vincenti L, de Cuneo MF, Ruiz RD, Emilia M. The effect of
965 alcohol, tobacco, and aspirin consumption on seminal quality among healthy young men.
966 *Arch Environ Health* 2004;**59**:548–52.
967 Swan SH, Liu F, Overstreet JW, Brazil C, Skakkebaek NE. Semen quality of fertile US males in
968 relation to their mothers' beef consumption during pregnancy. *Hum Reprod* 2007;**22**:1497–
969 1502.
970 Tremellen K. Oxidative stress and male infertility - a clinical perspective. *Hum Reprod Update*
971 2008;**14**:243–258.
972 Veaute C, Andreoli MF, Racca A, Bailat A, Scalerandi MV, Bernal C, Borel IM. Effects of
973 isomeric fatty acids on reproductive parameters in mice. *Am J Reprod Immunol*
974 2007;**58**:487–496.

975 Vignera S La, Condorelli RA, Balercia G, Vicari E, Calogero AE. Does alcohol have any effect
976 on male reproductive function? A review of literature. *Asian J Androl* 2013;**15**:221–225.
977 Vujkovic M, De Vries JH, Dohle GR, Bonsel GJ, Lindemans J, MacKlon NS, Van Der Spek PJ,
978 Steegers EAP, Steegers-Theunissen RPM. Associations between dietary patterns and
979 semen quality in men undergoing IVF/ICSI treatment. *Hum Reprod* 2009;**24**:1304–1312.
980 Wang M, Yu M, Fang L, Hu R-Y. Association between sugar-sweetened beverages and type 2
981 diabetes: A meta-analysis. *J Diabetes Investig* 2015;**6**:360–366.
982 Wathes DC, Abayasekara D, Aitken RJ. Polyunsaturated fatty acids in male and female
983 reproduction. *Biol Reprod* 2007;**77**:190–201.
984 WHO. *WHO laboratory manual for the examination and processing of human semen*. 2010.
985 Williams A, Ford W. The role of glucose in supporting motility and capacitation in human
986 spermatozoa. *J Androl* 2001;**22**:680–695.
987 Wong W, Merkus H, Thomas C, Menkveld R, Zielhuis G, Steegers-Theunissen R. Effects of
988 folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-
989 controlled trial. *Fertil Steril* 2002;**77**:491–498.
990 Xia W, Chiu Y, Williams P, Gaskins A, Toth T, Tanrikut C, Hauser R, Chavarro J. Men's meat
991 intake and treatment outcomes among couples undergoing assisted reproduction. *Fertil*
992 *Steril* 2015;**104**:972–979.
993 Young SS, Eskenazi B, Marchetti FM, Block G, Wyrobek AJ. The association of folate, zinc and
994 antioxidant intake with sperm aneuploidy in healthy non-smoking men. *Hum Reprod*
995 2008;**23**:1014–1022.
996 Zalata AA, Christophe AB, Depuydt CE, Schoonjans F, Comhaire FH. The fatty acid
997 composition of phospholipids of spermatozoa from infertile patients. *Mol Hum Reprod*
998 1998;**4**:111–118.
999 Zareba P, Colaci DS, Afeiche M, Gaskins AJ, Jorgensen N, Mendiola J, Swan SH, Chavarro JE.
1000 Semen quality in relation to antioxidant intake in a healthy male population. *Fertil Steril*
1001 2013;**100**:1572–1579.
1002
1003

TABLE CAPTIONS

Table I. Summary of the studies that investigated associations between nutrition and sperm parameters.

Table II. Summary of the studies that investigated associations between nutrition and fecundity.

FIGURE CAPTIONS

Figure I. Flow chart of the literature search and selection process.

Figure II. Nutrition-related factors reported in this review that were associated with male infertility. Different colors denote the type of association with male infertility: positive association in green, and negative association in orange.

Figure III. Diet-related factors reported in this review that were associated with fecundability. Different colors denote the type of association: negative associations in orange.~~, and controversial associations in blue.~~