RBM ONLINE

ELSEVIER

Review

Semen quality and alcohol intake: a systematic review and meta-analysis

Elena Ricci [a,*], ***Suha Al Beitawi*** [b], ***Sonia Cipriani*** [a], ***Massimo Candiani*** [b], ***Francesca Chiaffarino*** [a], ***Paola Vigano*** [c], ***Stefania Noli*** [a], ***Fabio Parazzini*** [a]

[a] *Dipartimento di Scienze Cliniche e di Comunità, Università di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy;*

[b] *Obstetrics and Gynaecology Department, IRCCS San Raffaele Scientific Institute, Milan, Italy;*

[c] *Reproductive Sciences Laboratory, Division of Genetics and Cell Biology, IRCCS Ospedale San Raffaele, Milan, Italy*

Elena Ricci is Consultant Biostatistician in the Department of Obstetrics and Gynecology, at the University of Milan in Italy. Her research focuses on identification of risk factors in different areas of gynaecology and andrology, with a particular interest in lifestyle factors. She is author of more than 100 peer-reviewed scientific articles.

KEY MESSAGE

The adage 'the dose makes the poison' is relevant when considering the relationship between alcohol intake and semen quality. High levels of alcohol intake do appear to be associated with changes in semen that may affect fertility, but this review finds no evidence for negative effects of occasional alcohol intake.

A B S T R A C T

Alcohol consumption is widespread in the Western world. Some studies have suggested a negative association between alcohol intake and semen quality although others have not confirmed this. MEDLINE and Embase were searched using 'alcohol intake' OR 'alcohol consumption' OR 'alcohol drinking' OR 'lifestyle' combined with 'semen quality' OR 'sperm quality' OR 'sperm volume' OR 'sperm concentration' OR 'sperm motility' for full-length observational articles, published in English. Reference lists of retrieved articles were searched for other pertinent studies. Main outcome measures were sperm parameters, if provided as means (standard deviation or standard error) or as medians (interquartile range). Fifteen cross-sectional studies were included, with 16,395 men enrolled. Main results showed that alcohol intake has a detrimental effect on semen volume (pooled estimate for no/low alcohol consumption 0.25 ml, 95% CI, 0.07 to 0.42) and normal morphology (1.87%, 95% CI, 0.86 to 2.88%). The difference was more marked when comparing occasional versus daily consumers, rather than never versus occasional, suggesting a moderate consumption did not adversely affect semen parameters. Hence, studies evaluating the effect of changes on semen parameters on the reproductive outcomes are needed in advance of providing recommendations regarding alcohol intake other than the advice to avoid heavy alcohol drinking.

* Corresponding author.
E-mail address: ed.ricci@libero.it (E Ricci).

http://dx.doi.org/10.1016/j.rbmo.2016.09.012
1472-6483/

Introduction

Alcohol consumption is widespread in the Western world. In Europe, according to the latest published data (Eurobarometer, 2010), an average 76% of citizens had consumed alcoholic beverages in the past 12 months, with proportions rising from the south (the lowest, 58%, in Portugal) to the north (the highest, 93%, in Denmark). In the USA (NIH, 2013), 70.7% of citizens were reported to have drunk alcohol in the past year and 56% to have drunk alcohol in the previous month.

Moderate alcohol consumption has been associated with reduced mortality and morbidity, albeit not consistently. Excessive alcohol intake, on the other hand, has a negative impact on health (e.g. coronary heart disease, stroke and liver disease) (Dawson et al., 2008; Farke and Anderson, 2007).

Some studies have also suggested a negative association between alcohol intake and semen quality (Gaur et al., 2010; Martini et al., 2004; Muthusami and Chinnaswamy, 2005; Stutz et al., 2004) although others did not confirm these findings (Hansen et al., 2012; López Teijón et al., 2007). In this context, it is difficult to make comparisons across studies, because populations as well as alcohol intake vary considerably among them. In addition, most studies only addressed average alcohol intake by use of a few questions, and within response categories consumption may vary considerably and is likely to be under-reported.

Mechanisms involved in association between alcohol consumption and reduction of semen quality have been suggested to be related to a direct adverse effect on both testosterone metabolism and spermatogenesis. The ratio between free oestradiol and free testosterone is modified by alcohol intake (Hansen et al., 2012) and spermatogenetic arrest and Sertoli-cell-only syndrome were found to be more frequently associated with high alcohol consumption (Pajarinen et al., 1996).

To summarize the currently available information, we conducted a systematic review and a meta-analysis of epidemiological data from observational studies on the relationship between alcohol consumption and semen quality.

Materials and methods

Identification of studies

We carried out a literature search of all observational studies published or in press as original articles in English, up to April 2016. We searched the electronic databases MEDLINE (1966 to 10 April 2016) and Embase (1985 to 10 April 2016) using 'alcohol intake' OR 'alcohol consumption' OR 'alcohol drinking' OR 'lifestyle' combined with 'semen quality' OR 'sperm quality' OR 'sperm volume' OR 'sperm concentration' OR 'sperm motility' (limit: 'human'). Furthermore, we reviewed reference lists of retrieved articles to search for other pertinent studies.

Two authors (ER and ABS) reviewed the papers and independently selected the articles eligible for the systematic review. Studies were selected for the review if they met all of the following criteria: observational studies reporting original data; parameters of semen quality provided as means and standard deviation (SD) or standard error (SE) or as medians and interquartile range (IQR); full-length articles, published in English. If multiple published reports from the same study were available, we included only the one with the most detailed information, or the more recently published.

Quality of studies

Study quality was independently evaluated by two reviewers using the STROBE checklist (von Elm et al, 2008).

Data collection for meta-analysis

Data were extracted independently by two investigators and discrepancies were resolved by discussion. For each study, the following information was collected in a standard form: first author's last name; year of publication; country of origin; number of subjects; mean age, if available; category of alcohol consumption, if available; mean and SD (or SE) or median and IQR; covariates adjusted for in the statistical analysis.

Statistical analysis

The inverse variance method was used to pool the mean difference. If data were provided as median and IQR these measures were transformed into mean and SD as indicated in the Cochrane Handbook (Higgins and Green, 2011). Estimates of the average effect of alcohol on semen parameters and 95% confidence intervals (CI) were calculated by using both fixed-effect and random-effect models. If the test for heterogeneity (apparent diversity in mean differences across studies) was significant, we presented the results of the random-effect model. Otherwise, estimated results based on a fixed-effect model were presented. If a study had two or more alcohol intake levels, an overall estimate was calculated to include the study in the ever vs never comparison (Higgins and Green, 2011).

Funnel plots and Egger's tests of all the measures were performed to detect publication bias.

Subgroup analyses

We planned two subgroup analyses, by level of alcohol intake and by type of men included in the study (fertile men, infertile men, unknown fertility status).

All analyses were performed using Review Manager (RevMan; computer program, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

Results

Running the search as in Materials and methods, we found 148 papers in MEDLINE and 200 in Embase, 169 of which were also recorded in MEDLINE, giving 31 more papers only present in Embase (**Figure 1**). Two authors read the abstracts of the 179 papers identified in the search. Out of these 104 were excluded for the following reasons: seven focused on fecundity, 10 on pregnancy outcome, 11 were laboratory studies, 30 considered exposure to chemicals, 16 were reviews or commentaries and 30 explored different issues such as time trend in semen quality, comparison between populations, methods to predict semen alterations, relationship between semen quality and mortality, effect of surgery or congenital defects or several diseases on sperm parameters, alternative medicine, or were intervention studies. The full text of the remaining 75 papers was retrieved for evaluation.

Among 75 papers read in full text, 60 articles were excluded for the following reasons: 30 reported that alcohol intake was adjusted

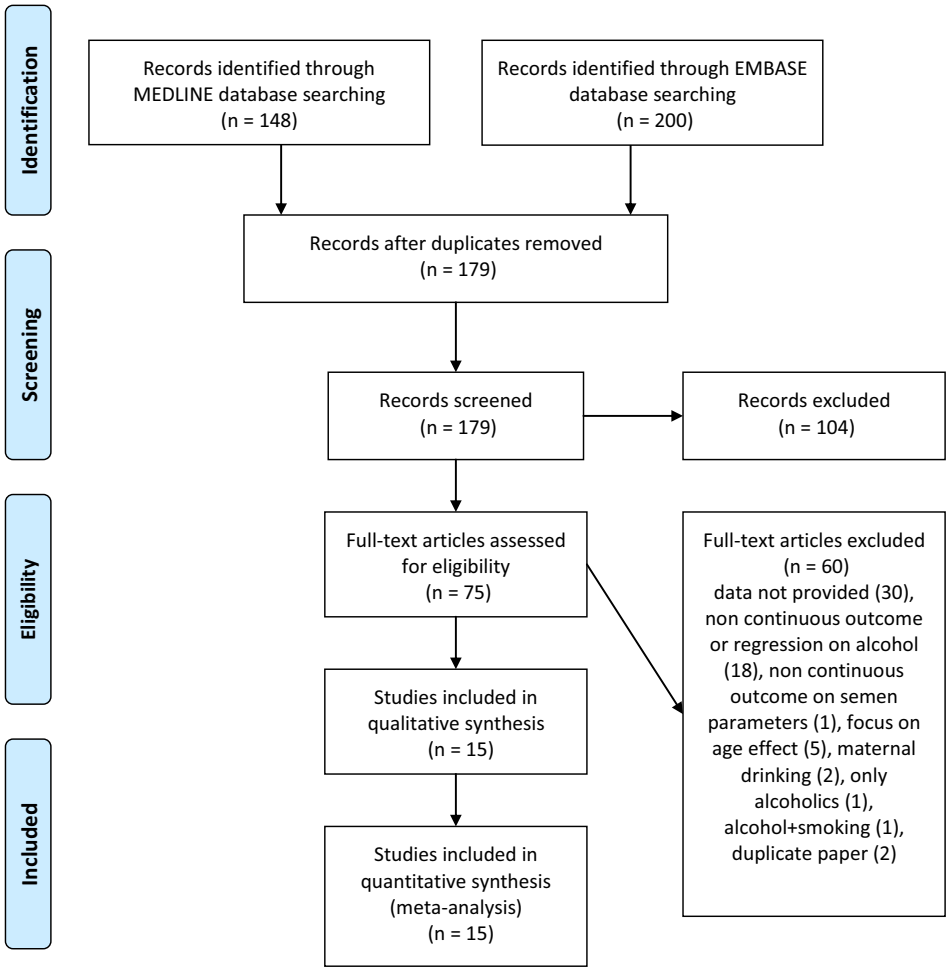

Figure 1 – Flow chart of literature research.

for, but the data were not provided, 18 reported non-continuous outcomes or the relationship between alcohol intake and sperm quality was expressed as a regression, five focused on age effect, two were on maternal drinking, one included only alcoholics, one reported results on alcohol and smoking together. One paper (Gaur et al., 2010) was excluded because semen variables were not published as such, but contributed to form summary categories (asthenozoospermia, teratozoospermia and oligozoospermia). Two duplicate papers were excluded. A total of 15 articles were included in the meta-analysis (Anifandis et al., 2014; Chia et al., 1998; Condorelli et al., 2015; Eskenazi et al., 2003; Goverde et al., 1995; Hansen et al., 2012; Hart et al., 2015; Jensen et al., 2014a, 2014b; Joo et al., 2012; Kumar et al., 2014; López Teijón et al., 2007; Martini et al., 2004; Muthusami and Chinnaswamy, 2005; Wogatzky et al., 2012).

Papers selected for systematic review and meta-analysis are described in **Table 1**. All studies had a cross-sectional design. Their quality was generally good, according to the STROBE criteria: the only issue, common to all studies, was that information about lifestyle habits (including alcohol intake) was collected by questionnaire.

In **Table 2**, we report the main findings as described by the authors. In their conclusion, some found no effect on semen parameters (Chia et al., 1998; Eskenazi et al., 2003; Hart et al., 2015; Jensen et al., 2014b; López Teijón et al., 2007; Martini et al., 2004; Wogatzky et al., 2012) and some underlined a detrimental effect of alcohol (Anifandis et al., 2014; Condorelli et al., 2015; Goverde et al., 1995; Hansen et al., 2012; Jensen et al., 2014a; Joo et al., 2012; Kumar et al., 2014; Muthusami and Chinnaswamy, 2005).

The most frequently reported measures were semen volume (ml), concentration (million/ml), motility (percentage of motile sperm) and morphology (percentage normal), usually provided as mean and SD or SE.

Data extraction showed that some studies (Hansen et al., 2012; Hart et al., 2015; Jensen et al., 2014a, 2014b) summarized information using median and IQR rather than mean and SD. Up-to-date meta-analyses on medians are not possible, and the Cochrane Handbook (Higgins and Green, 2011) suggests transforming median to mean and IQR to SD.

Moreover, concentration was summarized as arithmetic mean (Anifandis et al., 2014; Condorelli et al., 2015; Goverde et al., 1995; Joo et al., 2012; López Teijón et al., 2007; Martini et al., 2004; Muthusami and Chinnaswamy, 2005; Wogatzky et al., 2012), geometric mean (Chia et al., 1998), mean of log-transformed concentration (Eskenazi et al., 2003) or median (Hansen et al., 2012; Hart et al., 2015; Jensen et al., 2014a, 2014b). Medians were transformed to means and geometric and log-transformed means were excluded from the analysis.

Alcohol intake was categorized into classes in most papers: no versus any use (occasional or daily), or occasional versus daily use. Some authors quantify alcohol intake as units (Anifandis et al., 2014, 1 unit = 10 g; Condorelli et al., 2015, 1 unit = 12 g; López Teijón et al.,

Table 1 – Main characteristics of the studies on alcohol consumption and semen quality included in the meta-analyses.

Author (year), country	Cases	Controls	Sample size Cases/controls	Sample	Category of alcohol consumption	Guidelines for semen analysis
Anifandis et al. (2014), Greece	Alcohol intake[a]	No alcohol intake[a]	83/124	Men attending fertility clinic	0 to <7 units/day and ≥7/day vs no	WHO 2010
Chia et al. (1998), Singapore	Social drinkers	Teetotallers	97/146	Fertile men	<1 time/mo vs no	WHO 1992
Condorelli et al. (2015), Italy	Daily drinkers	Occasional drinkers	36/40	Fertile and infertile men	2–3 units per day vs <3/wk	WHO 2010
Eskenazi et al. (2003), USA	Ever drinkers	Never drinkers	63/34	Unknown fertility	Ever vs never	WHO 1992
Goverde et al. (1995), the Netherlands	Daily drinkers	Occasional drinkers	8/35	Poor semen quality	Daily vs occasional	WHO 1978
Hansen et al. (2012), Denmark	Alcohol intake[c]	No alcohol intake[c]	54/293	Young men, unknown fertility	1 – 5, 6 – 15, 16 – 120 vs 0 unit in the last month	WHO 1999
Hart et al. (2015), Australia	Alcohol intake[d]	No alcohol intake[d]	152/39	Young men, unknown fertility	Moderate vs no	WHO 1999
Jensen et al. (2014a), Denmark	Alcohol intake[b]	No alcohol intake[b]	431/122	Young men, unknown fertility	1 – 5, 6 – 10, 11 – 15, 16 – 20, 21 – 25, 26 – 30, 31 – 35, 36 – 40, >40 vs 0 units in the last month	WHO 1999
Jensen et al. (2014b), Denmark and USA	Alcohol intake[b]	No alcohol intake[b]	5339/1133 1312/560	Young men, unknown fertility Fertile men	1–10, 11–20, >20 vs 0 unit in the last week	WHO 1999
Joo et al. (2012), Korea	Daily drinkers	Occasional drinkers	33/29	Unknown fertility	>1 15.4 g per day vs <15.4 g per day	WHO 1999
Kumar et al. (2014), India	Alcohol intake[d]	No alcohol intake[d]	9/54	Men attending fertility clinic	Any vs no	WHO 2003
López Teijón et al. (2007), Spain	Daily drinkers	Occasional drinkers	527/440	Unknown fertility	>1 unit per day vs <1 unit per day	WHO 1999
Martini et al. (2004), Argentina	Daily drinkers	Never drinkers	236/3194	Men attending fertility clinic	4 units per day or more vs no	WHO 1999
Muthusami and Chinnaswamy (2005), India	Alcoholics	Occasional drinkers	66/30	Unknown fertility	Alcoholics vs no	WHO 1999
Wogatzky et al. (2012), Austria	Ever drinkers	No drinkers	1394/282	Men attending fertility clinic	Frequent and occasional vs no	WHO 2010 + MSOME criteria for morphology

[a] in the last year; [b]week prior to the visit; [c]5 days prior to the visit; [d]not specified.

MSOME = Motile Sperm Organelle Morphology Examination.

When combining subgroups to obtain a single estimate, as well as transforming medians and interquartile ranges into mean and SD, or geometric mean into mean, we used the methods suggested by the Cochrane Handbook (Higgins and Green, 2011).

Table 2 – Outcomes reported in the studies on alcohol consumption and semen quality included in the meta-analyses.

Study	Volume	Concentration	Motility	Morphology	Main findings as reported by the authors
Anifandis et al. (2014)	[a]	[a]	[a]	Not reported	Alcohol consumption, with or without smoking, has deleterious effects on sperm parameters.
Chia et al. (1998)	[a]	Geometric mean	[a]	[a]	Social alcohol consumption did not appear to affect sperm quality in this group of fertile men.
Condorelli et al. (2015)	[a]	[a]	[a]	[a]	Infertile patients in the group of daily drinkers had worse semen quality compared with other groups.
Eskenazi et al. (2003)	[a]	Log-transformed	[a]	Not reported	No difference emerged between ever/never drinkers as regards sperm characteristics.
Goverde et al. (1995)	[a]	[a]	[a]	[a]	A pattern of excessive alcohol consumption may decrease further an already low percentage of sperm with normal morphology.
Hansen et al. (2012)[b]	[a]	[a]	[a]	[a]	Alcohol intake was associated with impairment of most semen characteristics but without a coherent dose–response pattern.
Hart et al. (2015)[b]	Not reported	[a]	Not reported	Not reported	Alcohol was not associated with semen variables or concentration of circulating reproductive hormones.
Jensen et al. (2014a)[b]	[a]	[a]	[a]	[a]	Even modest habitual alcohol consumption of more than 5 units per week had adverse effects on semen quality.
Jensen et al. (2014b)[b]	[a]	[a]	[a]	[a]	No consistent association between any semen variable and alcohol consumption, which was low/moderate in this group (median weekly intake 8 units), either for total consumption or consumption by type of alcohol.
Joo et al. (2012)	[a]	[a]	[a]	[a]	Alcohol consumption was associated with increased numbers of morphologically abnormal sperm.
Kumar et al. (2014)	Not reported	Not reported	[a]	[a]	Deterioration in sperm parameters among alcohol consumers who had oligozoospermia (non-significant result).
López Teijón et al. (2007)	Not reported	[a]	[a]	[a]	No statistically significant differences in semen parameters were found between males who consumed alcohol daily versus less frequent drinkers.
Martini et al. (2004)	[a]	[a]	[a]	[a]	Alcohol or cigarette consumption did not alter the seminal parameters. However, a synergic or additive effect of these two toxic habits is possible.
Muthusami and Chinnaswamy (2005)	[a]	[a]	[a]	[a]	Chronic alcohol consumption has a detrimental effect on male reproductive hormones and on semen quality.
Wogatzky et al. (2012)	[a]	[a]	[a]	MSOME	No significant differences in semen parameters were found comparing non-alcohol consumers, occasional and frequent consumers.

[a] mean and SD or SE, either published as such or [b]calculated using median and interquartile range.
MSOME = Motile Sperm Organelle Morphology Examination.

2007, 1 unit = 10 g; Martini et al., 2004, 1 unit = 13 g; Hansen et al., 2012, Jensen et al., 2014a, 2014b, 1 unit = 12 g) or intake quantity (Joo et al., 2012, less and more than 15.4 g/day) or alcohol volume (Muthusami and Chinnaswamy, 2005), whereas others use the frequency of intake (Goverde et al., 1995; Hart et al., 2015; Wogatzky et al., 2012), or a dicothomic variable (never/ever) (Chia et al., 1998; Eskenazi et al., 2003; Kumar et al., 2014).

Some papers (Anifandis et al., 2014; Hansen et al., 2012; Jensen et al., 2014a, 2014b; Wogatzky et al., 2012) presented more than two categories: in this case, we summarized the classes as suggested by the Cochrane Handbook (Higgins and Green, 2011), using the lowest intake class as the reference.

In most papers, men participating in the studies were unselected for semen quality (general population), or fertility (partners of currently pregnant women), except for Goverde et al. (1995), who analysed a group of men with poor semen quality. Alcohol consumption was investigated through questionnaires and did not represent an enrolment criterion, except for Muthusami and Chinnaswamy (2005), who compared a sample of alcoholics versus a sample of teetotallers. For these reasons, we ran all analyses with and without data from these papers.

We found that one paper (Wogatzky et al., 2012) did not report SD for means of alcohol consumption; as this information was not provided by the authors, we used the SD reported in the same paper for other class variables with the same (or as similar as possible) means.

Figure 2 shows the forest plots summarizing the evidence from all selected articles (overall estimates). When the estimate was higher than 0, it meant that alcohol had a detrimental effect on semen parameters and men with no or low alcohol intake had better results (higher volume and concentration, better motility and morphology). Alcohol intake showed a detrimental effect on semen volume (pooled estimate for no/low alcohol consumption 0.25 ml, 95% confidence interval [CI], 0.07 to 0.42, $P = 0.005$) and normal morphology (1.87%, 95% CI, 0.86 to 2.88%, $P = 0.003$).

In **Figure 3**, the same analyses were performed using information from papers regarding men unselected for semen quality and alcohol intake use, thus excluding papers by Goverde et al. (1995), including men with poor semen quality, and Muthusami and

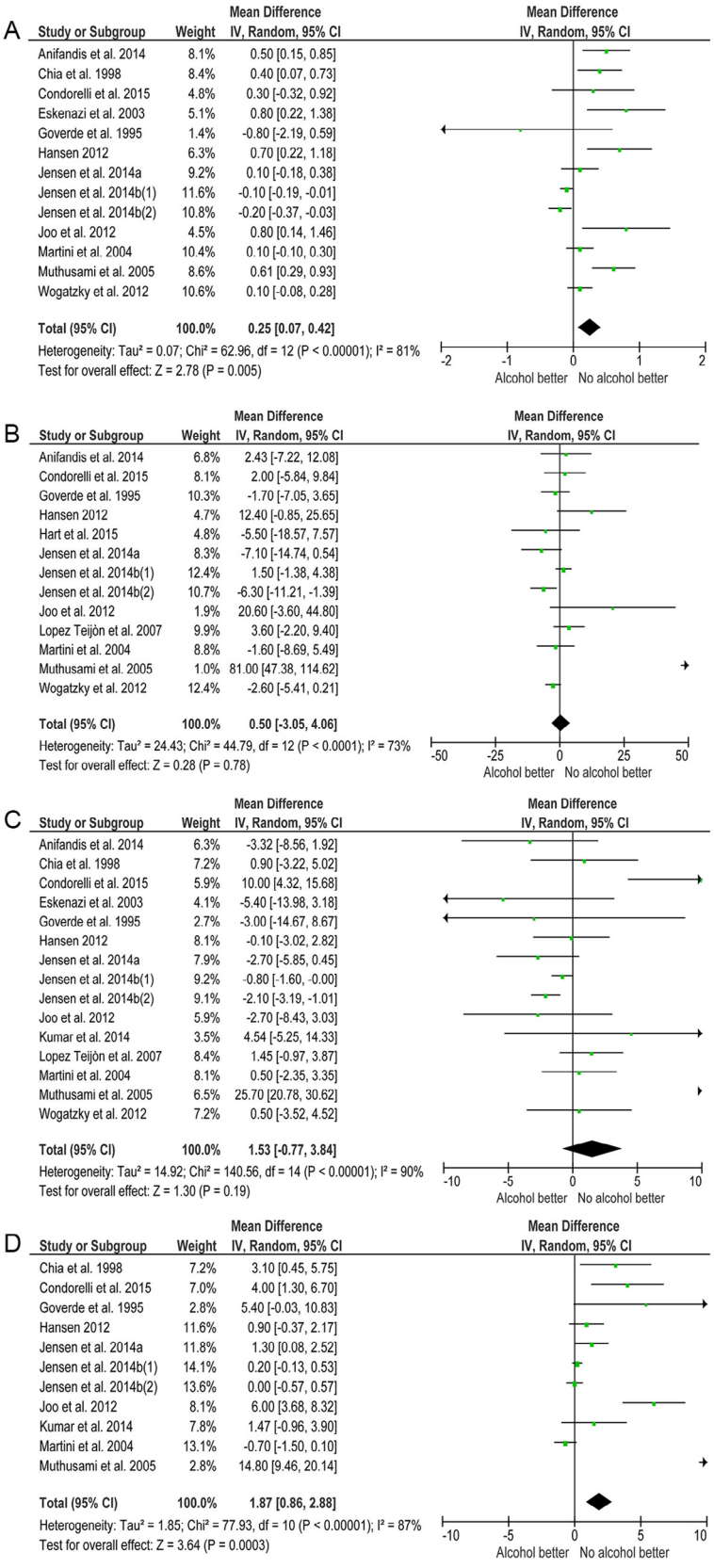

Figure 2 – Main analyses: (A) volume (ml); (B) concentration; (C) motility (a + b); (D) morphology. Jensen et al. 2014b(1): young men; Jensen et al. 2014b(2): fertile men.

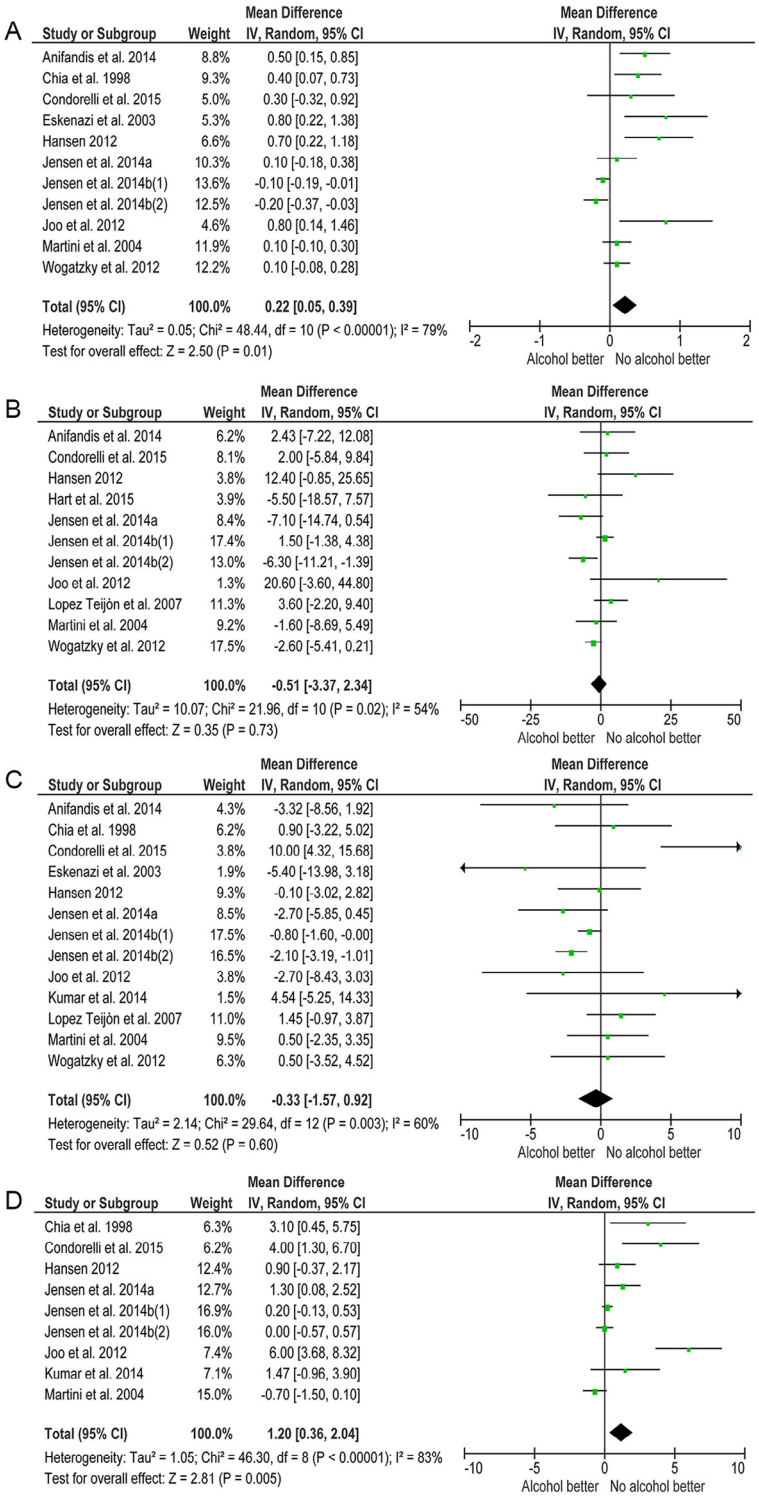

Figure 3 – Secondary analyses: (A) volume (ml); (B) concentration; (C) motility (a + b); (D) morphology. Jensen et al. 2014b(1): young men; Jensen et al. 2014b(2): fertile men.

Chinnaswamy (2005), comparing alcoholics to teetotallers. The positive effect of no/low alcohol consumption on semen volume (0.22 ml, 95% CI, 0.05 to 0.39, *P* = 0.01) as well as on normal morphology (1.20%, 95% CI, 0.36 to 2.04%, *P* = 0.005) was confirmed.

In **Table 3**, we report the analyses by subgroups. Overall, semen volume was better in the lower category of alcohol consumption than in the higher one. However, when dividing by comparison (no versus occasional and occasional versus daily), we found that between occasional versus daily drinkers the difference was 0.30 ml (95% CI, –0.39 to 1.00, not significant), whereas a lower estimate emerged comparing no and occasional alcohol consumption (0.18 ml, 95% CI, 0.01 to 0.35, *P* = 0.03).

Table 3 – Subgroup analyses (if mean > 0 then no/occasional alcohol intake was better than any/daily alcohol intake).

	Volume, ml Mean (95% CI)	Concentration*, 10^6/ml Mean (95% CI)	Motility, % Mean (95% CI)	Normal morphology, % Mean (95% CI)
Overall	0.25 (0.07 to 0.42)	0.50 (–3.05 to 4.06)	1.53 (–0.77 to 3.84)	1.87 (0.86 to 2.88)
Unselected for semen quality and alcohol intake	0.22 (0.05 to 0.39)	–0.51 (–3.37 to 2.34)	–0.33 (–1.57 to 0.92)	1.20 (0.36 to 2.04)
Fertile men	0.13 (–0.33 to 0.60)	–2.74 (–10.79 to 5.31)	2.39 (–3.74 to 8.52)	2.13 (–0.73 to 4.99)
Unknown fertility	0.38 (0.00 to 0.76)	1.44 (–3.54 to 6.42)	–0.69 (–1.85 to 0.47)	1.75 (0.12 to 3.38)
Fertility clinics-infertile	0.18 (–0.01 to 0.38)	–2.13 (–4.65 to 0.39)	0.08 (–2.00 to 2.16)	0.07 (–1.96 to 2.11)
Occasional vs never drinkers	0.18 (0.01 to 0.35)	–1.51 (–4.78 to 1.76)	–1.11 (–1.92 to –0.30)	0.93 (0.04 to 1.82)
Daily vs occasional drinkers*	0.30 (–0.39 to 1.00)	1.75 (–2.72 to 6.23)	2.02 (–3.24 to 7.28)	5.17 (3.50 to 6.85)

* excluding Muthusami and Chinnaswamy (2005); 95% CI = 95% confidence interval (if it excludes 0, the estimate is statistically significant).

As regards concentration and motility, no significant finding emerged from our analyses, except for slightly worse motility in never drinkers versus occasional alcohol drinkers (–1.11%, 95% CI, –1.92 to –0.30%). A better, although not statistically significant, motility was observed in men with unknown fertility status (–0.69%, 95% CI, –1.85 to 0.47%). On the contrary, percentage of normal morphology sperm was higher in men with no/low alcohol intake, as compared with those with higher alcohol intake, significantly after exclusion of men with known poor semen quality and alcoholics (1.20%, 95% CI, 0.36 to 2.04%, $P = 0.005$) (**Table 3**). Similar to the findings for semen volume, for morphology the greatest difference emerged between occasional and daily drinkers (5.17%, 95% CI, 3.50 to 6.85%, $P = 0.03$), whereas the difference between never and occasional drinkers was less marked (0.93%, 95% CI, 0.04 to 1.82%, $P = 0.05$, borderline statistical significance).

From the funnel plots, no indication of publication bias or small study effect was observed (figures not shown). Egger's tests, performed for all four considered measures, were not significant.

Discussion

The main finding of this meta-analysis is that any versus no use of alcohol would exert a consistent detrimental effect on semen volume and normal morphology. Concentration and motility did not seem to be consistently affected by alcohol intake. However, the effect seemed to be limited to daily drinkers, whereas occasional drinkers were apparently similar to never drinkers in terms of both volume and normal morphology.

This study has several limitations. The apparent heterogeneity of the obtained results – as clearly evident from the forest plots – represents a major restriction of the study that cannot be explained by the study design or patient selection. Even considering the most similar populations (young Danish men of unknown fertility) (Hansen et al., 2012; Jensen et al., 2014a), we found significant heterogeneities (volume: chi-squared = 4.50, $P = 0.03$, $I^2 = 78\%$; concentration chi-squared = 6.24, $P = 0.01$). Secondly, the authors classified alcohol use in different ways, as intake frequency, or units per day, or ever/never, and the reference categories were either no alcohol use or occasional use. A difference exists between definition of the alcohol unit, as it ranges from 10 to 13 g. Moreover, some authors just use the words 'alcohol serving' without further definition. However, in general a serving contains less wine than beer, and less spirit than wine: so, even if it is not defined, we may be confident that a proportion is maintained and more or less the same quantity of alcohol is consumed regardless of the type of alcoholic beverage.

Lastly, many variables were not normally distributed and we had to transform medians and IQR into means and SD to be able to include them in our meta-analysis. However, the results derived from the analyses did not differ whether parametric or non-parametric tests were used.

Similar findings – although to a lesser degree – were evident with a secondary analysis after excluding two 'extreme' papers, Goverde et al. (1995), which analysed poor semen quality samples, and Muthusami and Chinnaswamy (2005), who compared alcoholics and teetotallers. A statistically significant harmful effect of alcohol was observed on semen volume and a negative trend on the sperm morphology. As a result, it can be confidently concluded that alcohol, and specifically its daily intake, does have a detrimental effect on semen parameters. These findings are consistent with the idea that the greatest impact of alcohol consumption on sperm function is related to sex hormone levels and the tubular function of the testis. Hypotestosteronaemia may explain the observed reduction in the seminal plasma volume (Condorelli et al., 2015).

Performing a subgroup analysis provided a more in-depth view, and some different and interesting results can be observed considering each group separately, although the overall previously mentioned effect persisted. When comparing occasional versus never drinkers, alcohol was shown to have a statistically significant positive effect on sperm motility, and no statistically significant effect on concentration. Morphology was better in occasional drinkers compared with daily drinkers, but no other statistically significant differences in the semen parameters were found between these two groups. As such it can be deduced that some degree of alcohol would confer some benefits to semen parameters. It is known that beer or wine contain polyphenols such as resveratrol or xanthohuminol, which were demonstrated to have strong therapeutic and cell protective potential (Wogatzky et al., 2012). Accordingly, it could be suggested that these compounds might lie behind the observed beneficial effect of occasional drinking versus never drinking (on sperm motility) and versus daily drinking (on morphology). This advantage might be lost by the well-known toxic effect of alcohol and its metabolites in daily or heavy drinking. However, it is difficult to confirm which mechanism leads exactly to this effect due to the confounding effects of lifestyle behaviours, which are difficult to separate. Moreover, the diversity of the studied populations might also reflect different genetic backgrounds, which could influence the effect of alcohol on the body cells.

When considering fertility for categorizing subgroups, the detrimental effect of alcohol on semen volume persisted both in the fertile

and infertile groups as well as in men whose fertility status was unknown. On the other hand, alcohol was found to have a positive, although not statistically significant, effect on sperm motility in the group of men whose fertility status was unknown, supporting that opposite effects might be exerted by alcohol on different semen parameters and according to the amount consumed.

A potential new approach aimed at evaluating the role of alcohol intake on sperm quality is the analysis of the relationship between drinking and sperm DNA integrity. Because oxidative damage has been observed in both the testis and epididymis of animals exposed to alcohol (Abarikwu et al., 2016), and the main pathway leading to sperm DNA breaks is a process of apoptosis (Muratori et al., 2016), there is biological plausibility to support an increased production of spermatozoa with fragmented or degenerated DNA in association with alcohol use. Among the papers retrieved for this meta-analysis, Anifandis et al. (2014) failed to find a difference between alcohol consumption groups in term of sperm DNA fragmentation, possibly due to the small number of alcohol-abused men. Hansen et al. (2012) calculated the DNA fragmentation index (DFI), finding a minimal tendency towards lower DFI, but no coherent dose–response association. As management of patients with high levels of DNA fragmentation involves addressing modifiable medical, lifestyle and dietary contributing factors, further studies are necessary to establish the relationship between this parameter and alcohol intake.

It should be considered that while semen quality constitutes a health benchmark and an important instrument for epidemiological studies of environmental impact (Jurewicz et al., 2009), well-defined criteria of what constitutes a suitable model for the research process in studies of semen quality have only recently been developed (Sánchez-Pozo et al., 2013). Therefore, as there have been no specific standards for the appraisal of studies concerning semen quality until recently, biased results deriving from the older studies, in which quality controls were completely lacking, may have led to erroneous conclusions – potentially contributing to the heterogeneity observed.

In conclusion, we found that semen quality did not seem to be made worse by occasional alcohol intake, whereas both volume and morphology were negatively affected by daily consumption. Further, well-designed studies with predefined criteria for selecting the subjects, as well as defining categories of alcohol consumption, are essential for achieving good evidence on the effect of alcohol on semen parameters. Moreover, studies evaluating the effect of changes on semen parameters on reproductive outcomes are needed in advance of providing recommendations regarding alcohol intake other than the advice to avoid heavy alcohol drinking.

Acknowledgement

This work was partially funded by Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, in the framework of the activities of PRIN (Progetti di Ricerca di Interesse Nazionale).

ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form 21 September 2016
Accepted 22 September 2016

Declaration: The authors report no financial or commercial conflicts of interest.

Keywords:
alcohol consumption
lifestyle
meta-analysis
risk factors
semen quality
sperm parameters

REFERENCES

Abarikwu, S.O., Duru, Q.C., Chinonso, O.V., Njoku, R.C., 2016. Antioxidant enzymes activity, lipid peroxidation, oxidative damage in the testis and epididymis, and steroidogenesis in rats after co-exposure to atrazine and ethanol. Andrologia 48, 5485–5487. doi:10.1111/and.12478.

Anifandis, G., Bounartzi, T., Messini, C.I., Dafopoulos, K., Sotiriou, S., Messinis, I.E., 2014. The impact of cigarette smoking and alcohol consumption on sperm parameters and sperm DNA fragmentation (SDF) measured by Halosperm®. Arch. Gynecol. Obstet. 290, 777–782. doi:10.1007/s004040-143-281-x.

Chia, S.E., Tay, S.K., Lim, S.T., 1998. What constitutes a normal seminal analysis? Semen parameters of 243 fertile men. Hum. Reprod. 13, 3394–3398.

Condorelli, R.A., Calogero, A.E., Vicari, E., La Vignera, S., 2015. Chronic consumption of alcohol and sperm parameters: our experience and the main evidences. Andrologia 47, 368–379. doi:10.1111/and.12284.

Dawson, D.A., Li, T.K., Grant, B.F., 2008. A prospective study of risk drinking: at risk for what? Drug Alcohol Depend. 95, 62–72. doi:10.1016/j.drugalcdep.0720.12.007.

Eskenazi, B., Wyrobek, A.J., Sloter, E., Kidd, S.A., Moore, L., Young, S., Moore, D., 2003. The association of age and semen quality in healthy men. Hum. Reprod. 18, 447–454.

Eurobarometer, 2010. EU citizens' attitude towards alcohol. Special Eurobarometer 331, <http://ec.europa.eu/health/alcohol/docs/ebs_331_en.pdf>.

Farke, W., Anderson, P., 2007. Binge drinking in Europe. Adicciones 19, 333–339.

Gaur, D.S., Talekan, M.S., Pathak, V.P., 2010. Alcohol intake and cigarette smoking: impact of two major lifestyle factors on male fertility. Indian J. Pathol. Microbiol. 53, 35–40. doi:10.4103/03774-929.59180.

Goverde, H.J., Dekker, H.S., Jansen, H.J., Bastiaans, B.A., Rolland, R., Zielhuis, G.A., 1995. Semen quality and frequency of smoking and alcohol consumption – an explorative study. Int. J. Fertil. Menopausal Stud. 40, 135–138.

Hansen, M.L., Thulstrup, A.M., Bonde, J.P., Olsen, J., Håkonsen, L.B., Ramlau-Hansen, C.H., 2012. Does last week's alcohol intake affect semen quality or reproductive hormones? A cross-sectional study among healthy young Danish men. Reprod. Toxicol. 34, 457–462. doi:10.1016/j.reprotox.1220.06.004.

Hart, R.J., Doherty, D.A., McLachlan, R.I., Walls, M.L., Keelan, J.A., Dickinson, J.E., Skakkebaek, N.E., Norman, R.J., Handelsman, D.J., 2015. Testicular function in a birth cohort of young men. Hum. Reprod. 30, 27132–27724. doi:10.1093/humrep/dev244.

Higgins, J.P.T., Green, S. (Eds.), 2011. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 1120]*. The Cochrane Collaboration. <www.cochrane-handbook.org>.

Jensen, T.K., Gottschau, M., Madsen, J.O., Andersson, A.M., Lassen, T.H., Skakkebaek, N.E., Swan, S.H., Prikson, L., Juul, A., Jørgensen,

N., 2014a. Habitual alcohol consumption associated with reduced semen quality and changes in reproductive hormones; a cross sectional study among 1221 young Danish men. BMJ Open 4, e005462. doi:10.1136/bmjopen-14200-05462.

Jensen, T.K., Swan, S., Jørgensen, N., Toppari, J., Redmon, B., Punab, M., Drobnis, E.Z., Haugen, T.B., Zilaitiene, B., Sparks, A.E., Irvine, D.S., Wang, C., Jouannet, P., Brazil, C., Paasch, U., Salzbrunn, A., Skakkebæk, N.E., Andersson, A.M., 2014b. Alcohol and male reproductive health; a cross-sectional study of 8,344 healthy men from Europe and USA. Hum. Reprod. 29, 1801–1809. doi:10.1093/humrep/deu118.

Joo, K.J., Kwon, Y.W., Myung, S.C., Kim, T.H., 2012. The effects of smoking and alcohol intake on sperm quality: light and transmission electron microscopy findings. J. Int. Med. Res. 40, 23272–23335.

Jurewicz, J., Hanke, W., Radwan, M., Bonde, J.P., 2009. Environmental factors and semen quality. Int. J. Occup. Med. Environ. Health 22, 305–329. doi:10.2478/v100010-090-0361.

Kumar, S., Murarka, S., Mishra, V.V., Gautam, A.K., 2014. Environmental and lifestyle factors in deterioration of male reproductive health. Indian J. Med. Res. 140, S29–S35.

López Teijón, M., Garcia, F., Serra, O., Moragas, M., Rabanal, A., Olivares, R., Alvarez, J.G., 2007. Semen quality in a population of volunteers from the province of Barcelona. Reprod. Biomed. Online 15, 434–444.

Martini, A.C., Molina, R.I., Estofán, D., Senestrari, D., Fiol de Cuneo, M., Ruiz, R.D., 2004. Effects of alcohol and cigarette consumption on human seminal quality. Fertil. Steril. 82, 3743–3777.

Muratori, M., Tarozzi, N., Cambi, M., Boni, L., Iorio, A.L., Passaro, C., Luppino, B., Nadalini, M., Marchiani, S., Tamburrino, L., Forti, G., Maggi, M., Baldi, E., Borini, A., 2016. Variation of DNA fragmentation levels during density gradient sperm selection for assisted reproduction techniques: a possible new male predictive parameter of pregnancy? Medicine (Baltimore) 95, e3624. doi:10.1097/MD.0000000000003624.

Muthusami, K.R., Chinnaswamy, P., 2005. Effect of chronic alcoholism on male fertility hormones and semen quality. Fertil. Steril. 84, 99919–99924.

NIH, 2013. National Institute on Alcohol Abuse and Alcoholism. Alcohol facts and statistics. Substance Abuse and Mental Health Services Administration (SAMHSA). National Survey on Drug Use and Health (NSDUH). Table 2.41B – Alcohol Use in Lifetime, Past Year, and Past Month among Persons Aged 18 or Older, by Demographic Characteristics: percentages, 1220 and 1320. <https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/alcohol-facts-and-statistics>.

Pajarinen, J., Karhunen, P.J., Savolainen, V., Lalu, K., Penttila, A., Laippala, P., 1996. Moderate Alcohol consumption and disorders of human spermatogenesis. Alcohol. Clin. Exp. Res. 20, 3323–3337.

Sánchez-Pozo, M.C., Mendiola, J., Serrano, M., Mozas, J., Björndahl, L., Menkveld, R., Lewis, S.E., Mortimer, D., Jørgensen, N., Barratt, C.L., Fernández, M.F., Castilla, J.A., on behalf of the Special Interest Group in Andrology (SIGA) of the European Society of Human Reproduction and Embryology, 2013. Proposal of guidelines for the appraisal of SEMen QUAlity studies (SEMQUA). Hum. Reprod. 28, 10–21. doi:10.1093/humrep/des355.

Stutz, G., Zamudio, J., Santillán, M.E., Vincenti, L., de Cuneo, M.F., Ruiz, R.D., 2004. The effect of alcohol, tobacco, and aspirin consumption on seminal quality among healthy young men. Arch. Environ. Health 59, 548–552.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., STROBE Initiative, 2008. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. J. Clin. Epidemiol. 61, 3449.

Wogatzky, J., Wirleitner, B., Stecher, A., Vanderzwalmen, P., Neyer, A., Spitzer, D., Schuff, M., Schechinger, B., Zech, N.H., 2012. The combination matters–distinct impact of lifestyle factors on sperm quality: a study on semen analysis of 1683 patients according to MSOME criteria. Reprod. Biol. Endocrinol. 10, 115. doi:10.1186/14777-8271-01-15.

World Health Organization, 1978. *WHO Laboratory Manual for the Examination of Human Semen and Cervical Mucus-Semen Interaction*, 2nd ed. Cambridge University Press.

World Health Organization, 1992. *WHO Laboratory Manual for the Examination of Human Semen and Cervical Mucus-Semen Interaction*, 3rd ed. Cambridge University Press.

World Health Organization, 1999. *WHO Laboratory Manual for the Examination of Human Semen and Cervical Mucus-Semen Interaction*, 4th ed. Cambridge University Press.

World Health Organization, 2003. *WHO Laboratory Manual for the Examination of Human Semen and Cervical Mucus-Semen Interaction*, 4th ed. Cambridge University Press. reprint.

World Health Organization, 2010. *WHO Laboratory Manual for the Examination of Human Semen and Cervical Mucus-Semen Interaction*, 5th ed. Cambridge University Press.