Review Article

Association of the Effect of Alcohol Consumption on Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), and Testosterone Hormones in Men: A Systematic Review and Meta-Analysis

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Abstract

Background: The present study is a systematic review and meta-analysis aiming to investigate the effects of alcohol consumption on male sex hormones in humans. **Methods:** We conducted searches on PubMed, Scopus, Science Direct, and Google Scholar from June 2020 to June 2022. We included observational studies (cohorts, case-controls, and cross-sectional studies) comparing FSH, LH, or testosterone levels in alcohol consumers versus non-consumers. Subgroup analysis based on alcohol intake levels was conducted to explore potential heterogeneity sources. The meta-analysis was done by STATA version 11. Seventeen studies met the criteria. **Results:** Combining data from these studies, the standardized mean differences for FSH, LH, and testosterone in alcohol-exposed versus non-exposed groups were −0.00 (95% CI: −0.099–0.099), 0.04 (95% CI: 0.00–0.12), and 0.03 (95% CI: −0.11–0.16), respectively, showing no statistical significance. Subgroup analysis indicated a significant difference in FSH levels between moderate/high and low alcohol consumption groups (−0.04, 95% CI: −0.08 to −0.00). Similarly, compared to non-exposed individuals, testosterone levels differed significantly in groups with moderate (0.22, 95% CI: 0.12–0.32) and low (0.19, 95% CI: 0.04–0.35) alcohol intake. Given the notable alterations observed in testosterone levels among individuals with alcohol use disorder and the associated feedback changes in LH levels, it has been concluded that alcohol overuse should be recognized as a factor with destructive effects. **Conclusions:** It is suggested that future research includes comprehensive studies to investigate the changes in the hypothalamus-pituitary-testis axis induced by alcohol consumption.

Keywords: *Alcohol, follicle-stimulating hormone, gonadal steroid hormones, infertility, luteinizing hormone, testosterone*

Introduction

Sex hormones, also known as gonadal steroid hormones, play an essential role in many aspects of human physiology. Sex hormones are in charge of regulating sexual differentiation and creating secondary sexual characteristics and behavioral patterns.[1,2] The most important regulatory pathway for these hormones in men is the hypothalamic-pituitary-gonadal axis, which involves the action of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and high intratesticular testosterone concentration.[3]

The target cells for LH are the Leydig cells located in the interstitial space of the testes, while the target cells for FSH are the Sertoli cells found within the seminiferous tubules. LH stimulates the production of testosterone by influencing Leydig cells, whereas FSH, in synergy with testosterone, stimulates Sertoli cells, thereby facilitating the production of regulatory molecules and nutrients necessary for spermatogenesis.[4] Testosterone plays a critical role in the development of male reproductive organs and sexual characteristics, including the growth of body hair and the increase in muscle and bone mass. In addition, testosterone contributes to overall health and well-being. Insufficient levels of testosterone in men can lead to various problems such as infertility, diabetes, and osteoporosis.[5]

Throughout history, humans have utilized alcohol for various purposes. However, in contemporary times, recreational alcohol consumption has evolved into a global health-threatening issue.[6] Studies have shown that young people, particularly

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those aged 18–25 years, are at a higher risk of alcohol consumption. Initiating alcohol consumption at younger ages is directly associated with the long-term adverse effects and complications on health caused by alcohol consumption.[7]

Alcohol consumption is recognized as a potentially harmful factor in male infertility. This is attributed to its influence on semen parameters and reproductive hormone levels.[8] Numerous studies have been conducted on the relationship between alcohol consumption and sex hormones. The results have shown contradictory findings, particularly among women.[1,9] In some studies, the levels of gonadotropins (LH and FSH) in men who consume alcohol are reported to be higher, while in others, they are lower compared to the control group. In addition, some studies have found no significant difference between the alcohol-consuming group and the control group regarding gonadotropin levels. This variability in findings also applies to testosterone levels.[10]

In this study, we assessed the impact of alcohol consumption on LH, FSH, and testosterone in men through a systematic review. We conducted a comprehensive evaluation and meta-analysis of human studies, focusing on determining the direction of alcohol's effects on hormones, namely LH, FSH, and testosterone.

Material and Methods

This study has been reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, whose protocol was registered in The International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42017071557).

Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined based on PECO. In the present study, participants (P) included individuals who reported alcohol consumption; exposure (E) stands for exposure to alcohol; comparison (C) states the individuals without alcohol consumption; and outcome (O) is the level of FSH, LH, and testosterone hormones.

Inclusion criteria

1. Original and peer-reviewed studies were conducted on human male participants
2. Observational studies with a cohort, case-control, or cross-sectional design.
3. Studies that evaluated changes in FSH, LH, or testosterone hormones in people with alcohol consumption.
4. Studies reporting the mean level of FSH, LH, or testosterone hormones in each group.

Exclusion criteria

1. Studies with samples other than humans.
2. Studies designed other than cohort or case-control, such as case reports, clinical trials, and experiments.
3. Studies that did not report sufficient data, such as the mean level of hormones in participants in each group and the size of each group.
4. Studies with unavailable full text.

Search strategy

PubMed/Medline, Scopus, Science Direct, and Google Scholar databases, as well as search engines, were searched using the following search strategy. We designed our search strategy by utilizing Mesh and EMTREE keywords, in addition to the keywords obtained from experts in the fields of infertility and alcoholism. The search covered the databases from June 2020 to June 2022. The search strategy is as follows (full form of search strategy presented in supplementary file):

"Alcohol" OR "primary alcohols" OR "R-CH2OH" OR "secondary alcohols" OR "R2-CHOH" OR "tertiary alcohols" OR "R3-COH" OR "Ethanol" OR "Amino Alcohols" OR "Ethanolamines" AND "Fertility hormone" OR "prolactin" OR "FSH" OR "LH" OR "testosterone" OR "T" OR "sex hormone" OR "semen" OR "Luteinizing Hormone" OR "Follicle-stimulating hormone"

We also used the Google Scholar search engine, and the reference lists of included studies were considered during a manual search to avoid missing any related studies.

Screening and selection process

To begin, duplicate documents were removed. The screening process entailed evaluating the titles and abstracts of primary studies against the eligibility criteria. Irrelevant studies were omitted during this phase, and the full text of the remaining studies was obtained. Subsequently, the full text of the articles was assessed, and studies that met our eligibility criteria were selected. The screening and selection processes were independently conducted by two researchers (A.H. and K. R.), with any disagreements resolved through consensus.

Data extraction

The data were independently extracted by two individuals (S. A. and K. H.). Any potential disagreements were

resolved through consensus. The variables extracted from the primary studies included the last name of the first author; the article's title; the journal's name; the publication year; the study location; the publication language; the sample size of the group exposed to alcohol; the sample size of the group without alcohol exposure; the mean and standard deviation of FSH, LH, and testosterone in both the group exposed to alcohol and the comparison group; and the amount of alcohol consumed in the group exposed to alcohol.

Quality assessment

The risk-of-bias assessment was conducted using the Newcastle-Ottawa Scale (NOS) checklist, which evaluates the quality of non-randomized studies.[11] This checklist comprises three components: selection, comparability, and exposure. The total score on the checklist ranges from 0 to 9, with the selection criterion having a maximum of 4 points, the comparability criterion capped at 2 points, and the exposure criterion allowing a maximum of 3 points. It is noteworthy that the evaluation was independently performed by two individuals, namely F. M. and M. A. Any potential disagreements were resolved through consensus. Included articles were classified into three groups based on their quality: weak quality (score: 0–3), moderate quality (score: 4–6), and high quality (score: 7–9).

Risk-of-bias assessment and sensitivity analysis

To evaluate the risk of publication bias, both a graphical approach (funnel plot) and a quantitative method (Egger's linear regression test) were utilized in assessing potential publication biases within the included studies. In addition, the trim and fill test was performed to estimate the number of possible missing evidence, when appropriate.

Furthermore, a sensitivity analysis was performed to assess how the exclusion of each study individually, one at a time, influenced the aggregated estimates.[12]

Statistical methods

For data analysis, STATA version 11 was utilized. The statistical heterogeneity among the included studies was assessed using the I^2 statistic. The random or fixed-effect model, along with the inverse variance method, was employed to estimate the standardized mean difference of FSH, LH, and testosterone in subjects exposed to alcohol compared to the control group (those not exposed to

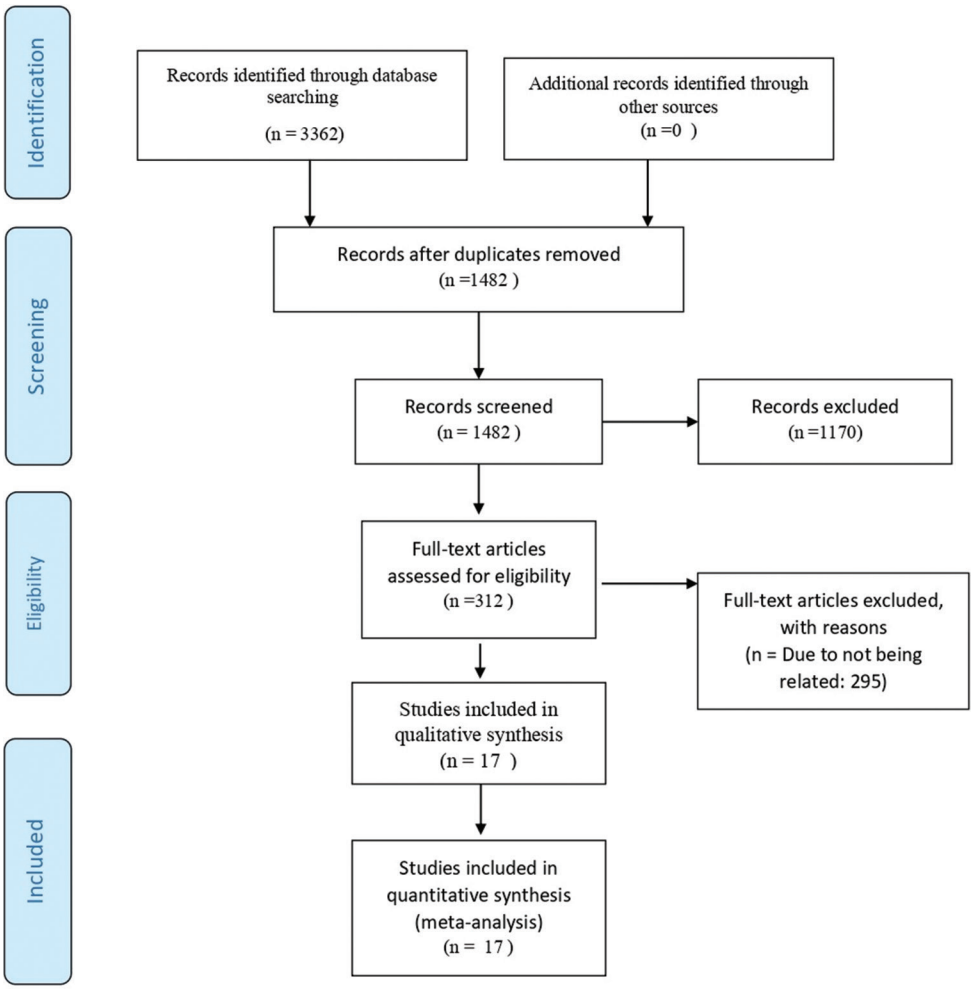

Figure 1: Process for searching and selecting primary studies

Table 1: Properties of primary studies extracted evidence in terms of the comparison of FSH, LH, and testosterone between two groups exposed and not exposed to alcohol

First Author (reference)	Country	Study type	Alcohol consumption severity	Sample size		FSH-exposed group		FSH-non-exposed group		LH-exposed		LH-non-exposed		T- exposed		T-non-exposed		QA
				Exposed	Non- exposed	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Boeri[13]	Italy	Cohort	Moderate	77	67	7.7	7.4	5.9	4.4	4.4	2.7	4.2	1.8	4.6	1.6	4.6	1.7	8
Boeri[13]	Italy	Cohort	High	45	67	8.5	7.2	5.9	4.4	4.7	2.1	4.2	1.8	3.9	1.3	4.6	1.7	7
Hart[14]	Australia	Cohort	Moderate	154	39	4.76	2.81	4.66	1.92	10.6	3.25	10.7	4	4.67	1.59	4.44	1.88	7
Hart[14]	Australia	Cohort	High	101	39	4.43	2.44	4.66	1.92	10.8	3.4	10.7	4	4.9	1.42	4.44	1.88	8
Iturriaga[15]	Chile	Cohort	High	30	15	7.7	4	10.8	2.7	12.9	4.1	13.5	4.1	6.9	2.5	8.2	1.4	8
Kurniawan[16]	Taiwan	Cross-sectional	Unknown	699	2584	4.7	3.1	4.6	6.2	3.3	1.5	3.3	2.4	5.3	1.6	4.9	1.8	8
Muthusami[17]	India	Cohort	High	66	30	7.41	4.16	4.60	1.94	7.22	3.07	4.69	2.43	4.41	1.03	5.88	2.07	7
Meng Rao[18]	China	Cross-sectional	Unknown	2982	1260	9.87	5.84	13.51	14.50	6.19	4.23	7.32	6.33	4.73	1.93	4.83	1.76	8
Shen[19]	China	Cross-sectional	Unknown	668	498					6.29	4.43	7.42	5.89	4.81	1.43	4.9	1.36	8
Zhang[20]	China	Cross-sectional	Unknown	16	48	4.16	2.36	5.05	2.39	4.52	2.28	5.32	2.36	4.51	2.47	5.34	1.96	6
Ho[21]	USA	Cross-sectional	Unknown	29	29	10.3	9.8	8	15.9	6.9	10.7	4.6	5.1	4.18	2.76	3.66	1.77	7
Errico[22]	USA	Cross-sectional	High	58	29	7.6	4.7	6.7	3.7	5.2	3.9	4.3	2	6.459	2.439	5.411	1.617	7
Maneesh[23]	India	Cohort	Unknown	46	55	8.03	0.14	8.18	0.48	5.63	0.22	5.65	0.13	4.96	0.16	7.56	0.13	7
Walter[24]	Germany	Cohort	High	51	43									11.8	3.8	11.3	3.2	7
Jensen[25]	Europe and America	Cohort	Low	883	560	3.2	1.55	3.36	1.62	3.5	1.25	3.56	1.33	5.77	1.73	5.2	2.05	8
Jensen[25]	Europe and America	Cohort	Moderate	261	560	3.5	1.62	3.36	1.62	3.66	1.48	3.56	1.33	5.88	1.66	5.2	2.05	8
Jensen[25]	Europe and America	Cohort	High	168	560	3.26	1.62	3.36	1.62	3.73	1.33	3.56	1.33	5.95	1.89	5.2	2.05	7
Jensen[25]	Europe and America	Cohort	Low	2467	1133	2.93	1.62	3.03	1.62	3.7	1.4	3.63	1.4	6.43	1.88	6.2	1.88	7
Jensen[25]	Europe and America	Cohort	Moderate	1635	1133	2.86	1.55	3.03	1.62	3.7	1.4	3.63	1.4	6.63	2.05	6.2	1.88	8
Jensen[25]	Europe and America	Cohort	High	1237	1133	2.76	1.48	3.03	1.62	3.7	1.4	3.63	1.4	6.72	1.86	6.2	1.88	7
Gomathi[26]	India	Cross-sectional	Unknown	5	5									4.1	0.67	7	1.78	5
Hansen[27]	Denmark	Cross-sectional	Low	48	54	3.13	1.55	2.7	1.25	4.26	1.33	3.96	1.48	4.71	1.46	4.61	1.26	7
Hansen[27]	Denmark	Cross-sectional	Moderate	98	54	3.36	1.77	2.7	1.25	4.43	1.92	3.96	1.48	4.71	1.46	4.61	1.26	7
Hansen[27]	Denmark	Cross-sectional	High	109	54	3	1.62	2.7	1.25	4.46	1.55	3.96	1.48	5.08	1.7	4.61	1.26	7

FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone, QA: Quality Assessment, SD: Standard Deviation

alcohol). The choice between the random or fixed-effect model was determined by the heterogeneity among the studies included in the meta-analysis.

The point estimate of the standardized mean difference for FSH, LH, and testosterone, along with a 95% confidence interval, was illustrated using forest plots. In these plots, the size of each square represents the weight of each study, and the lines on its sides indicate the 95% confidence interval.

Results

After searching the databases, a total of 3362 results (including 12,013 cases with and 6617 cases without alcohol consumption) were identified. Upon removing duplicate cases, 1482 unique records remained. Subsequently, a screening of titles and abstracts led to the exclusion of 1170 records. The full texts of 312 articles were then evaluated, resulting in the removal of 294 articles. Ultimately, 17 articles entered the systematic review and meta-analysis process [Figure 1]. The characteristics of the primary studies included in this meta-analysis are presented in Table 1. The publication years of these studies ranged from 1991 to 2021.

Quality assessment

Based on the conducted quality assessment shown in Table 1, 14 of the included studies were of high quality, while three of them were of moderate quality.

Risk-of-bias assessment

The results of funnel plots [Figure 3] and Egger's test ($\beta = 1.83$, $P = 0.048$) revealed publication bias. Considering the publication bias, the trim and fill test was performed to estimate the number of the possible missing evidence, and this test identified six cases of possible missing evidence. By adding these six evidence, the standardized mean difference of FSH in the group exposed to alcohol was estimated as −0.12 (95% CI: −0.22 to −0.02) when compared to the group not exposed to alcohol. It has to be noted that this effect size was statistically meaningful.

In addition, based on the results of the sensitivity analysis, the impact of removing each included study was negligible as the overall estimate did not significantly change with the elimination of any individual study.

The Egger's test was also performed for the meta-analysis of the standardized mean difference (SMD) of testosterone

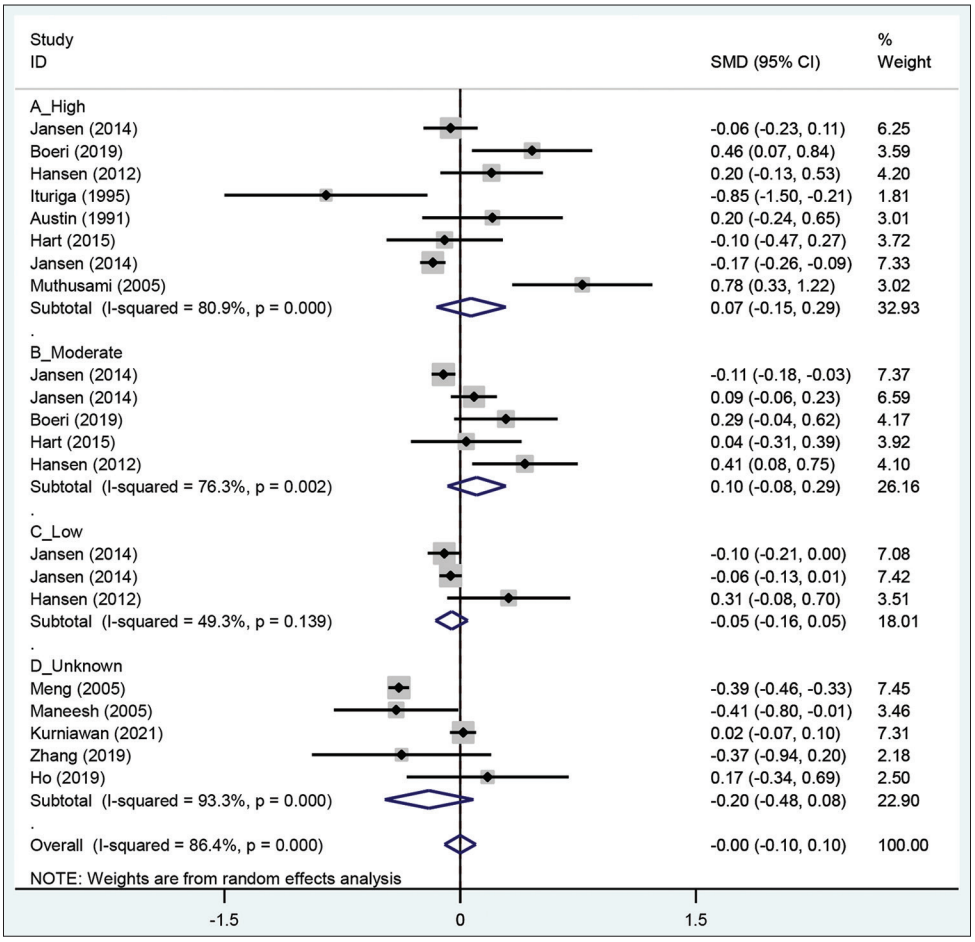

Figure 2: Standardized mean difference of FSH between the groups exposed and not exposed to alcohol

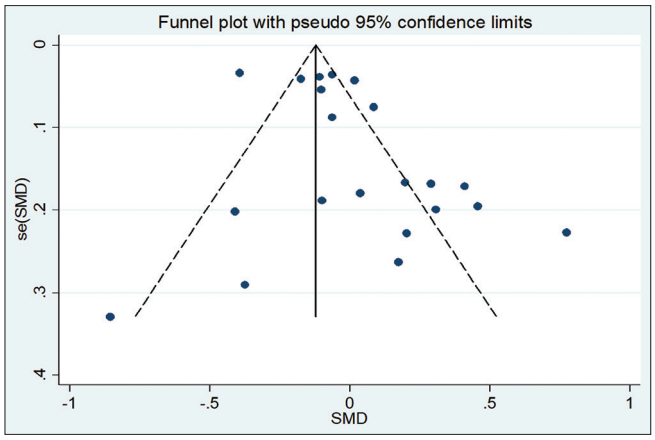

Figure 3: Funnel plot for assessing the publication bias of the standardized mean difference of FSH between the two groups

between the groups exposed and non-exposed to alcohol. According to the results of Egger's test (β = −2.07, $P = 0.086$), no publication bias was observed. Furthermore, the sensitivity analysis indicated that the deletion of each original study had no significant impact on the overall estimate.

Relationship between alcohol and FSH

A) In 21 primary studies, the average FSH levels were compared between groups exposed and not exposed to alcohol. Among these studies, alcohol consumption was classified as high in eight, moderate in five, low in three, and unknown in five. In 10 of the primary studies, the average FSH levels were lower in the group exposed to alcohol compared to the non-exposed group, with statistical significance observed in five of these cases. Conversely, in 11 studies, the average FSH levels were higher in the alcohol-exposed group, with statistical significance seen in three studies. Details of the subgroup analysis based on alcohol consumption dose are provided in Table 2.

The heterogeneity indices indicated high heterogeneity among the results of the primary studies (I-square: 86.4%, Q: 147.29, $P < 0.001$). By combining the data from these 21 primary studies by using the random effects model, inverse-variance method, and Cohen›s statistics, the standardized mean difference of FSH hormone in the alcohol-exposed group was estimated as −0.00 (95% CI: −0.099–0.099) compared to the non-exposed group. The confidence interval suggests that this difference was not statistically significant [Figure 2].

Furthermore, the subgroup analysis revealed that the differences in the standardized mean of FSH between the alcohol-exposed and non-exposed groups, categorized by alcohol dose (high, medium, low, and unknown), were not statistically significant. Specifically, the differences were estimated as 0.07 (95% CI: −0.15–0.9), 0.10 (95% CI: −0.08–0.29), −0.05 (95% CI: −0.16–0.05), and −0.20 (95% CI: −0.48–0.08), respectively.

Table 2: Properties of the primary studies extracted evidence in terms of the comparison of FSH, LH, and testosterone between the group exposed to moderate and high doses of alcohol and the group exposed to low doses of alcohol

First Author	Country	Alcohol consumption severity	Sample size		FSH- exposed group		FSH- low exposed group		LH- exposed group		LH- low exposed group		T- exposed group		T- low exposed group		QA
			Exposed	Non-exposed	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Boeri[13]	Italy	High	45	77	8.5	7.2	7.7	7.4	4.7	2.1	4.4	2.7	39	1.3	4.6	1.6	8
Hart[14]	Australia	High	101	154	4.43	2.44	4.76	2.81	10.8	3.4	10.6	3.25	4.9	1.42	4.67	1.59	7
Lwow[28]	Poland	High	44	128	5.23	7.4	4.4	5.55	6.26	6.88	5.33	5.4	6.53	5.03	6.33	4.22	7
Condorelli[29]	Italy	High	20	24	5.6	3.5	3.9	4	5.6	3.5	4.2	2.2	4.4	1.4	6.6	3.3	6
Condorelli[29]	Italy	High	16	16	7.5	3.7	5.5	2	8.1	4.2	6.1	5.6	3.5	2.2	5.9	2.2	6
Jansen[25]	Europe and America	Moderate	261	883	3.3	1.62	3.2	1.55	3.66	1.48	3.5	1.25	5.88	1.66	5.77	1.73	8
Jansen[25]	Europe and America	High	168	883	3.26	1.62	3.2	1.55	3.73	1.33	3.5	1.25	5.95	1.89	5.77	1.73	8
Jansen[25]	Europe and America	Moderate	1635	2467	2.86	1.55	2.93A	1.62	3.7	1.4	3.7	1.4	6.63	2.05	6.43	1.88	8
Jansen[25]	Europe and America	High	1237	2467	2.76	1.48	2.93	1.62	3.7	1.4	3.7	1.4	6.72	1.86	6.43	1.88	8
Hansen[27]	Denmark	Moderate	98	48	3.36	1.77	3.13	1.55	4.43	1.92	4.26	1.33	4.71	1.46	4.71	1.46	7
Hansen[27]	Denmark	High	109	48	3	1.62	3.13	1.55	4.46	1.55	4.26	1.33	5.08	1.7	4.71	1.46	7

Exposed group: The group with moderate and high doses of alcohol consumption

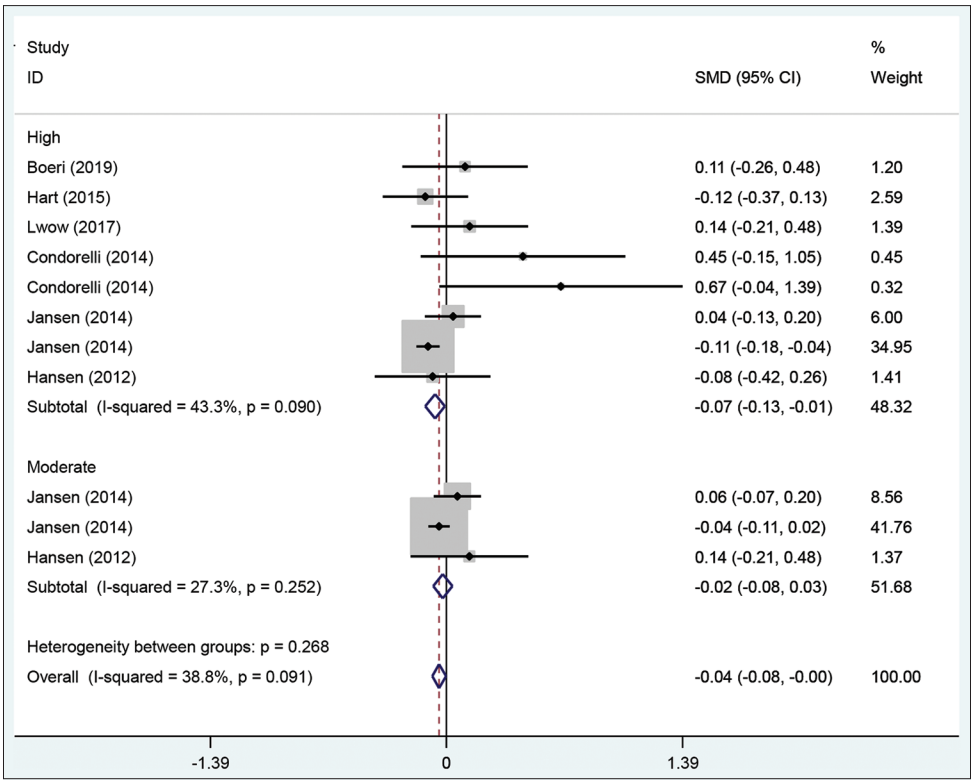

Figure 4: Standardized mean difference of FSH between the two groups exposed to moderate and high alcohol consumption compared to the group exposed to low alcohol consumption

B) Comparison of FSH levels between groups exposed to moderate and high alcohol consumption and those exposed to a low level of alcohol: The comparison of FSH levels between groups exposed to moderate and high alcohol consumption versus those exposed to a low level of alcohol was reported in eight and three primary evidence cases, respectively. Among the eight cases comparing FSH levels between high and low alcohol consumption groups, the average FSH level was lower in the high alcohol consumption group in three cases, with statistical significance observed in only one case. Combining the results of these eight cases by using the fixed effect model (I-squared: 43.3%, Q: 12.35, $P = 0.090$), the standardized mean difference of FSH in the high alcohol consumption group was estimated as −0.07 (95% CI: −0.13 to −0.01) compared to the low alcohol consumption group, with statistical significance [Figure 4].

Among the three cases comparing FSH levels between moderate and low alcohol consumption groups, the average FSH level was lower in the moderate alcohol consumption group in one case, although this difference was not statistically significant. Combining the results of these three cases by using the fixed effect model (I-squared: 27.3%, Q: 2.75, $P = 0.252$), the difference in standardized mean FSH between the moderate and low alcohol consumption groups was estimated as −0.02 (95% CI: −0.08–0.03), which was not statistically significant [Figure 4].

Furthermore, combining the results of all 11 cases by using the fixed effect model, the difference in standardized mean FSH between groups exposed to medium and high doses of alcohol compared to those exposed to low doses was calculated as -0.04 (95% CI: −0.08 to −0.00), with statistically significant differences observed [Figure 4].

Relationship between alcohol consumption and LH

A) Comparison of LH between groups exposed and not exposed to alcohol: The average LH levels between groups exposed and not exposed to alcohol were compared in 22 cases derived from 17 primary studies. Alcohol consumption levels were categorized as high in eight cases, moderate in five, low in three, and unknown in six. Among the primary evidence, seven cases showed lower average LH levels in the alcohol-exposed group, with statistically significant differences observed in two cases. Conversely, in 15 cases, the average LH levels were higher in the alcohol-exposed group, with only one case showing statistically significant differences. The heterogeneity indices indicated high heterogeneity among the results of the primary studies (I-square: 78%, Q: 95.26, $P < 0.001$).

Combining these 22 cases by using the random effects model, inverse variance method, and Cohen's test, the standardized mean difference of LH in the alcohol-exposed group was estimated as 0.04 (95% CI: −0.04–0.12) compared to the non-exposed group, with no statistically significant difference observed. Subgroup analysis revealed

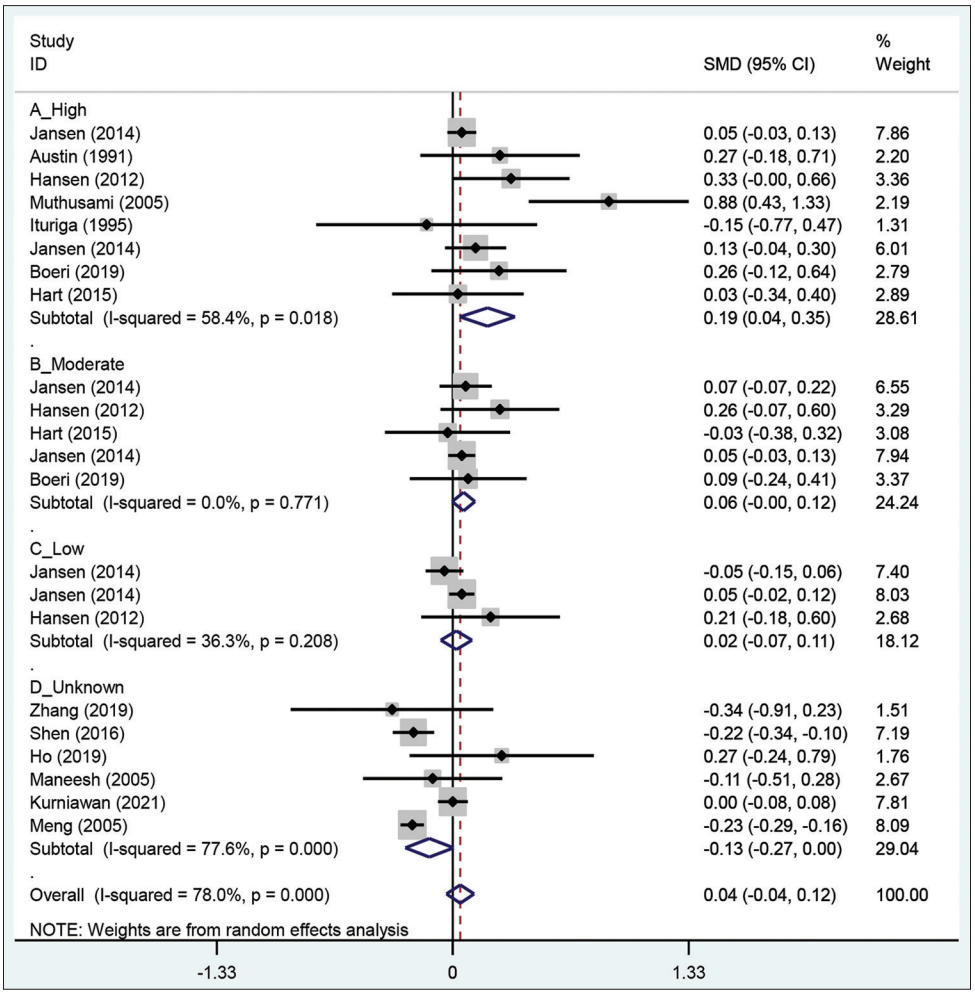

Figure 5: Standardized mean difference of LH between the two groups exposed and not exposed to alcohol

average standardized differences of LH in the high, medium, low, and unknown alcohol dose groups as 0.19 (95% CI: 0.04–0.35), 0.06 (95% CI: −0.00–0.12), 0.02 (95% CI: −0.07–0.11), and −0.13 (95% CI: −0.27–0.00), respectively, compared to the non-exposed group, with statistically significant differences observed only in the high-dose alcohol consumption group [Figure 5].

Egger's test (β = 1.24, P = 0.093) indicated no publication bias. In addition, sensitivity analysis showed that the effect of each primary study on the overall estimate was similar [Figure 7].

B) Comparison of LH between groups exposed to high and moderate alcohol consumption and those exposed to low alcohol: The comparison of LH levels between groups exposed to high and moderate alcohol consumption and those exposed to low alcohol was reported in eight and three primary evidence cases, respectively. Among the eight cases comparing LH levels between high and low alcohol consumption, all eight cases showed higher average LH levels in the high alcohol group compared to the low alcohol group, with statistically significant differences observed in only one case. Combining the results of these eight cases by using the fixed effect model (I-squared: 15.5%, Q: 8.29, P = 0.308), the average standardized difference of LH in the high alcohol group was estimated as 0.04 (95% CI: −0.01–0.10) compared to the low alcohol group, with no statistically significant difference observed [Figure 6].

Among the three cases comparing LH levels between moderate and low alcohol abuse, all three cases showed higher average LH levels in the moderate alcohol abuse group compared to the low alcohol abuse group, but this difference was not statistically significant. Combining the results of these three cases by using the fixed effect model (I-squared: 25.7%, Q: 69, P = 0.260), the standardized mean difference of LH in the moderate alcohol group compared to the low alcohol group was estimated as 0.02 (95% CI: −0.03–0.08), which was not statistically significant. [Figure 6]

Furthermore, combining the results of all 11 cases by using the fixed effect model, the average standardized difference of LH in the moderate and high alcohol consumption group compared to the low alcohol consumption group was estimated as 0.03 (95% CI: −0.01–0.07). It is important to

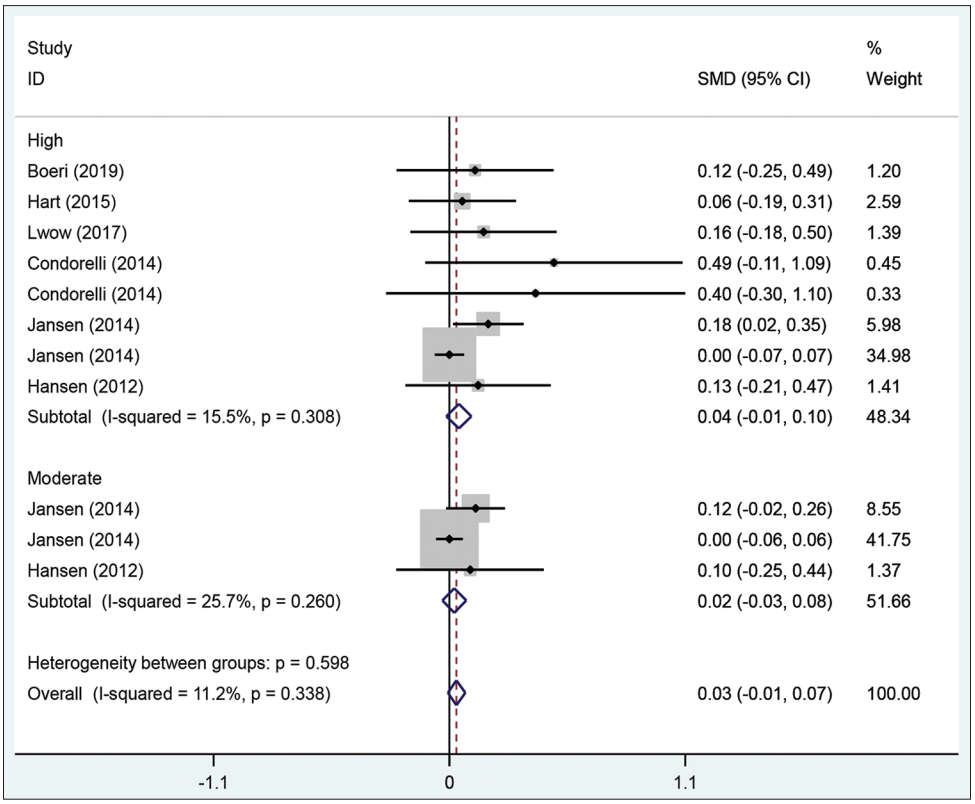

Figure 6: Standardized mean difference of LH between the two groups exposed to moderate and high alcohol consumption compared to the group exposed to low alcohol consumption

note that these differences were not statistically significant.

Relationship between alcohol consumption and testosterone

A) Comparison of testosterone between groups exposed and not exposed to alcohol: Testosterone levels were compared between groups exposed and not exposed to alcohol in 24 cases derived from primary studies. Alcohol consumption levels were categorized as high in nine cases, moderate in five, low in three, and unknown in seven. Among the primary evidence, eight cases showed lower average testosterone levels in the alcohol-exposed group compared to the non-exposed group, with statistically significant differences observed in four cases. In 16 cases, statistically significant differences were observed.

The results of the subgroup analysis based on alcohol consumption dose are provided in Table 2. Heterogeneity indices revealed high heterogeneity among the results of primary studies (I-square: 93.2%, Q: 340.13, $P < 0.001$).

Combining these 24 cases by using the random effects model, inverse variance method, and Cohen's test, the standardized mean difference of testosterone in the alcohol-exposed group was estimated as 0.03 (95% CI: −0.11–0.16) compared to the non-exposed group. The confidence interval suggests that this difference was not statistically significant. Furthermore, according to the subgroup analysis, the average standardized difference of testosterone in the high, medium, low, and unknown alcohol dose groups was estimated as 0.03 (95% CI: −0.21–0.27), 0.22 (95% CI: 0.12–0.32), 0.19 (95% CI: 0.04–0.35), and −0.53 (95% CI: −0.94 to −0.12), respectively, compared to the non-exposed group. Statistically significant differences were observed in the medium and low-dose alcohol groups.

B) Comparing testosterone between the group exposed to high and medium alcohol with the group exposed to low alcohol: comparison of testosterone between the group exposed to high and medium alcohol and the group exposed to low alcohol was reported in eight and three cases of the primary evidence, respectively. Among eight cases of the documents comparing the T levels between high alcohol dose and low alcohol dose, in three cases, the average T level in the group with high alcohol dose was lower than that of the group with low alcohol dose. By combining the results of these eight cases of the evidence by using the fixed effect model (I-squared: 77.1%, Q: 30.54, $P < 0.001$), the average standardized difference of testosterone in the group exposed to high doses of alcohol was estimated as −0.06 (95% CI: −0.25–0.13) compared to the group exposed to low doses. This difference was statistically significant. Among the three cases of the documents comparing the T levels between moderate alcohol dose and low alcohol dose, in all three cases of the evidence, the average T level in the group with moderate alcohol consumption dose was higher than that of the group with low alcohol consumption dose. The

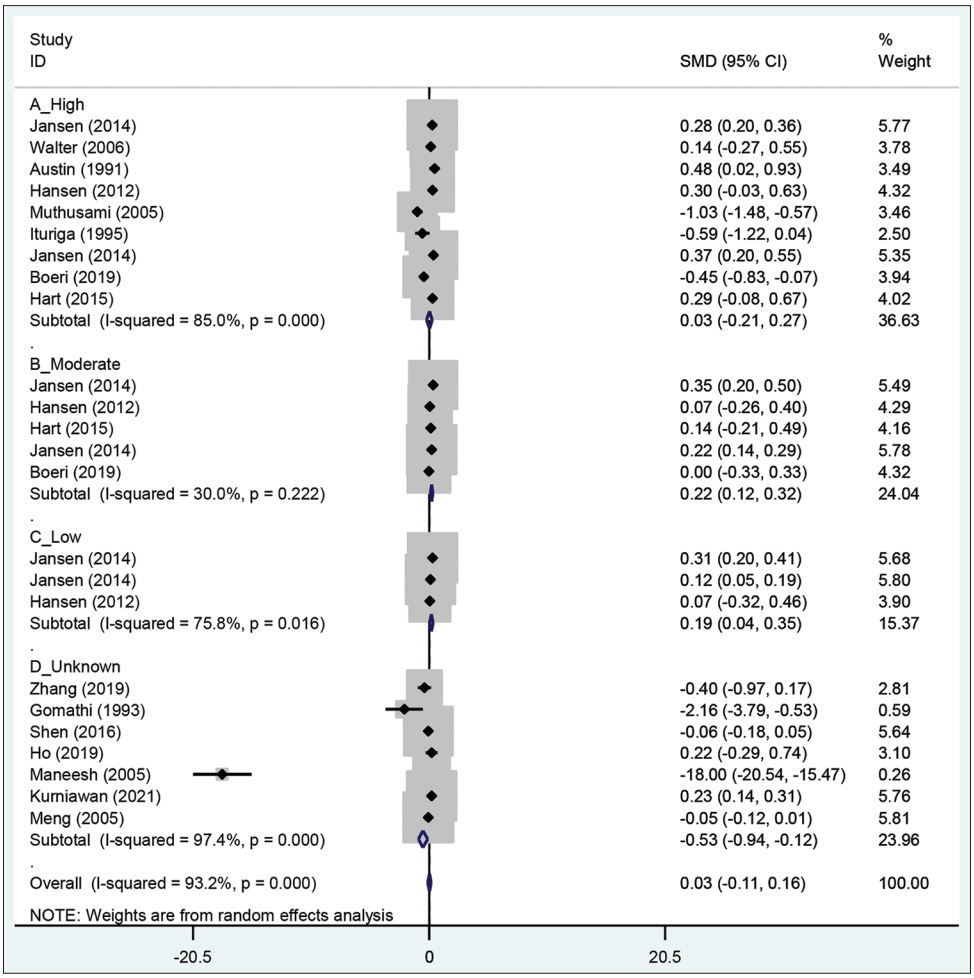

Figure 7: Standardized mean difference of testosterone between two groups exposed and not exposed to alcohol

differences were statistically meaningful in only one of the cases. By combining the results of these three cases of the evidence by using the fixed effect model (I-squared: 0%, Q: 0.54, $P = 0.765$), the average standardized difference of testosterone in the group exposed to a medium dose of alcohol was estimated as 0.09 (95% CI: −0.04–0.15) compared to the group exposed to a low dose of alcohol, which was not statistically significant. In addition, by combining the results of these 11 cases of the evidence by using the fixed effect model, the average standardized difference of testosterone in the group exposed to medium and high alcohol consumption was estimated as 0.04 (95% CI: −0.06–0.14) when compared to the group exposed to low alcohol consumption. It is required to state that the differences were statistically significant [Figure 8].

Discussion

The present systematic review and meta-analysis investigated the effects of alcohol consumption on LH, FSH, and testosterone in men. The research findings revealed changes in the serum levels of these hormones in individuals consuming alcohol compared to those not consuming alcohol or consuming minimal amounts. It was observed that as alcohol consumption increased, the level of LH also increased. However, the combined results indicated a decline in testosterone levels.

In men, testosterone is primarily produced in Leydig cells. The quantity of active Leydig cells is directly influenced by LH and FSH. Testosterone production is ultimately regulated by LH and controlled by the hypothalamus-pituitary-testis axis[30,31] If Leydig cells fail to adequately produce testosterone, the concentration of LH increases as a feedback mechanism to stimulate testosterone secretion. Several studies have analyzed the effect of ethanol on Leydig cell function, with results indicating negative impacts on testosterone production. Generally, ethanol's adverse effects on testosterone production from Leydig cells are associated with increased production of free radicals and dysfunction of enzymes involved in testosterone synthesis.[32,33] In Widenius' study, the increased ratio of NADH/NAD+ in Leydig cells resulting from the exposure to ethanol suppressed the reactions catalyzed by 3 beta-hydroxy-5-ene-steroid dehydrogenase/5-ene-4-ene isomerase, which indicates the negative effect of the exposure to methanol on testosterone synthesis.[34,35] The combination results in our study also demonstrate decreased testosterone concentration and

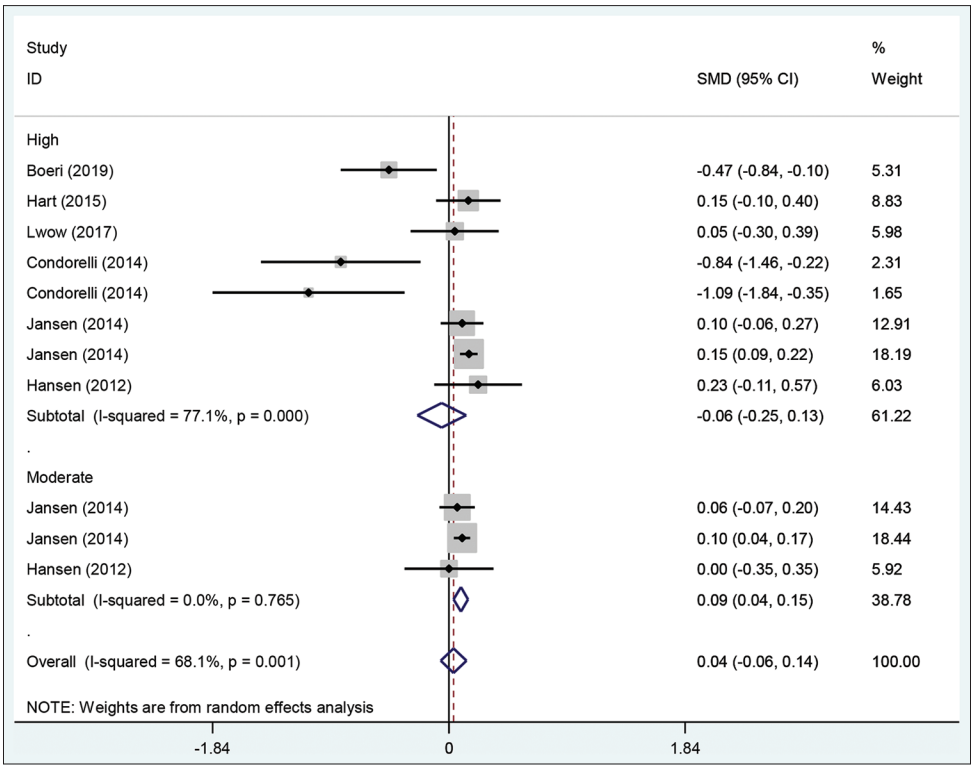

Figure 8: Standardized mean difference of testosterone between the two groups exposed to moderate and high alcohol consumption compared to the group exposed to low alcohol consumption

increased LH concentration (which is probably done to stimulate the secretion of testosterone) in individuals who consume alcohol compared to those not consuming alcohol or consuming a small amount of alcohol, which reported it not being statistically significant.

Sperm production in the testis is influenced by testosterone; therefore, as the study results display, it is expected that following the testosterone production decrease in individuals with heavy alcohol consumption, some degree of sperm production disorder is also expected to be observed. During a meta-analysis study surveying the alcohol consumption effect on semen quality, it was pointed out that daily alcohol consumption leads to negative effects on semen volume and morphology.[36] Despite the importance of the observed complication, it is not completely clear whether it is permanent or temporary, and some longitudinal studies are required to deal with this issue.

Other studies investigated the alcoholism risk based on sex hormone level, the results of which were not conclusive, but generally there was a greater chance of alcoholism in human and animal subjects with higher estrogen levels.[1] Although the studies reviewed in our meta-analysis were designed and performed pursuing the goal to analyze the alcohol effects on the levels of male sex hormones, other assumptions should also be considered.

The present study had several limitations, among which the following can be mentioned: 1) There was significant statistical heterogeneity among the included studies. To address this issue, subgroup analyses were conducted to identify the potential sources of heterogeneity; 2) Limited data of the study subjects and the impossibility of further subgroup analyses; 3) Different categories of alcohol consumption in different studies, including the frequency of alcohol consumption, the volume of alcohol consumption per day or week, and the consumption of low quantities of alcohol versus no alcohol consumption.

The results of the present study were largely consistent with previous review studies. Nguyen-Thanh *et al*.[37] also reported decreased levels of LH, FSH, and testosterone in individuals using alcohol, alongside other changes in semen analysis. The slight differences observed between the two distinct studies underscore the importance of revising the methods used in primary studies.

Conclusions

Pursuant to the results of our study, the negative significant effect of alcohol consumption on LH and testosterone levels was reported. According to the study results, it is better to focus on the effects of heavy alcohol consumption on male fertility in addition to the psychological and social effects of alcohol. Moreover, Designing comprehensive studies would aid in evaluating the impact of consuming various amounts of alcohol on the hypothalamus-pituitary-testis hormonal system and its subsequent influence on male fertility.

Ethics approval and consent to participate

The present study was approved by Mazandaran University of Medical science ethical committee (IR.MAZUMS.REC.1397.1097). All ethical principles of the Helsinki ethical declaration have been met and written informed consent were obtained from all the participants

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MA, AH, KH, KR, SA, MA, AB, RN, MK, FM and MM acquired data, performed the risk of bias, data extraction, statistical analyses, interpreted data, and drafted and revised the manuscript for important intellectual content and approved the final version. SK and MM interpreted data, reviewed the analyses and approved the final version. All authors have read and approved the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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