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REVIEW ARTICLE

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The association between cannabis use and testicular function in men: A systematic review and meta-analysis

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Abstract

Objective: To evaluate the association between cannabis use and testicular function (as assessed through semen quality and serum hormone levels) in different populations.

Evidence Review: Systematic review and meta-analysis of population-based retrospective cohort studies. PRISMA guidelines were used for abstracting data and assessing data quality and validity. Data were pooled using a fixed-effects or random-effects model depending on the heterogeneity of studies included. Pooled risk ratio (RR) of having any sperm abnormality and testosterone, FSH, and LH standardized mean differences among male cannabis users and non-users, and meta-regression analysis according to age and year of publication.

Results: Nine studies were evaluated which included 4014 men with semen data and 4787 with hormonal data. Overall among 1158 cannabis users, 44.9% had impaired semen parameters, compared with 24.5% of the 2856 non-users. The relative risk among cannabis users for any abnormal semen parameter was 1.159 (95% CI: 0.840; 1.599, $P = 0.369$). The standardized mean difference between user and non-user testosterone levels was −0.139 (95% CI: −0.413; 0.134, $P = 0.318$). For FSH, the standardized mean difference estimate was −0.142 (95% CI: −0.243; −0.0425, $P = 0.005$), while for LH the standardized mean difference estimate was −0.318 (95% CI: −0.810-0.175; $P = 0.206$).

Conclusions: The current evidence does not suggest clinically significant associations between cannabis use and testicular function. However, we cannot exclude an effect of cannabis because of the limited and heterogeneous studies. Additionally, well-designed studies will be needed to define the association between cannabis use and the male reproductive system.

KEYWORDS
cannabis, FSH, LH, male infertility, spermatozoa, testosterone

1 | INTRODUCTION

Approximately 15% of couples are not able to achieve pregnancy after 1 year of trying and are classified as infertile.[1] Within couples, male factor infertility contributes roughly 50% of cases.[2] Cannabis use has been implicated in impaired fertility; however, its effect on semen parameters and reproductive hormone profiles remains uncertain.[3,4]

Cannabis is one of the most commonly used drugs and is becoming increasingly legalized within the United States and worldwide. The number of US cannabis users increased by 60% between 2007 and 2017, and almost 10 million are daily or near-daily users. Roughly 3.8 percent of the global population aged 15-64 years used cannabis at least once in 2017.[5] To date, in the United States, thirty-three states and the District of Columbia have passed laws broadly legalizing cannabis[6] and other countries are following.

The active component of cannabis is D9-tetrahydrocannabinol (THC), which binds cannabinoid receptors present in the brain, the nervous system, and, among other locations, the reproductive organs.[7] There has been conflicting literature regarding the effect of cannabis on the reproductive system; however, recent reviews and studies using both animal and human systems have suggested that cannabis impairs male fertility, semen quality, and hormones levels.[8-13] In contrast, others have reported no changes in semen parameters and testosterone levels among cannabis users.[14-17] In addition, many studies have been conducted among men with very high intake and are therefore may not be applicable to all users.

As most of the cannabis consumers are males of reproductive age[18] and prior literature is heterogeneous regarding the association between cannabis use and testicular function, it is important to further investigate. The aim of this systematic review and meta-analysis was to critically evaluate the literature for the association between cannabis use and testicular function (ie, semen parameters, testosterone, and gonadotropins).

2 | MATERIALS AND METHODS

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following research question was established based on the PICO criteria[19]: What is the association in men of smoking cannabis and testicular function as measured by semen quality, testosterone levels, and gonadotropins? Furthermore, our goal was to compare current evidence within available studies.

2.1 | Evidence acquisition

We performed a systematic review of the literature in PubMed, Embase, and Cochrane from inception to January 2020, to identify studies that evaluated cannabis use, semen analysis, and hormonal profiles. Search terms included "marijuana/cannabis and semen parameters", "marijuana/cannabis and sperm concentrations"," marijuana/cannabis and sperm count", "marijuana/cannabis and sperm morphology", "marijuana/cannabis and testosterone", "marijuana/cannabis and FSH levels", "marijuana/cannabis and LH levels"; secondary fields: male general health; male infertility; male hypogonadism; male factor infertility; infertility.

The reference lists of the included studies were also screened for relevant articles. Nine original population-based retrospective cohort studies, one original prospective population-based cohort study, and two cross-sectional studies were included and critically evaluated (Level of Evidence: III-2).

2.2 | Selection of the studies and criteria of inclusion

This analysis was restricted to data collected from original articles that examined men using cannabis presenting with semen analysis and/or hormonal profiles (testosterone, FSH/LH). Studies were considered eligible if an internal or external control populations enrolled were defined by age-matched men (age > 18 years old) who had never consumed cannabis also presenting with semen analysis and/or hormonal profiles (testosterone, FSH/LH).

Articles were excluded if they met one or more of the following criteria: presence of men who have undergone testosterone replacement or other gonadotoxic hormonal treatments. Case-control cohort studies, case reports, abstracts, and meeting reports were excluded from the analysis.

Two authors (FB and FDG) independently screened the titles and abstracts of all articles. The full-text articles were examined independently by three authors (FB, FDG, and AK) to determine whether or not they met the inclusion criteria. Final inclusion was determined by the consensus of all investigators. Selected articles meeting the inclusion criteria were then critically analyzed.

The following data were extracted from the included studies by using a standardized form: country of origin, publication year, sample size, participant age, number of cannabis smokers, numbers of control, population description, and main findings of the study.

2.3 | Assessment of quality for studies included and statistical analysis

To assess the risk of bias (RoB), each report was reviewed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[20] The authors independently assessed the methodological quality based on sequence generation, allocation concealment, enrollment of control groups, incomplete outcome data, selective outcome reporting, and additional sources of bias. Publication bias was tested by visual assessment of the Deeks' funnel plot.[21] We compared effects on subfertile semen parameters using pooled relative risk and 95% confidence intervals (CIs). Variability in

the intervention effects as a consequence of clinical or methodological diversity, for example, the reason for semen analysis, among the studies was evaluated in form of heterogeneity.[22] According to heterogeneity assessment, the pooled relative risk estimate was calculated using a fixed-effects or random-effects model.[23] We compared effects on total testosterone, LH, and FSH using the pooled standardized mean difference estimate as the studies we included presented their results in terms of average hormone levels. Our results are graphically displayed as forest plots, with pooled relative risk and standardized mean difference indicating overall risk for cannabis using men to present with impaired semen and hormonal analyses, respectively. Evaluation for presence of heterogeneity was done using[24] (a) Cochran's Q test with $P < 0.05$ signifying heterogeneity; (b) Higgins I^2 test with inconsistency index (I^2) = 0%–40%, heterogeneity might not be important; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75%–100%, considerable heterogeneity. Sensitivity analysis with and without men recruited in fertility clinic was performed for testosterone, FSH, and LH in order to investigate possible bias, but no differences were observed. The number of studies investigating semen parameters in men not recruited in a fertility clinic was too small to perform a sensitivity analysis.

Meta-regression was performed to explore potential bias to the overall effects, and the proportion of the studies was assessed by a random-effects regression model. Calculations were accomplished using the Comprehensive Meta-Analysis Software, version v.2 0.0 (CMA, Biostat).

3 | RESULTS

3.1 | Search results

The initial search yielded 274 articles (PubMed: 208; Cochrane: 55; and Embase: 11). 183 were excluded as they were duplicates appearing in multiple databases. Of the remaining 91, 76 were further excluded as they either did not examine cannabis effects on conventional semen parameters,[1] contained animal experiments,[17] or were review papers or editorials.[10] Full-text articles were then reevaluated and critically analyzed for the remaining 15 articles. After another in-depth review, a further six did not meet the inclusion criteria. The remaining nine studies were included in our review (Figure 1); four of them were used in the semen parameters analysis, six for the testosterone analysis, and four for the gonadotropin analysis. RoB assessment according to NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies for each of the individual studies is illustrated in Figure S1.

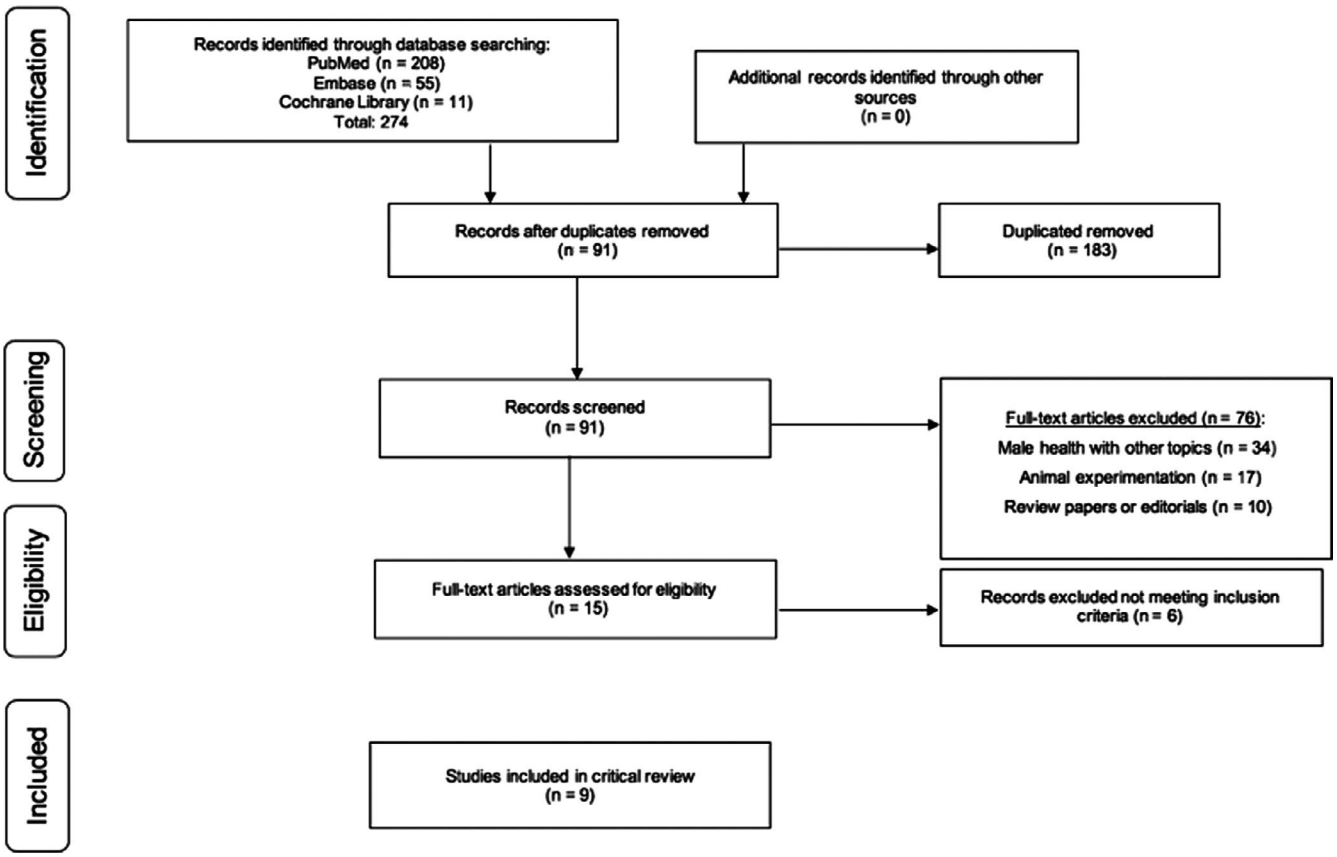

FIGURE 1 PRISMA flow diagram

3.2 | Study location, types, and populations

The patient description, main findings, and study characteristics of each article are summarized in Table 1. Of the nine studies included, five were conducted in the United States,[9,14-17] three in Europe (Denmark, UK, and Italy),[10-12] and one in Jamaica.[13] Four studies investigated only hormone levels in a cannabis user group versus a non-user group.[9,10,14,19] Five studies recruited men evaluated at an infertility clinic.[11,13,17,18,20] One study examined semen parameters and hormone profile in cannabis users who participated in the Danish military draft,[12] while two studies analyzed data from male participants of the US National Health and Nutrition Examination Survey (NHANES).[15,19] The final study recruited physically active men from a university campus.[16]

3.3 | Study sample sizes, participant ages, and meta-regression results

In total, 520 (44.9%) men had impaired semen parameters among 1158 cannabis users. Among 2856 non-users, 699 (24.5%) men had an impaired semen analysis which was defined as the presence of any abnormal parameter according to the WHO 5th edition reference values. A man was then defined as having "normal" sperm if all values were within the normal reference range or "subfertile" spermatozoa if any value was abnormal. With regard to testosterone levels, there were a total of 1717 cannabis users and 1458 non-users while LH and FSH levels were assessed in 735 cannabis users and 823 non-users. Detailed information regarding the frequency/duration of cannabis use was not consistently available and thus a sub-analysis could not be performed. Meta-regression analyses were performed in order to investigate the association of moderator variables on study effect size using regression-based techniques. The regression results showed that the year of publication affected overall effects of cannabis use on semen parameters (slope estimate: −0.129; 95% CI: −0.190, −0.069; $P < 0.001$) and testosterone levels (slope estimate: 0.026; 95% CI: 0.003, 0.048; $P = 0.026$), while age affected semen parameters (slope estimate: −0.021; 95% CI: −0.033, −0.010; $P < 0.001$) and FSH levels (slope estimate: −0.019; 95% CI: −0.032, −0.005; $P = 0.007$) (Figure S2).

3.4 | Association between cannabis use and semen parameters

The six studies analyzing semen parameters reported the association of any abnormality (using WHO 5th edition reference values) with cannabis consumption with a range of RR estimates from 0.829 to 1.502. The pooled relative risk for any abnormal semen parameter under a random-effects model was 1.159 (95% CI: 0.840;1.599, $P = 0.369$) (Figure 2A) with evidence for heterogeneity between the studies (Q = 19.4813 ($df = 3$), $P = 0.0002$; $I^2 = 84.60\%$). A sub-analysis of the three studies with morphology data (ie, men with <4% of morphologically normal spermatozoa) was performed (Figure 3B). The pooled relative risk of abnormal morphology with cannabis use under a random-effects model was 0.899 (95% CI: 0.557; 1.451, $P = 0.663$) with a considerable heterogeneity between the studies: Q = 12.9128 ($df = 2$), $P = 0.0016$; $I^2 = 84.51\%$.

3.5 | Association between cannabis use and total serum testosterone concentration

The eight studies analyzing testosterone levels in relation to cannabis consumption had standardized mean difference estimates from −2.259 to 0.192. The pooled standardized mean difference estimate under a random-effects model was −0.139 (95% CI: −0.413; 0.134, $P = 0.318$) (Figure 3) with evidence of heterogeneity between the studies (Q = 39.1372 ($df = 5$), $P < 0.0001$; $I^2 = 87.22\%$). Inspection of the funnel plot suggests that there was a small-study effect with Kolodny et al's analysis tending to have smaller standardized mean difference estimates. Therefore, we developed a second analysis without this particular study which revealed a pooled standardized mean difference estimate under a fixed-effects model of 0.0999 (95% CI: 0.0288-0.171) ($P = 0.006$) without significant heterogeneity between the studies (Q = 4.6084 ($df = 4$), $P = 0.3299$; $I^2 = 13.20$).

3.6 | Association between cannabis use and serum FSH and LH concentrations

The five studies analyzing serum FSH and LH levels in relation to cannabis consumption reported standardized mean difference estimates from −3.207 to 0.136 for LH and −0.718 to −0.0000000160 for FSH. For FSH, the pooled standardized mean difference estimate under a fixed-effects model was −0.142 (95% CI: −0.243; −0.0425, $P = 0.005$) with an absence of considerable heterogeneity between the studies (Q = 10.3188 ($df = 3$), $P = 0.0160$; $I^2 = 70.93\%$) (Figure 4A). For LH, the pooled standardized mean difference estimate under a random-effects model was −0.318 (95% CI: −0.810 to 0.175; $P = 0.206$) with considerable heterogeneity between the studies (Q = 28.3352 ($df = 3$), $P < 0.0001$; $I^2 = 89.41\%$) (Figure 4B).

4 | DISCUSSION

The present meta-analysis did not identify an association between cannabis use and testicular function. Specifically, the current analysis was unable to demonstrate impairment of semen quality in general, or on morphology, specifically with cannabis use. With regard to the association of cannabis on reproductive hormones, total testosterone levels did not differ significantly between cannabis users and non-users. LH levels were not different between cannabis users and non-users, while FSH levels were lower in cannabis users compared with non-users. While the effects of cannabis on FSH levels were statistically significant, the changes were quantitatively small

TABLE 1 Characteristics the studied included assessing association between cannabis use and fertility status, sperm morphology, testosterone, FSH, and LH levels

Author	Year	Country	Study Design	Sample size	Age (years)	Population description	Outcome analyzed	Main findings
Kolodny et al	1974	USA	Prospective cohort study	20 users 20 controls Total:40	18-28	Heterosexual men with continuing pattern of marihuana smoking	Testosterone	Decreased mean value of testosterone in cannabis users compared to non-users.
Cushman et al	1975	USA	Cross-sectional cohort study	25 users 13 controls Total: 38	18-28	Marijuana smokers were recruited from a major New York City university	Testosterone, FSH, LH	No differences in testosterone, FSH, and LH levels in cannabis users compared with non-users.
Vescovi et al	1992	Italy	Cross-sectional cohort study	10 users 10 control Total: 20	29-20	Ten male chronic marijuana users	FSH, LH	Reduced LH levels in cannabis users compared to non users
Pacey et al	2014	UK	Cross-sectional cohort study	318 cases 1652 controls Total: 1970	18-51+	Men with poor sperm morphology (< 4% normal forms based on 200 sperm assessed) recruited in a fertility clinic	Fertility status, sperm morphology	The use of cannabis in men aged <= 30 years is a risk factor for poor sperm morphology
Gundersen et al	2015	Denmark	Cross-sectional cohort study	554 users 661 controls Total: 1215	Average age: 18.1	Danish men attending a compulsory medical examination to determine their fitness for military service	Fertility status, sperm morphology, testosterone, FSH, LH	Regular marijuana smoking was associated with a 28% lower sperm concentration and a 29% lower total sperm count. Increased testosterone levels in cannabis users compared with non-users
Thistle net al	2017	USA	Cross-sectional cohort study	962 users 614 controls Total: 1576	18-50+	Men from the 2011-2012 US National Health and Nutrition Examination Survey (NHANES)	Testosterone	No differences in testosterone levels between cannabis users and non-users
Lisano et al	2017	USA	Cross-sectional cohort study	10 users 11 control Total: 21	Average age: 23.71 +- 4.78	Physically active (at least 150 min of moderate intensity or 75 min of vigorous intensity exercise per week) males recruited in a collage campus	Testosterone	No differences in testosterone levels between cannabis users and non-users
Nassan et al	2019	USA	cross-sectional cohort study	365 users 297 controls Total:662	Average age: 36.3 +- 5.11	Men recruited in a fertility clinic	Fertility status, testosterone, FSH, LH	Cannabis users had a significantly higher sperm concentrations and significantly lower follicle-stimulating hormone (FSH) concentrations
Carrol et al	2019	Jamaica	cross-sectional cohort study	107 users 122 controls Total: 229	Average age: 37.63 +- 7.56	Men recruited in a fertility clinic	Fertility status, sperm morphology	Cannabis users were at greatest risk of being diagnosed with abnormal motility (asthenozoospermia) and to be diagnosed with abnormal morphology (teratozoospermia)

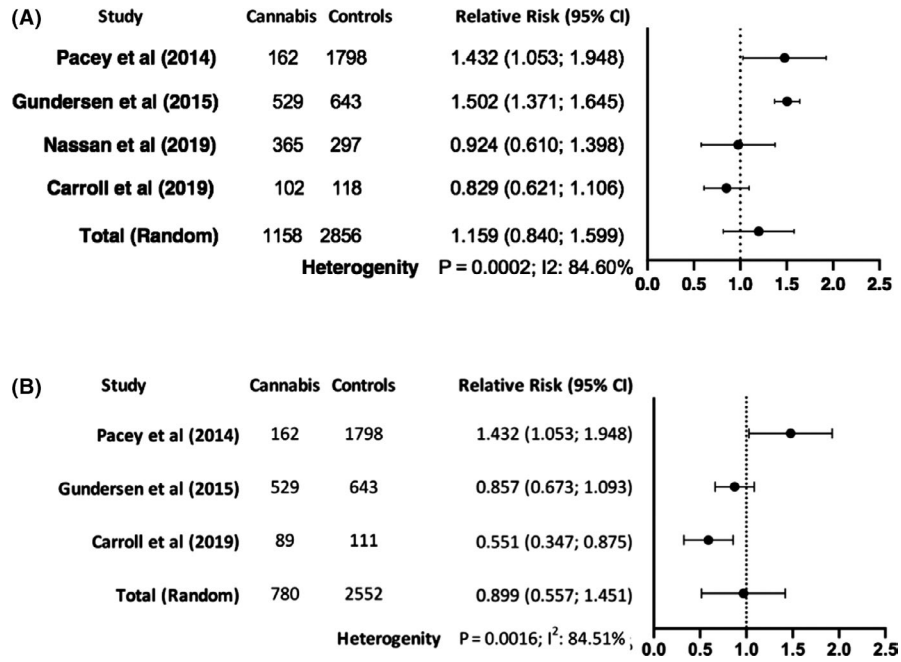

FIGURE 2 Relative risk of (A) impaired semen quality; (B) sperm morphology abnormalities in cannabis users. CI: confidence interval; I^2: inconsistency

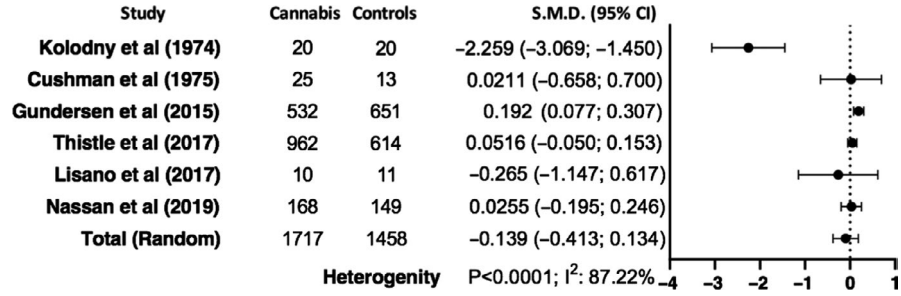

FIGURE 3 Standardized mean difference in testosterone levels between cannabis users and non-users. S.m.d.: standardized mean difference; CI: confidence interval; I^2: inconsistency

making the clinical significance uncertain. By meta-regression analysis, it was found that the year of publication was associated with the relative risk of cannabis use and impaired semen parameters as well as the standardized mean differences in testosterone levels in cannabis users and non-users suggesting a temporal trend in the reported associations. Importantly, the lack of any negative associations between cannabis use and semen quality does not imply evidence of safety.

The existing literature is heterogenous in describing the associations of cannabis on male fertility. In particular, current studies appear to be conflicting with several demonstrating a possible link between cannabis consumption and abnormal semen analysis while others do not. Pacey et al compared 318 cannabis users to 1652 non-users and demonstrated that cannabis use is a risk factor for poor sperm morphology.[11] Gundersen et al examined 1215 men, median 19 years old, from the general population, and thus were unselected regarding testicular function. They detected that cannabis use was associated with lower sperm concentration and total sperm count.[12] Similarly, Carrol and colleagues reported that cannabis users examined in a fertility clinic were at greater risk of being diagnosed with asthenozoospermia and teratozoospermia.[13] In contrast, Nassan et al showed that cannabis users among men from infertile couples had significantly higher sperm concentrations.[17]

The literature is similarly discordant regarding the effect of cannabis use on total testosterone levels. Most studies in our analyses suggest that there is no difference in testosterone levels between cannabis users and non-users; however, several showed a significant effect.[14-16] Two studies suggested that cannabis users had higher testosterone levels.[12,15] In contrast, Kolodny et al reported a decrease in mean total testosterone levels in subjects using cannabis.[9] This study of forty men showed a small-study effect evident in the funnel plot and different results compared with the other studies on the subject.

The association between cannabis and gonadotropins is also mixed in the literature with studies showing positive, negative, and absent associations. The populations studied also varied. While most studies analyzed young men (18-37 years old), two studies examined

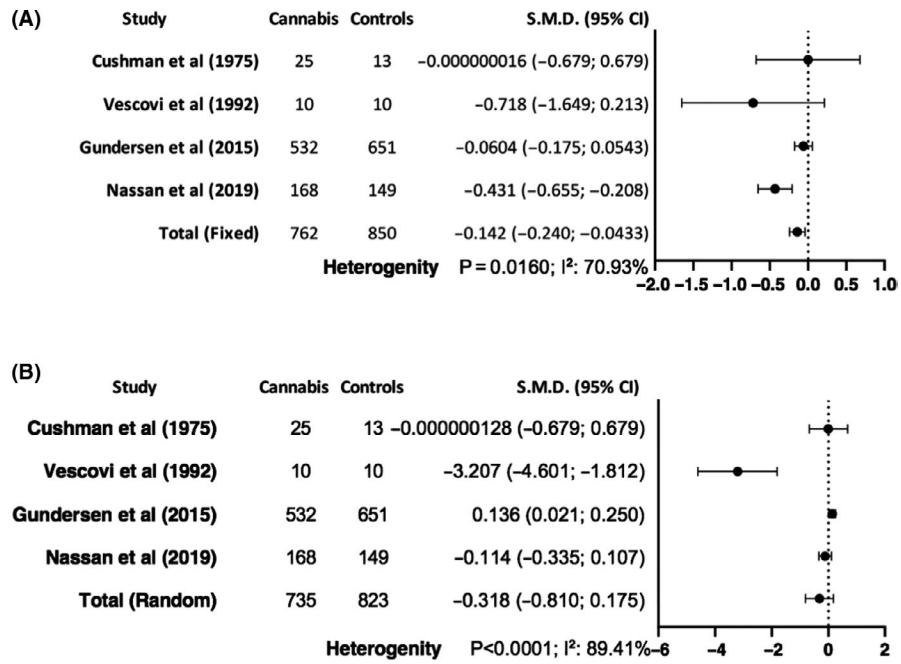

FIGURE 4 Standardized mean difference in (A) FSH levels; (B) LH levels between cannabis users and non-users. S.m.d.: standardized mean difference; CI: confidence interval; I^2: inconsistency

men up to the age of 50.[11,15] Populations were also heterogenous with regard to recruitment. Three studies recruited men from fertility clinics,[11,13,17] and two studies recruited men from college campuses complicating comparisons between reports.[14,16] The rate of cannabis use in our study is different from the one reported by 2019 WHO Drug report (41.3% vs 3.9%) as most of the studies we included analyzed similar numbers of users and non-users (case-control design) to better compare testicular function in the two populations.

As the clinical utility of semen values has been questioned,[25,26] cannabis use has also been investigated in relation to fecundability. Kasman et al examined a representative sample of US men and women and found no significant association between cannabis use and time to pregnancy across all cannabis user groups including daily smokers.[27] Wise et al analyzed data from couples attempting to conceive and found male cannabis consumption at levels of ≥ 1 time/week was associated with an increase in fecundability.[28] Nassan et al followed 421 women who underwent 730 ART cycles and evaluated the association of baseline cannabis smoking with ART outcomes. 200 of these women (368 cycles) were part of a couple in which the male partner's cannabis use was also studied. No statistically significant differences have been showed in the probabilities of implantation, clinical pregnancy, or live birth according to women's cannabis use. In contrast, when the male partner reported cannabis use at enrollment, the couple had a significantly higher probability of live birth, independent of the women's cannabis smoking status.[29] Given the increasing legalization of cannabis worldwide, particularly in the United States, this subject requires further research in regard to both laboratory and clinical endpoints. This is particularly true for those undergoing IVF, as Domar et al found many infertility patients do not follow recommendations on lifestyle habits while undergoing IVF such as utilizing cannabis.[30]

Several limitations warrant mention. First, cannabis use profiles were not reported in most studies which limits the interpretability of the results as the differences in frequency and quantity of cannabis use are common.[31] Such variability in the profiles of cannabis use also prevented the examination of a dose-dependent effect of cannabis use. In addition, while we used a categorization of semen quality according to the WHO reference levels, we cannot exclude the possibility of a difference between users and non-users of cannabis if we analyzed the actual values of semen variables. Additionally, the absence of pregnancy outcomes limits the ability to assess the most important reproductive clinical endpoints of cannabis use. Furthermore, recruitment methods may lead to bias, either related to age or recruitment location (eg, universities versus fertility clinics). Finally, all studies utilized self-reported cannabis use which may be not reliable because of the social stigma or fear of repercussions. However, the current literature does suggest the validity of survey methodology.[32]

5 | CONCLUSION

Currently, the number and quality of the studies focusing on cannabis and reproductive and sexual health remain limited. However, our systematic review and meta-analysis suggests a negligible clinical effect of cannabis use on testicular function. Because of the low number of studies and the heterogeneity of the existing studies, we cannot exclude a potential effect of cannabis on testicular function and the current analysis does not prove safety. Future studies in diverse populations with detailed information on cannabis use are needed to further examine the association between cannabis and male reproductive health.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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