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ORIGINAL ARTICLE

Effects of recreational cannabis on testicular function in primary infertile men

Federico Belladelli[1,2] | Giuseppe Fallara[1,2] | Edoardo Pozzi[1,2] | Christian Corsini[1,2] | Simone Cilio[1,3] | Massimiliano Raffo[1,2] | Alessia d'Arma[1] | Luca Boeri[4] | Paolo Capogrosso[5] | Michael Eisenberg[6] | Francesco Montorsi[1,2] | Andrea Salonia[1,2]

[1]Division of Experimental Oncology/Unit of Urology, URI-Urological Research Institute, University Vita-Salute San Raffaele, Milano, Italy

[2]Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele

[3]Azienda Ospedaliera Universitaria, Federico II, Naples, Italy

[4]Foundation IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milano, Italy

[5]ASST Sette Laghi – Circolo e Fondazione Macchi Hospital, Varese, Italy

[6]Department of Urology, School of Medicine, Stanford University, Stanford, California, USA

Correspondence
Andrea Salonia, Division of Experimental Oncology/Unit of Urology, URI-Urological Research Institute, University Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy.
Email: salonia.andrea@hsr.it

Abstract

Background: Male factor contributes to up to 50% of cases of couples experiencing infertility. Cannabis is one of the most commonly used recreational drugs, and its effects on the reproductive system have been largely debated in the literature.

Objectives: The aim of this study is to evaluate the effect of recreational cannabis use on total T (tT) levels, gonadal status, and sperm parameters in a cohort of primary infertile non-Finnish, white-European men.

Materials and methods: Data of 2074 white-European men visited for primary couple's infertility were analyzed. Lifestyle factors and cannabis use were investigated in all participants. Semen analyses were based on the 2010 World Health Organization reference criteria. Serum hormones were evaluated, and patients were subdivided based on their gonadal status. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI). Descriptive statistics and linear regression analyses were used to test the association between cannabis use, sperm parameters, and hormonal levels. Logistic regression analyses tested potential predictors for abnormal sperm parameters and gonadal status.

Results: Of 2074, 225 (10.9%) patients reported cannabis use in their lifetime. Total Testosterone levels were lower in cannabis users compared to nonusers (p = 0.03). In a multivariable linear regression analysis, cannabis use was inversely associated with tT levels (ß = −0.372 ng/ml; p = 0.005) but not with follicle-stimulating hormone nor with luteinizing hormone levels. Conversely, at multivariable logistic regression model cannabis use was not associated with the type of hypogonadism.

At multivariable linear regression analysis, cannabis use was inversely associated with sperm morphology ($p = 0.007$), while not with both sperm concentration and sperm motility. Similarly, at adjusted logistic regression analysis cannabis use resulted associated with teratozoospermia ($p = 0.039$) but not with oligo-, astheno-, and azoospermia.

Conclusions: Infertile men using cannabis are at higher risk of having lower testosterone levels and altered sperm morphology as compared with nonusers.

KEYWORDS
male infertility, cannabis, testosterone

1 | INTRODUCTION

Overall, 15% of couples are unable to achieve pregnancy after 1 year of intercourse and are classified as infertile, according to the definition of the World Health Organization (WHO).[1] A male factor contributes to up to 50% of cases of couples experiencing infertility.[2] Some modifiable factors have been associated with male factor infertility (MFI), such as diet, obesity, smoking habits, alcohol abuse, and physical exercise.[3,4] Recreational drug use has also been associated with a reduced fertility in up to 4.1% of overall infertile male cases.[5] Hypogonadism is a clinical condition in the male combining low concentrations of circulating testosterone and specific symptoms associated with impaired hormone production.[6]

Cannabis is one of the most commonly used recreational drugs, as worldwide data reported that up to 4% of the adult population used cannabis in their lifetime.[7] The main cannabis active component, Delta-9-tetrahydrocannabinol (THC),[8] acts by binding specific receptors in the central nervous system. Both CB1 and CB2 receptors are expressed also in the reproductive system, thus THC might hypothetically have an impact on reproductive function.[9] Overall, cannabis's effects on the reproductive system have been largely debated in the literature. Several studies and recent reviews involving both animals and humans suggested that cannabis might have negative effects on overall male fertility, by impacting both semen quality and the hormonal milieu.[10–12] Conversely, other studies observed no differences in semen analyses and sex hormone levels between cannabis users and nonusers.[13,14]

Given that infertility has been associated with a reduction of overall men's health,[15,16] that a significant negative association between T levels and mortality has been demonstrated,[6,17] and that infertile men reported a higher use of recreational drugs than other urological patients,[5] the importance of understanding cannabis effects on men's reproductive system is of utmost importance for health practitioners and patients. Thereof, the aim of this study is to evaluate the effect of recreational cannabis use on total T (tT) levels, gonadal status, and sperm parameters in a cohort of primary infertile non-Finnish, white-European men.

2 | METHODS

2.1 | Study population, variables, and outcomes definitions

Data for this retrospective cross-sectional study were obtained from a cohort of the last 2074 non-Finnish white-European men seeking first medical help for primary couple's infertility at a tertiary-referral andrological center. Primary couple infertility was defined as a disease of the reproductive system defined by the failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[1] Data were prospectively collected from medical chart, and all patients were evaluated in a consistent and homogeneous way with a thorough self-reported medical history including age at first visit for fertility assessment, co-morbidities, and a clinical examination at the time of first investigation for couple's infertility.[18]

Measured body mass index (BMI), defined as weight in kilograms by height in square meters, was obtained for each patient. Health-significant comorbidities were scored with the Charlson Comorbidity Index (CCI),[19] further categorized as CCI = 0 or ≥1.[15] Data on cannabis use and other illicit drugs (heroin, cocaine, MDMA et others) habits are commonly collected as a routine question throughout the diagnostic work-up of every infertile man at our center. In this context, cannabis use was defined as a current (>1 time/month in the 12 months before the visit) and/or a past (>1 time/month before the 12 months before the visit) use of the substance. Patients reporting sporadic cannabis assumption (<1 time every 12 months) were considered nonusers. Patients were then segregated into cannabis users versus nonusers. Information on alcohol use and smoking habits were also collected for each case. Testicular volume (TV) was assessed in all cases using Prader's orchidometer estimation by the same urologist.

Venous blood samples were drawn from each patient between 7 and 11 AM after an overnight fast and follicle-stimulating hormone (FSH), luteinizing hormone (LH), tT, and free testosterone were measured at the same Institution. Thereafter, patients were stratified into four groups according to Tajar et al. and Ventimiglia et al[20,21]: eugonadal (tT ≥3.03 ng/ml and LH ≤9.4 mUI/ml), secondary

hypogonadal (tT ≤3.03 ng/ml and LH ≤9.4 mUI/ml), primary hypogonadal (tT ≤3.03 ng/ml and LH ≥9.4 mUI/ml), and compensated hypogonadal patients (tT ≥3.03 ng/ml and LH ≥9.4 mUI/ml). All patients underwent semen coltures and analyses according to WHO 2010 laboratory criteria for semen parameters.[22]

Data collection followed the principles outlined in the Declaration of Helsinki; all patients signed an informed consent agreeing to deliver their own anonymous information for future studies. The study was approved by the IRCCS San Raffaele Hospital Ethical Committee (Prot. 2014—Pazienti Ambulatoriali).

2.2 | Statistical Analysis

Normal distribution of data was tested with the Shapiro-Wilk test. Continuous variables were presented as medians and interquartile ranges (IQRs), categorical variables as numbers and proportions. Student's *T* test and chi-square test were used to assess differences in clinical characteristics, metabolic status, and hormonal parameters between cannabis users and nonusers for continuous and categorical variables, respectively. Univariable and multivariate linear regression analyses were used to test the association of cannabis use and tT levels. In addition, univariable and multivariable logistic regression models tested the association of cannabis use and gonadal status (i.e., primary hypogonadism, secondary hypogonadism and compensated hypogonadism vs. eugonadism, respectively).[20,21] Multivariable analyses were adjusted for other factors possibly associated with MFI, that is, age—according to both EAU and AUA/ASRM guidelines, which indicate higher rates of infertility and offspring health disorders in case of father age over 35 years[2,23]—BMI, CCI, alcohol, cigarette use, and use of other substances of abuse (heroin, cocaine, etc).[3,24,25] The same analyses were performed also to investigate the association between cannabis use and sperm parameters. Statistical tests were performed using RStudio statistical software version 3.4.3 (The R Foundation for Statistical Computing). All tests were two-sided, with a significance level set at 0.05.

3 | RESULTS

3.1 | Characteristics of the study population

Table 1 depicts clinical and sperm characteristics of patients according to cannabis use. Of 2074, 225 (10.9%) patients reported cannabis use in their lifetime. Cannabis users versus nonusers were younger ($p = 0.01$) and had more attitude toward alcohol intake ($p < 0.0001$) and cigarette smoking ($p < 0.0001$). Of note, cannabis users tT levels resulted lower when compared to nonusers ($p = 0.03$). No other significant differences were observed between groups. Of all, 468 (22.6%) patients were hypogonadal, of which 62 (13.3%), 274 (58.5%), and 132 (28.2%) patients depicted criteria for primary, secondary, and compensated hypogonadism, respectively. Figure 1 displays tT levels distribution according to cannabis use and stratified into gonadal status categories.

3.2 | Cannabis use, sperm parameters, and testosterone levels

At multivariable linear regression analysis, cannabis use was inversely associated with tT levels (ß = −0.372 ng/ml; $p = 0.005$) but not with FSH nor with LH levels (Table 2). Conversely, at adjusted logistic regression model cannabis use was not identified as an independent predictor of gonadal status (Table 3). Groups did not differ in terms of sperm concentration and rates of total progressive sperm motility and azoospermia. Conversely, the proportion of men with normal sperm morphology was lower in regular cannabis users versus nonusers ($p = 0.004$). This difference remained significant also when analyzing men with an FSH < 8 UI/L ($p = 0.048$) and > 8 UI/L ($p = 0.020$). At multivariable linear regression analysis, cannabis use was inversely associated with sperm morphology ($p = 0.007$), while not with both sperm concentration and sperm motility (Table 4). Similarly, at adjusted logistic regression analysis cannabis use resulted as an independent predictor of teratozoospermia ($p = 0.039$), but not with oligo-, astheno-, and azoospermia (Table 5). Both logistic and linear regression analyses remained significant also when stratifying men based on whether their FSH levels were < or > 8 UI/L.

4 | DISCUSSION

In many ways, cannabis use has been stigmatized as deleterious to male reproductive health. However, a final statement on the impact of cannabis use on testosterone levels and the spermatogenetic path in infertile men is far from being proposed, since literature is still inconsistent. Here, we observed an inverse association between cannabis use and tT in primary infertile men, while a crystal clear association was not found in terms of impaired gonadal status. Thereof, we may speculate that it is likely that the impact was quantitatively too small to have clinical significance at least when a single measurement at a single time point is evaluated, without the option to follow potential further abnormalities over time and continuous substance use. Likewise, we did not have detailed data to explore the association between the overall amount of cannabis used and tT levels. Moreover, current findings showed that cannabis use was significantly associated with abnormal sperm morphology at semen analysis, thus confirming the actual impact of the illicit substance toward macroscopic factors of male fertility potential. It is unknown exactly how cannabis impacts hormone levels and semen quality biologically. THC, the cannabis active compound, binds to the CB1 and CB2 cannabinoid receptors in humans. Testis, vas deferens, and human sperm cells all have CB1 receptors,[26] which when activated result in a dose-dependent reduction in sperm motility and a reduction in spermatozoa's mitochondrial activity.[9]

The existing literature did not reach a consensus regarding the association of cannabis and testosterone production. Indeed, several

TABLE 1 Characteristics of the whole cohort of patients according to cannabis users versus nonusers

	Cannabis users	Non-users	*p*-Value
Number of patients (number [%])	225 (10.9)	1849 (89.2)	
Age (years)			
Median (IQR)	35 (32 – 39)	36 (33 - 40)	0.014
BMI (kg/m^2)			
Median (IQR)	24.9 (22.9 – 26.6)	25.1 (23.3 – 27.4)	0.213
CCI (n. [%])			0.983
0	204 (90.7)	1671 (90.4)	
≥1	21 (9.3)	178 (9.6)	
Alcohol use (n. [%])			
Yes	208 (92.4)	1511 (81.7)	<0.0001
No	17 (7.5)	338 (18.3)	
Cigarette smoking (n. [%])			
Yes	112 (49.8)	487 (26.3)	<0.0001
No	113 (50.2)	1361 (73.6)	
Hard drugs use (n. [%])			
Yes	5 (2.2)	54 (2.9)	0.702
No	220 (97.8)	1795 (97.1)	
TV (ml^2)			
Median (IQR)	15 (12–20)	15 (12–20)	0.123
Hormones levels			
FSH (mIU/ml)			
Median (IQR)	5.5 (3.6–12.5)	5.8 (3.4–11.8)	0.845
LH (mIU/ml)			
Median (IQR)	4.4 (3.2–6.5)	4.3 (2.9–6.2)	0.381
tT (ng/ml)			
Median (IQR)	4.2 (3.3–5.6)	4.6 (3.5–5.8)	0.033
Gonadal status [n. (%)]			
Eugonadism	167 (78.2)	1439 (77.8)	0.521
Primary hypogonadism	9 (4.0)	53 (2.9)	
Secondary hypogonadism	35 (15.6)	239 (12.9)	
Compensated hypogonadism	14 (6.2)	118 (6.4)	
Sperm parameters			
Number of azoospermic patients (no. [%])	52 (23%)	432 (23%)	0.137
Sperm concentration (x10^6/ml)			
Median (IQR)	20.0 (6.0–42.5)	21.0 (7.0–50.0)	0.089
Total progressive motility (%)			
Median (IQR)	25.0 (10.0–39.5)	26.0 (12.0–40.0)	0.211
Normal morphology (%)			
Median (IQR)	1.3 (1.0–4.0)	2.0 (1.0–6.0)	0.004
Semen Culture (%)			
Negative	63 (28%)	582 (30%)	0.058
Positive	27 (12%)	232 (13%)	
Not performed	135 (60%)	1035 (57%)	

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidities Index; FSH, Follicle stimulating hormone; IQR, interquartile range; LH, luteinizing hormone; tT, total testosterone; TV, Testicular Volume.

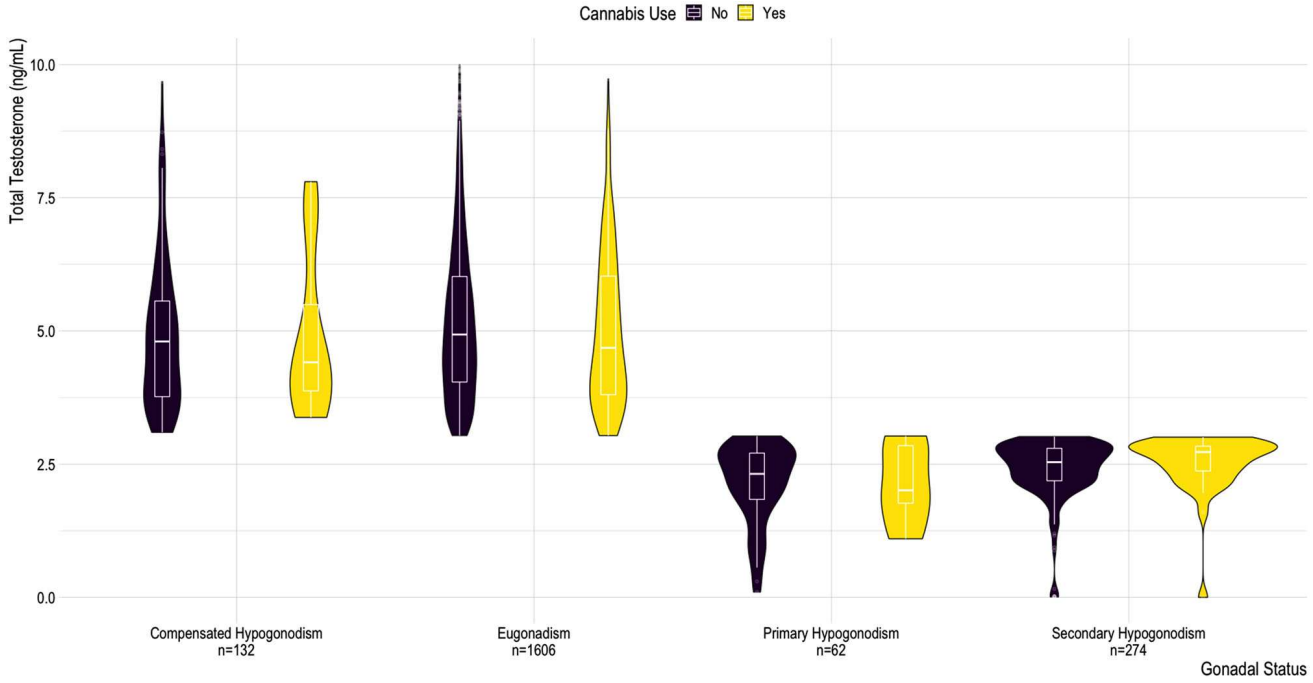

FIGURE 1 Testosterone levels distribution according to cannabis use and gonadal status

TABLE 2 Unadjusted and adjusted linear regression models predicting hormone levels

	Total testosterone				FSH				LH			
	Univariable		Multivariable*		Univariable		Multivariable*		Univariable		Multivariable*	
	β est.	*p*-Value	β est.	*p*-Value	β est.	*p*-Value	β est.	p value	β est.	p value	β est.	p value
Age	−0.013	0.037	−0.007	0.240	0.021	0.577	0.015	0.690	−0.032	0.346	0.215	0.001
BMI	−0.122	<0.0001	−0.121	<0.0001	−0.081	0.225	−0.128	0.057	0.212	0.001	−0.052	0.146
CCI	−0.126	0.392	0.052	0.710	4.483	<0.0001	4.393	<0.0001	1.117	0.147	1.054	0.186
Alcohol use	0.088	0.442	0.020	0.859	−2.416	<0.0001	−2.274	<0.0001	−0.678	0.261	−0.471	0.461
Cigarette smoking	0.131	0.170	0.193	0.037	1.289	0.019	1.723	0.002	0.426	0.396	0.423	0.417
Cannabis use	−0.296	0.033	−0.372	0.005	−0.540	0.501	−0.683	0.397	0.132	0.856	0.085	0.910
Hard drugs use	0.133	0.610	0.064	0.797	−0.146	0.922	−0.592	0.692	−0.153	0.911	−0.311	0.823

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidities Index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; tT, total testosterone.

studies suggested that cannabis use does not impact on testosterone levels.[27] Paradoxically, Gundersen et al. investigated a total of 1215 young Danish men aged 18–28 years recruited between 2008 and 2012 and observed higher levels of testosterone in men using cannabis.[12] Similarly, Fantus et al. analyzed data in the National Health and Nutrition Examination Survey from 5146 men between 2011 and 2016 and observed that cannabis use was associated with an increase in testosterone levels.[28] Conversely, a paper published in 1974 reported a lower tT levels in cannabis users.[29] The results on the association between cannabis and gonadotropin levels are also inconsistent in literature, with studies showing no,[30] negative[14] or even positive[31] associations. A recent meta-analysis pooled data from most of these studies and observed that sexual hormones levels did not significantly differ when comparing men using cannabis and those who do not. Only FSH levels were lower in cannabis users but the changes appeared to be quantitatively small, making the clinical significance of these changes uncertain.[27] Our findings showed that in the specific subset of primary infertile men, the use of cannabis was associated with a lower level of tT but that likely such a lower level was not sufficient to determine an increase of hypogonadism prevalence in cannabis users. Of course, the lack of follow-up makes it impossible to understand if these lower levels of testosterone associated with cannabis use might have an impact on gonadal status in the long term. In addition, we were not able to investigate the impact of amount/frequency of cannabis used with tT and gonadotropin levels.

Moreover, the association between cannabis and sperm parameters is also debated. Pacey et al., for instance, investigating 1970 cannabis users and nonusers observed an increased risk for poor sperm

TABLE 3 Multivariable logistic regression models assessing the risk of primary, secondary, and compensated hypogonadism for cannabis users after adjusting for age, body mass index, comorbidity, alcohol use, cigarette smoking and hard drugs use

	Primary hypogonadism*		Secondary hypogonadism*		Compensated hypogonadism*	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Cannabis use						
No	Ref		Ref		Ref	
Yes	1.66 (0.84–3.05)	0.196	1.42 (0.99–1.98)	0.097	0.95 (0.56–1.54)	0.875
Age	1.01 (0.98–1.04)	0.520	1.01 (0.99–1.02)	0.523	0.97 (0.94–1.01)	0.312
BMI	1.12 (1.07–1.17)	<0.0001	1.17 (1.13–1.20)	<0.0001	1.01 (0.96–1.05)	0.820
CCI						
0	Ref		Ref		Ref	
≥1	2.01 (1.05–3.60)	0.063	1.45 (1.01–2.05)	0.087	2.57 (1.64–3.93)	0.001
Alcohol use						
No	Ref		Ref		Ref	
Yes	0.41 (0.251–0.68)	0.003	1.05 (0.77–1.44)	0.815	0.57 (0.39–0.85)	0.016
Cigarette smoking						
No	Ref		Ref		Ref	
Yes	1.09 (0.65–1.78)	0.771	0.80 (0.62–1.04)	0.162	1.88 (1.36–2.60)	0.001
Hard drugs use						
No	Ref		Ref		Ref	
Yes	0.63 (0.06–2.50)	0.653	0.61 (0.25–1.31)	0.330	1.64 (0.77–3.19)	0.246

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidities Index; OR, odds ratio; tT, total testosterone.
*The reference group is represented by eugonadal men in each of the three models.

TABLE 4 Uni- and multivariable linear regression models assessing the association of sperm parameters (sperm concentration, progressive motility and morphology) with cannabis use after accounting for age, body mass index, comorbidity, alcohol use, cigarette smoking and hard drugs use

	Sperm concentration				Total progressive motility				Morphology			
	Univariable		Multivariable*		Univariable		Multivariable*		Univariable		Multivariable*	
	β est.	*p*-Value	β est.	*p*-Value	β est.	*p*-value	β est.	*p*-Value	β est.	*p*-Value	β est.	*p*-Value
Age	−0.198	0.844	0.019	0.987	−0.450	0.382	0.004	0.753	−0.073	0.827	0.006	0.988
BMI	−0.221	0.041	−2.084	0.055	−1.157	0.037	0.021	0.139	0.032	0.926	0.023	0.988
CCI	−1.412	0.184	−1.44	0.217	−0.979	0.079	0.013	0.428	−0.142	0.695	−0.123	0.757
Alcohol use	−0.145	0.956	1.895	0.491	2.628	0.055	−0.065	0.074	−1.586	0.073	−0.390	0.667
Cigarette smoking	−2.799	0.177	−2.164	0.306	−0.240	0.822	−0.004	0.878	−1.041	0.128	−0.531	0.441
Cannabis use	−0.392	0.178	−3.319	0.295	−1.194	0.421	0.034	0.421	−2.578	0.007	−1.949	0.048
Hard drugs use	−3.823	0.535	−0.602	0.927	3.892	0.212	-0.039	0.647	−3.580	0.082	−1.763	0.416

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidities Index.

morphology in men using cannabis.[11] Gundersen et al. in a population-based study found that cannabis was a risk factor for abnormal sperm concentration and total sperm count.[12] In a recent paper by Nassan et al., men using cannabis resulted to present with significantly higher sperm concentrations.[14] Our findings suggest that cannabis use was not associated with sperm concentration or motility, while could have an impact in terms of normal morphology status.

The question of a potential negative impact of cannabis use in terms of overall reproductive health has been investigated also in basic science. Indeed, preclinical animal and in vitro studies have found that cannabis use was negatively associated with testosterone levels in human sperm cells,[32] and a significant reduction in testicular testosterone synthesis was observed in rats to which THC had been administered.[33] In rat models, CB1 receptors are

TABLE 5 Multivariable logistic regression models assessing the risk of azoospermi, oligozoospermia, asthenozoospermia, and teratozoospermia for cannabis users after adjusting for age, body mass index, comorbidity, alcohol use, cigarette smoking, and hard drugs use

	Concentration < 15 (10^6/ml)		Total Progressive Motility < 32 (%)		Morphology < 4 (% of normal forms)		Azoospermia	
	OR (95% CI)	p value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Cannabis use								
No	Ref		Ref		Ref		Ref	
Yes	1.08 (0.81–1.43)	0.654	1.16 (0.86–1.56)	0.422	1.48 (1.09–2.03)	0.039	0.80 (0.60–1.05)	0.189
Age	1.05 (0.95–1.16)	0.427	1.02 (0.92–1.13)	0.768	0.98 (0.89–1.09)	0.802	0.97 (0.96–0.99)	0.001
BMI	1.13 (1.02–1.27)	0.043	1.11 (0.99–1.26)	0.147	1.07 (0.96–1.20)	0.343	1.01 (0.99–1.04)	0.296
CCI								
0	Ref		Ref		Ref		Ref	
≥1	1.05 (0.94–1.16)	0.477	1.06 (0.94–1.189)	0.429	0.99 (0.89–1.11)	0.916	2.07 (1.59–2.70)	<0.0001
Alcohol use								
No	Ref		Ref		Ref		Ref	
Yes	0.93 (0.73–1.20)	0.644	0.75 (0.58–1.98)	0.221	1.11 (0.86–1.43)	0.478	0.69 (0.56–1.86)	0.763
Cigarette smoking								
No	Ref		Ref		Ref		Ref	
Yes	1.05 (0.87–1.27)	0.669	0.98 (0.81–1.19)	0.868	1.12 (0.92–1.37)	0.349	1.31 (1.09–1.58)	0.017
Hard drugs use								
No	Ref		Ref		Ref		Ref	
Yes	0.95 (0.52–1.71)	0.895	0.85 (0.47–1.56)	0.646	1.27 (0.66–2.58)	0.566	0.81 (0.47–1.34)	0.502

Abbreviations: CCI, Charlson Comorbidities Index; OR, odds ratio; adjusted for age; BMI; CCI; alcohol, cigarette, and hard drugs use; tT, total testosterone.

present both in pituitary gland and GnRH releasing neurons in the hypothalamus, and endocannabinoids act by reducing the secretion of thyroid-stimulating hormone, LH, growth hormone and prolactin by the pituitary gland, and by reducing secretion of GnRH by the hypothalamus, respectively.[34] The impairment of the hypothalamic-pituitary-gonadal axis might then exert negative effects also on the spermatogenesis.

Our work is certainly not devoid of limitations, mostly owing to its retrospective nature and its cross-sectional design. First, daily cannabis use frequency and quantity were not available, which indeed might have an impact on the actual understanding of its systemic and deleterious effects on the reproductive system.[35] This is clearly associated with the fact that cannabis use surveys may be affected by under-reporting because of social stigma. Moreover, the lack of follow-up makes it impossible to understand the effects of circulating testosterone reduction among cannabis users on long-term follow-up. Third, a comparison with same-race, age-matched cohort of fertile individuals is also still lacking.

5 | CONCLUSIONS

These findings showed that primary infertile men who have used or currently use cannabis are at higher risk of having lower testosterone levels and altered sperm morphology as compared with nonusers. However, these changes were quantitatively small, thus making their clinical impact uncertain and debatable.

AUTHOR CONTRIBUTIONS

Conceptualization: AS and FB. *Data curation*: FB, EP, CC, SC, MR, and AD. *Formal analysis*: FB. *Supervision*: GF, LB, and PC. *Writing—original draft*: FB and GF. *Writing—review and editing*: ME, FM, and AS.

CONFLICT OF INTEREST

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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ORCID

Giuseppe Fallara https://orcid.org/0000-0001-7872-2650
Alessia d'Arma https://orcid.org/0000-0002-0595-7165
Paolo Capogrosso https://orcid.org/0000-0003-2347-9504

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