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The Association between Monthly, Yearly, and Lifetime Cannabis Use, and Semen Parameters in Asian-American Men

Federico Belladelli[1,2,3], Tony Chen[3], Satvir Basran[3], Daniel R. Greenberg[3], Francesco Del Giudice[3,4], Evan Mulloy[3], Che-Hong Chen[5], Yu-Sheng Cheng[6], Andrea Salonia[1,2], Michael L. Eisenberg[3]

[1]Division of Experimental Oncology/Unit of Urology; URI; IRCCS Ospedale San Raffaele, [2]School of Medicine, University Vita-Salute San Raffaele, Milan, Italy, [3]Department of Urology, School of Medicine, Stanford University, Stanford, CA, USA, [4]Department of Urology, University Sapienza, Rome, Italy, [5]Department of Chemical and Systems Biology, School of Medicine, Stanford University, Stanford, CA, USA, [6]Department of Urology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Purpose: Medicinal and recreational cannabis use has grown exponentially, however, its effect on testicular function and spermatogenesis remains uncertain. The aim of this study was to evaluate the association between cannabis use and semen parameters in a cohort of Asian-American men with unknown fertility.

Materials and Methods: Asian men were recruited to complete an online survey and submit a semen sample. Semen analysis, demographic data, lifestyle factors, and cannabis use habits were collected. Linear and logistic regression analyses were used to determine.

Results: Among the 112 men included in this study, 51 used cannabis at least once in their lifetime, 30 men used cannabis at least once in the last 12 months, and 26 men used cannabis at least once in the last 30 days. Adjusted linear regression analyses identified an association between cannabis use in the previous 30 days and worse sperm morphology (β: -0.45, p=0.025) and sperm motility (β: -1.64, p=0.016). However, when stratifying by subfertile semen quality (*i.e.*, WHO criteria), no association was identified between semen quality and cannabis use. Lower sperm morphology and motility are partially associated with recent cannabis use, while all other semen parameters are not.

Conclusions: We did not observe any consistent associations between cannabis use on any semen parameters in Asian-American men. Further studies within the field are needed to explore racial and ethnic differences in semen quality and lifestyle factors.

Keywords: Asian Americans; Cannabis; Male infertility; Semen analysis

INTRODUCTION

It is estimated that 15% of couples are unable to achieve pregnancy after 1one year of intercourse and are classified as infertile [1]. Within couples experiencing infertility, a male factor contributes in 50% of

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Correspondence to: Michael L. Eisenberg https://orcid.org/0000-0001-5482-0141
Department of Urology, School of Medicine, Stanford University, 300 Pasteur Drive, Stanford, CA 94305, USA.
Tel: +1-650-725-5746, **Fax:** +1-650-498-5346, **E-mail:** eisenberg@stanford.edu

The World Journal of MEN's HEALTH

cases [2]. During an evaluation, clinicians search for modifiable factors to improve a man's reproductive health. Several lifestyle factors such as diet, exercise, obesity, smoking, substance use (*e.g.*, alcohol, cannabis, *etc*), and exercise have been investigated as modifiable determinants of semen quality [3,4]. However, to date, the effects of cannabis on semen parameters and male fertility remain uncertain [5]. Moreover, as a man's reproductive and overall health are intertwined, the opportunity exists to improve a man's health as reproductive harms are identified [4,6].

Four percent of the global population between ages 15–64 have used cannabis at least once [7]. In the United States (US), almost 10 million people are daily or near-daily users, making it one of the most commonly used illicit drugs in the US and worldwide. D9-tetrahydrocannabinol (THC), the active component of cannabis, binds cannabinoid receptors primarily present in the central nervous system, but also present in the reproductive organs [8]. Recent animal and human studies suggest that cannabis impairs male fertility, semen quality, and hormone levels [9-14]. Conversely, other groups have reported no changes in semen parameters and testosterone levels among cannabis users [15-17]. Moreover, a recent systematic review and meta-analysis reported no clinically meaningful association between cannabis use and semen quality [5]. Importantly, all of the studies were in Western countries (*i.e.*, US, Denmark, UK, Jamaica) and only one study examined non-Caucasian men. Thus the generalizability to other populations remains uncertain.

Given that important differences in semen parameters between different races have been observed [18,19], an examination of the association between cannabis and semen quality in other populations is necessary. Indeed, studies have demonstrated differences in semen quality between Caucasians and Asians [18-20]. The present study aims to investigate the association between cannabis use and semen parameters within a cohort of Asian-American men.

MATERIALS AND METHODS

1. Ethics statement

All men signed an informed consent form. The study was approved by the Institutional Review Board at Stanford University (IRB-44065).

2. Study population

Asian-American men without known fertility status were recruited in the San Francisco area between 2018 and 2021 and invited to participate in a study on semen parameters.

Baseline demographics obtained included age, calculated body mass index (BMI), ethnicity, education level, typical weekly physical activity, and current or past alcohol and smoking habits. The general health of the subjects was assessed using a self-administered questionnaire with the following possible answers: excellent, very good, good, fair, and poor.

Men were surveyed on marijuana use using a self-administered online questionnaire. They were first surveyed on 'ever' or 'never' usage. Men that never used cannabis and did not report other conditions influencing semen parameters (*i.e.*, hormone abnormalities, presence of varicocele, medications, or orchidopexy) were designated as controls. Among ever users, we also assessed the number of days they used cannabis or hashish throughout the 30 days prior to survey administration and in the previous 12 months. The questionnaire had similar questions about other drug use (cocaine, heroin, *etc*). Exposure questions were based on the methodology of the Centers for Disease Control and Prevention's National Survey of Family Growth (https://www.cdc.gov/nchs/nsfg/index.htm).

Participants produced and submitted a semen sample at the Stanford University clinic after 3 to 5 days of abstinence. Specimens were placed in an incubator within five minutes to induce liquefaction and were processed within 30 to 60 minutes to assess semen parameters in accordance with the World Health Organization (WHO) Laboratory Manual for the Examination and Processing of Human Semen [21]. Semen samples were analyzed using the Bonraybio LensHooke Semen Quality Analyzer X1 Pro (LensHooke, Taichung City, Taiwan).

Abnormal values for each semen parameter was determined according to WHO reference criteria [21], which include the following as lower threshold for normality: pH <7.2, ejaculate volume <1.5 mL, sperm concentration <15 M/mL, total sperm count <39 M, morphology <4%, total sperm motility <40%, and progressive motility <32% [21]. Subfertile men were defined as having at least one semen parameter below the WHO standard.

3. Statistical analysis

Patients' characteristics are presented as median (interquartile range [IQR]). Chi-squared analyses were used to compare categorical variables while Student's t-test was used for continuous variables. Univariate and multivariate linear regression models were used to evaluate the association of cannabis lifetime use, cannabis use in 12-month and 30-day intervals before survey completion, and semen parameters. Binary univariate logistic regression analyses were performed to identify confounders for the final logistic regression model. Adjusted regressions models were performed with a stepwise methodology. Age, BMI, ethnicity, education level, typical weekly physical activity, alcohol and smoking habits, and general health were the variables included in the adjusted regressions. All p-values from Wald F-tests were reported. Statistical tests were performed using RStudio statistical software version 3.4.3 (The R Foundation for Statistical Computing), and the results were presented with 95% confidence interval (CI) at $p<0.05$.

RESULTS

1. Population characteristics

Among the 112 men included in this study, 51 used cannabis at least once in their lifetime, 30 men used cannabis at least once in the last 12 months, and 27 men used cannabis at least once in the last 30 days. Among all men, the average number of days of cannabis use in the last 30 days was 2.37 days. When cannabis use in the last 12 months were considered, 22, 11, 9, 3, 4, and two men reported using cannabis less than once per month, at least once per month, 2–3 times per month, 4–8 times per month, 9–24 times per month, 25–30 times per month, respectively. Men who have used cannabis recently had a median (IQR) age of 26.4 years (24.0–31.3 years), BMI of 23.4 kg/m^2 (21.6–25.0

Table 1. Population characteristics

Characteristic	Cannibas use in last 30 days		p-value
	No (n=85)	Yes (n=27)	
Age (y)	30.3 (25.7–35.4)	26.4 (24.0–31.3)	0.017
Body mass index (kg/m^2)	23.6 (21.8–25.1)	23.4 (21.6–25.0)	0.407
Sperm concentration (10^6/mL)	63.0 (34.0–107.4)	55.0 (31.5–89.0)	0.174
Total sperm count (10^6 per ejaculate)	169.2 (78.8–315.3)	115.5 (69.3–192.0)	0.309
Sperm morphology (% normal forms)	10.0 (6.0–16.0)	7.0 (6.0–11.5)	0.034
Total sperm motility (% motile cells)	41.0 (21.0–56.0)	33.0 (10.0–43.0)	0.016
Education			0.018
High school	5 (5.9)	3 (11.1)	
Some college	1 (1.2)	2 (7.4)	
College graduate	28 (32.9)	13 (48.1)	
Some graduate/prof school	6 (7.1)	4 (14.8)	
Graduate/prof school	45 (52.9)	5 (18.5)	
Smoking			0.034
Yes	14 (16.5)	5 (18.5)	
No	71 (83.5)	22 (81.5)	
Alcohol			0.034
Yes	64 (75.3)	26 (96.3)	
No	21 (24.7)	1 (3.7)	
Exercise			0.250
Yes	68 (80.0)	26 (96.3)	
No	17 (20.0)	1 (3.7)	
Hard drugs			<0.001
Yes	4 (4.7)	9 (33.3)	
No	81 (95.3)	18 (66.7)	

Values are presented as median (interquartile range) or number (%).

The World Journal of MEN's HEALTH

kg/m^2), sperm concentration of 55.0 ×10^6/mL (31.5–89.0 ×10^6/mL), a total count of 115.5 ×10^6 per ejaculate (69.3–192.0 ×10^6 per ejaculate), normal morphology of 7.0% (6.0%–11.5%), and total motility of 33.0% (10.0%–43.0%). Men who consumed cannabis recently were younger (p=0.017), had a lower education (p=0.018), and were more commonly smokers (p=0.034) and hard drugs users (p<0.001) when compared to cannabis non-users. Moreover, cannabis consumers had a lower percentage of morphologically normal (p=0.034) and motile (p=0.016) sperm (Table 1).

2. Cannabis and sperm parameters

Lifetime cannabis use and cannabis consumption in the last 12 months were not associated with any semen parameters. In contrast, cannabis use within the past month was associated with sperm morphology and motility. The unadjusted model showed that cannabis use in the previous 30 days was associated with worse sperm morphology (β: -0.35, p=0.005) (Fig. 1A) and sperm motility (β: -1.63, p=0.0012) (Fig. 1B). When fully adjusted, both association to sperm morphology (β: -0.45, p=0.025) and sperm motility remained significant (β: -1.64, p=0.016) (Table 2). Interestingly, the distribution of sperm morphology and motility based on age groups (18–25, 26–35, and ≥36 y) did not present major differences when comparing men who consumed cannabis in the 30 days (Fig. 2) and the 12 months (Fig. 3) prior to survey administration and men who did not consume cannabis in that period.

However, when stratifying by men with subfertile semen quality (*i.e.*, below WHO 5th edition criteria), no association was identified between semen quality (*i.e.*, sperm concentration, total sperm count, motility, or mor-

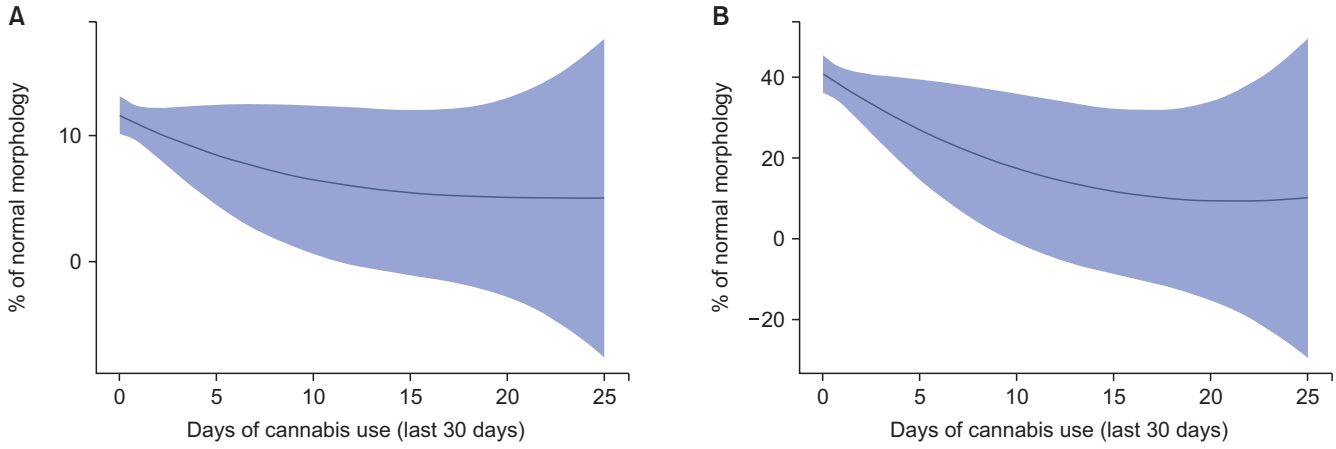

Fig. 1. (A) Morphology (% of normal forms) and (B) motility (% of motile cells) as a function of cannabis use in the last 30 days.

Table 2. Linear regression analyses investigating association between cannabis use and semen parameters

Time measures of cannabis use	Concentration (10^6/mL)		Total count (10^6 per ejaculate)		Morphology (normal forms, %)		Motility (total motile cells, %)	
	Beta estimate	p-value	Beta estimate	p-value	Beta estimate	p-value	Beta estimate	p-value
Cannabis use (lifetime)								
Univariate	-10.86	0.366	-32.70	0.294	-2.06	0.140	-3.38	0.448
Multivariate[a]	-8.91	0.942	-27.61	0.401	-2.28	0.105	-1.23	0.798
Cannabis use (30 d)								
Univariate	-0.18	0.919	-0.63	0.892	-0.35	0.005	-1.63	0.012
Multivariate[a]	-0.14	0.941	-2.50	0.595	-0.45	0.025	-1.64	0.016
Cannabis use (12 mo)								
Univariate	-6.27	0.227	-11.73	0.385	0.61	0.310	-4.70	0.136
Multivariate[a]	-6.42	0.286	-18.65	0.221	0.04	0.954	-4.44	0.245

[a]Adjusted for age, body mass index, smoke, hard drugs, alcohol, general health, and education.

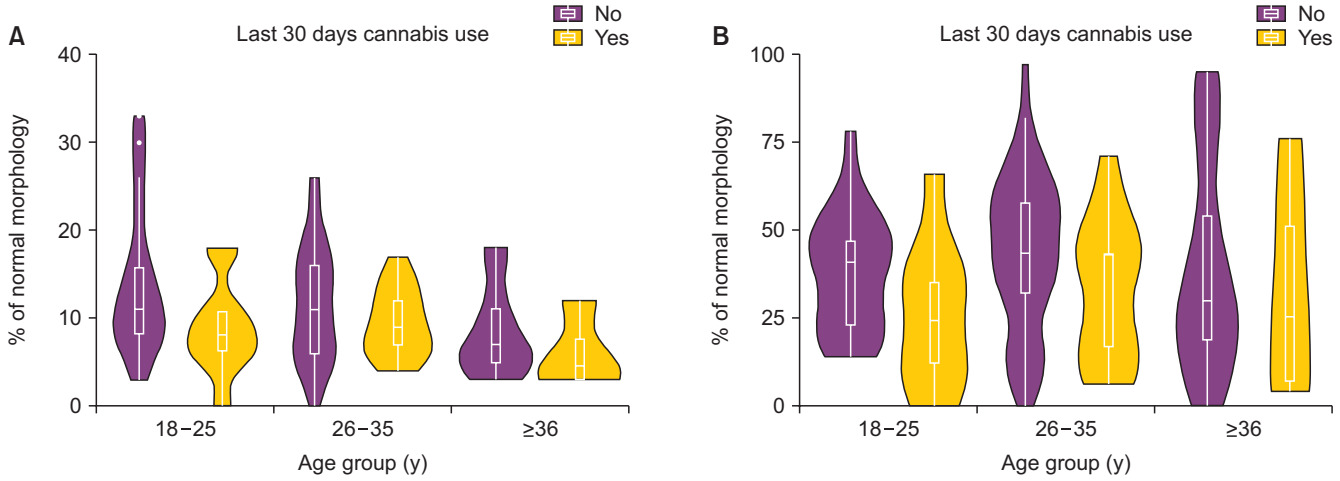

Fig. 2. (A) Morphology (% of normal forms) and (B) motility (% of motile cells) distribution based on cannabis use in the last 30 days and age groups.

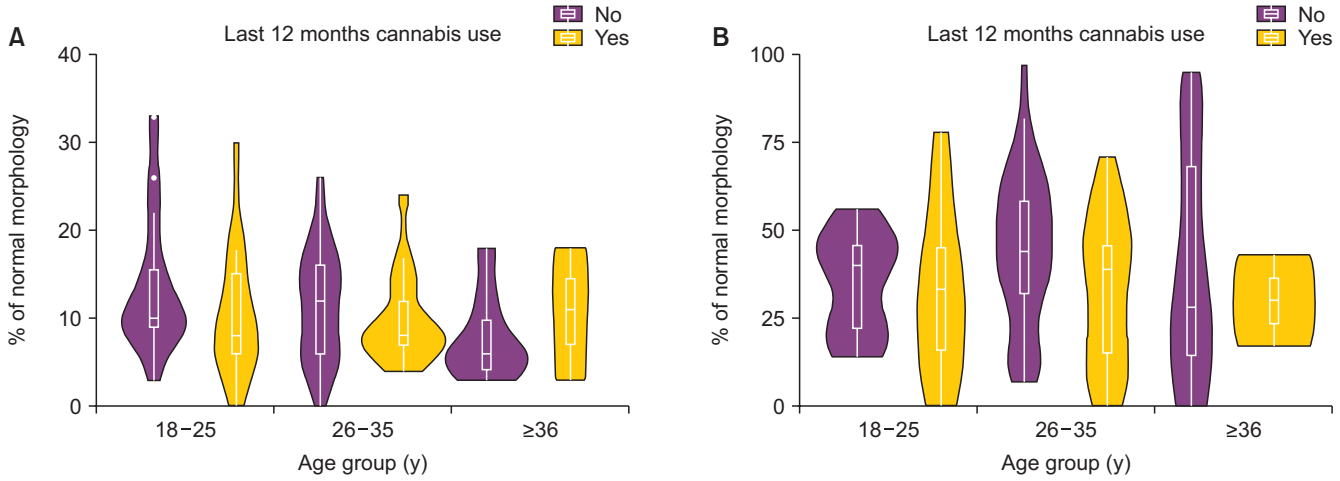

Fig. 3. (A) Morphology (% of normal forms) and (B) motility (% of motile cells) distribution based on cannabis use in the last 12 months and age groups.

phology) and cannabis use when assessed as lifetime cannabis use, monthly frequency of cannabis use, or use of cannabis in the past year. For example, the adjusted odds of a lower sperm concentration was 1.08 (95% CI, 0.03–41.25; p=0.920) for lifetime cannabis use, 1.07 (95% CI, 0.30–3.79; p=0.923) when analyzing cannabis use in the prior 30 days, and 1.79 (95% CI, 0.55–12.47; p=0.945) for cannabis use in the prior 12 months (Table 3).

DISCUSSION

The present study outlined a modest association between cannabis use and semen quality in Asian American men unselected for fertility. Specifically, we observed an association between cannabis use in the prior 30 days and sperm morphology and motility when analyzed as a continuous variable. However, when semen parameters were examined based on clinically relevant levels (*i.e.*, WHO criteria), cannabis use did not emerge as an independent predictive factor for semen impairment. Moreover, we observed no association between sperm concentration, total sperm count, and morphology, and cannabis use (*i.e.*, over the previous 30 days, previous 12 months, or lifetime). Thus the current study suggests that acute (examing use in the prior month *vs.* year/lifetime) cannabis use can impact sperm morphology and motility but the clinical impact remains uncertain. To our knowledge, this is the first study regarding cannabis and male fertility taking into account different time-frames (*i.e.*, monthly, yearly, and

The World Journal of MEN's HEALTH

Table 3. Logistic regression analyses investigating association between cannabis use and semen parameters

Semen parameter	unOR (95% CI)	p-value	aOR (95% CI)[a]	p-value
Concentration <15 (10^6/mL)				
Cannabis use (lifetime)				
No	Reference	-	Reference	-
Yes	1.42 (0.31–7.61)	0.708	1.08 (0.03–41.25)	0.920
Days of cannabis use (use in last 30 d)	0.78 (0.07–4.13)	0.827	1.07 (0.30–3.79)	0.923
Days of cannabis use (use in last 12 mo)	1.50 (0.90–2.33)	0.139	1.79 (0.55–12.47)	0.945
Total count <39 (10^6 per ejaculate)				
Cannabis use (lifetime)				
No	Reference	-	Reference	-
Yes	2.45 (0.65–12.19)	0.296	1.57 (0.28–8.95)	0.640
Days of cannabis use (use in last 30 d)	2.53 (0.63–9.43)	0.245	1.24 (0.30–5.67)	0.250
Days of cannabis use (use in last 12 mo)	1.82 (0.23–2.70)	0.110	0.79 (0.07–8.98)	0.846
Morphology <4 (% of normal forms)				
Cannabis use (lifetime)				
No	Reference	-	Reference	-
Yes	1.18 (0.37–3.90)	0.814	1.36 (0.22–16.55)	0.653
Days of cannabis use (use in last 30 d)	1.65 (0.44–5.39)	0.503	1.85 (0.42–7.34)	0.470
Days of cannabis use (use in last 12 mo)	1.06 (0.60–1.59)	0.847	1.06 (0.60–1.69)	0.835
Total motility <40 (% of motile sperm cells)				
Cannabis use (lifetime)				
No	Reference	-	Reference	-
Yes	1.03 (0.50–2.13)	0.942	1.55 (0.89–22.31)	0.761
Days of cannabis use (use in last 30 d)	1.91 (0.88–4.18)	0.171	2.31 (0.93–5.84)	0.131
Days of cannabis use (use in last 12 mo)	1.21 (0.90–1.65)	0.927	1.37 (0.96–2.01)	0.156

unOR: unadjusted odds ratio, CI: confidence interval, aOR: adjusted odds ratio, -: not available.
[a]Adjusted for age, body mass index, smoke, hard drugs, alcohol, general health, and education.

lifetime) regarding exposure to cannabis, and the first investigating Asian-Americans as an ethnic group.

Animal and *in vitro* studies have demonstrated a negative association between cannabis and semen quality. Both mouse and dog models demonstrated that cannabis use was associated with a reduction in total sperm count and concentration [22]. Morgan et al [23] reported *in vitro* and *in vivo* mouse sperm studies that THC inhibited sperm motility. In addition, Whan et al [24] showed similar results on human sperm. Furthermore, inhibition of the spontaneous acrosome reaction and lower sperm motility was observed in sperm incubated with THC [23]. These findings are consistent with the results from the current analysis demonstrating a negative association with sperm motility and cannabis use within the last 30 days. Importantly, no association was identified with lifetime cannabis use. Thus, it is possible that recent cannabis use could alter semen parameters more severely. This is supported also by the consideration that normal spermatogenesis lasts about 74 days so that past use (even high quantities) may not have a measured effect if enough spermatogenic cycles have passed from the last use [25].

Despite preclinical data, the association of cannabis use on a man's fertility potential is heterogeneous in the literature. Pacey et al [12] compared 318 cannabis users to 1,652 non-users and observed worse sperm morphology in cannabis users. Gundersen et al [13] examined 1,215 men and described an association between cannabis use and lower sperm concentration and total sperm count. Similarly, Caroll et al [14] reported that cannabis use is a risk factor for being diagnosed with asthenozoospermia and teratozoospermia. In contrast, Nassan et al [17] observed higher sperm concentrations in cannabis users among men from infertile couples.

Cannabis use has also been investigated in relation to fecundability. In this context, Kasman et al [26] found no significant association between cannabis use

and time to pregnancy across all cannabis user groups, including daily smokers in a representative sample of US men and women. Wise et al [27] observed that male cannabis consumption at levels of ≥1 time/week was associated with an increase in fecundability in couples trying to conceive. The mixed clinical studies could be explained by the diversity in racial/ethnic compositions between the various studies. While most prior studies focused on men with Caucasian ancestry, the current report is the first to examine men of Asian ancestry. Indeed, prior reports have demonstrated racial differences in semen quality [18].

In addition, many prior studies have been conducted in men attending infertility clinics, thus limiting the applicability of their results to the general population. The current report was conducted on men unselected for testicular or reproductive function, improving the study's generalizability.

This study has several limitations that warrant mention. First, the limited number of subjects impairs the ability to detect small differences between cannabis users and nonusers. However, based on the current numbers, an association between cannabis use in the prior 30 days and sperm morphology and motility when analyzed as a continuous variable was observed. Nevertheless, cannabis use did not emerge as an independent predictive factor for semen impairment categorized using WHO criteria. Moreover, the absence of pregnancy outcomes limits the ability to make conclusions regarding male fertility. Furthermore, the recruitment from a single university campus may limit generalizability to other locations and may introduce possible biases in term of cannabis use patterns. In fact, this study reported lower cannabis use when compared to other studies. In addition, the lack of specific quantification of daily/lifetime cannabis use or other measures of testicular function (*e.g.*, testosterone, varicocele, etc) prevents more granular analyses. Importantly, the current literature does support the validity of the survey methodology employed in this study despite a concern that self-reported cannabis use may not be reliable due to the social stigma or fear of repercussion [28].

CONCLUSIONS

Our study is the first to examine the association of cannabis use in different time frames on the semen quality of Asian-American men. An association between cannabis use in the prior 30 days and impaired sperm morphology and motility was observed when analyzed as a continuous variable, but not to the degree beyond which could be stratified as subfertile by WHO standards. We did not observe any consistent associations between cannabis use on any semen parameters. Future studies are needed to explore racial and ethnic differences in semen quality and lifestyle factors.

Conflict of Interest

The authors have nothing to disclose.

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None.

Author Contribution

Conceptualization: MLE. Data curation: SB, DRG. Formal analysis: FB. Investigation: FB. Methodology: FDG, FB, MLE. Project administration: TC, MLE. Supervision: MLE, AS. Writing – original draft: FB. Writing – review & editing: MLE, EM, AS, CHC, YSC.

Data Sharing Statement

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

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