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Cannabis and Tinnitus in People with and without HIV

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Abstract:

Introduction/Objective: The relationship between cannabis use and tinnitus is unclear, particularly among people with HIV. The relationship between cannabis use and tinnitus prevalence and its severity in the MACS/WIHS Combined Cohort Study (MWCCS) was examined.

Methods: Cross-sectional data collected between October 1, 2020, and September 30, 2022, were drawn from the MWCCS. Tinnitus was defined as bothersome ringing, roaring, or buzzing in the ears or head that lasted for 5 minutes or more in the past 12 months. Tinnitus severity (among those reporting tinnitus) was dichotomized as no/small problem versus moderate to very big problem. Cannabis use was self-reported as the frequency of use in the past six months. Modified Poisson regression models were used to estimate associations adjusted for age, sex, race/ethnicity, HIV status, loud noise exposure, self-rated hearing, smoking, depression, as well as HIV viral load suppression and years of nucleoside reverse transcriptase inhibitors medication use (only for those with HIV).

Results: Among 3,437 participants (mean age=55; 55% female; 63% PWH), 31% reported cannabis use and 16% reported tinnitus. There was no statistically significant association between cannabis use and tinnitus prevalence. However, any cannabis use was significantly associated with a 29% lower prevalence of reporting moderate-to-severe tinnitus severity (aPR=0.71; 95% CI: 0.54–0.94). Stratified analyses also showed that any cannabis use was associated with a lower prevalence of reporting moderate-to-severe tinnitus severity (aPR=0.58; 95% CI: 0.37–0.90) among persons without HIV.

Discussion: Cannabis use was not associated with tinnitus prevalence but was associated with lower perceived tinnitus severity, particularly among participants without HIV. These findings suggest that cannabis may influence the subjective burden of tinnitus rather than its occurrence, although the underlying mechanisms remain unclear and may involve factors such as symptom perception or coping.

Conclusion: In this large cohort, cannabis use was not associated with the presence of tinnitus but was associated with lower reported tinnitus severity. Given the cross-sectional design and potential for residual confounding, these findings should be considered hypothesis-generating and warrant confirmation in longitudinal studies.

Keywords: Tinnitus, cannabis use, HIV, Tinnitus severity, MACS/WIHS combined cohort study, Epidemiology of hearing disorders.

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1. INTRODUCTION

Tinnitus is the perception of sounds, like ringing, buzzing, or hissing in the ears or head when there is no external source of these sounds [1]. Approximately 10% of adults in the U.S reported tinnitus, with higher prevalence and increased severity of tinnitus observed among older adults [2]. Tinnitus is associated with sleep disturbances, cognitive dysfunction, depression, anxiety, and lower quality of life [3-5]. Although the etiology of tinnitus is not fully understood, it has been proposed that loud noises or neck injuries, and resulting damage to the cochlea, can trigger abnormal neuronal hyperactivity in the brain's auditory pathways, which may lead to the perception of tinnitus [6].

Persons with HIV (PWH) report a higher prevalence of tinnitus than persons without HIV (PWoH). For example, in a study by Millar *et al*. (2020) among PWH, 57% reported experiencing tinnitus compared to 34% of PWoH [7]. Another study found that PWH exhibited greater tinnitus symptoms than PWoH [8]. Tinnitus might be more prevalent among PWH than PWoH because of potential adverse ototoxic effects of antiretroviral therapy (ART) [7], as well as higher prevalence of risk factors for tinnitus such as hypertension, cardiovascular disease, smoking, and chronic kidney disease [9-11]. Tinnitus symptoms are typically managed by the use of hearing aids, anti-anxiolytics, neurofeedback, and cognitive behavioral therapy [12-13]. However, many individuals with tinnitus continue to experience persistent symptoms that significantly impact their quality of life [14-15].

Cannabis is one of the most commonly used substances in the U.S. [16]. Additionally, cannabis use among PWH is 2–3 times higher that in the general population [17-18]. With the expansion of medical and recreational cannabis laws, cannabis is increasingly being used to manage symptoms associated with chronic conditions, including tinnitus. For instance, among patients with a primary presenting symptom of tinnitus in a tertiary neuro-otology clinic, 96% reported that they would consider cannabis as a treatment for their tinnitus symptoms [19], despite limited data from animal or human studies showing that cannabis can alleviate symptoms of tinnitus [6].

Previous epidemiological studies on the association between cannabis and tinnitus have been few and have produced mixed findings. Two analyses of nationally representative data from the National Health and Nutrition Examination Survey identified a statistically significant association between cannabis use and the presence of tinnitus, but no link to tinnitus severity [20, 21]. In contrast, a study by Han *et al*. (2010) using data from the National Survey on Drug Use and Health, another nationally representative dataset, reported no significant association between cannabis use and tinnitus [22]. Given the mixed findings from prior literature, additional research is warranted to clarify the potential link between cannabis use and tinnitus. Notably, no published studies have investigated the association between cannabis use and the presence of tinnitus or severity among PWH. Because both cannabis use and tinnitus have been reported to be prevalent at higher rates among PWH than PWoH, understanding the potential relationship between cannabis use and tinnitus may also have important implications for symptom management and overall quality of life for persons aging with HIV. Given mixed findings from prior literature, we examined the association between cannabis use and (a) the presence of tinnitus symptoms and (b) perceived tinnitus severity in a sample of PWH and PWoH.

2. MATERIALS AND METHODS

2.1. Study Population and Analytic Sample

The Multicenter AIDS Cohort Study (MACS) [23, 24] enrolled men who have sex with men, with initial enrollment during 1984–1985 in four cities across the U.S. The Women's Interagency HIV Study (WIHS) [25] enrolled women with initial enrollment taking place in 1994–1995 in six cities across the U.S. Both cohorts enrolled PWH and PWoH who were at increased risk for HIV. In 2019, the cohorts merged to form the MACS/WIHS Combined Cohort Study (MWCCS) [26]. MWCCS participants attend annual visits for standardized clinical examinations, specimen collection, and self-reporting of sociodemographic, behavioral, and medical data. Tinnitus data were collected during 2 visits conducted between October 1, 2020, and September 30, 2022. For this cross-sectional analysis, we included only the first response provided by each participant within the study period and retained observations where cannabis use was assessed at or prior to the tinnitus assessment, resulting in an analytic sample comprising 3,437 participants. The Institutional Review Boards for each of the sites and the data coordinating center approved this study.

2.2. Outcome Measure: Tinnitus

Tinnitus was assessed with the following question: "*In the past 12 months, have you been bothered by ringing, roaring, or buzzing in your ears or head that lasts for 5 minutes or more?*" The response options were (yes or no). Among those who answered "yes", tinnitus problem severity was assessed with the question: "How much of a problem is the ringing, roaring, or buzzing in your ears or head? Would you say…" The response options were "no problem", "a small problem", "a moderate problem", "a big problem", or "a very big problem". We created a binary categorization for tinnitus severity as: "no significant problem (no problem or small problem)" and "significant problem (moderate, big, or very big problem).

2.3. Independent Variable: Cannabis Use

Cannabis use was assessed with the following question: *"Since your last study interview, have you used marijuana or hash?"* Among those who responded "yes," frequency of use was asked with the following question: *"On average, how often did you take or use marijuana or hash since your last study interview?"* with the following response options: "less than once a month", "at least once a month, but less than once a week", "once a week", "2-3 times a week", "4-6 times a week", "once a day", and "more than once a day." For this analysis, we categorized participants' cannabis use as any use (yes/no) and by frequency of use as: (1) heavy use (defined as ≥4 times a week, (2) occasional to moderate use (defined as use between less than once a month and 3 times a week), compared to (3) no cannabis use.

2.4. Covariates

The chronological age at study visit was derived from the self-reported date of birth and date of survey administration. Race/ethnicity was categorized as Black, non-Hispanic, white, non-Hispanic, Hispanic, and Other (Asian/ Pacific Islander, Native American/Alaskan, or Other). Participants self-reported whether they smoked cigarettes in the past 12 months (yes/no). Participants' self-rated hearing was assessed with the question: "*Would you say your hearing is excellent, good, that you have a little trouble, moderate trouble, a lot of trouble, or are you deaf*?" We recategorized this variable into a binary format: **"**yes**"** for any hearing trouble (including responses of "little trouble," "moderate trouble," "a lot of trouble," or "deaf") and **"**no**"** for "excellent" or "good" hearing. Loud noise exposure was self-reported as: (1) *ever experiencing loud noise at a job for 4 hours or more per day, several days a week*, or (2) *ever exposed to loud noise or music for 10 or more hours a week that was outside of a job* (yes/no). Depression symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D) [27]. We defined significant depression symptoms as scores of 16+ on the CES-D.

2.5. Statistical Analysis

The study used descriptive statistics (*e.g*., means and proportions) to describe the sample as well as stratified by tinnitus status. χ^2 Tests or Fisher's exact tests (for categorical variables) and Kruskal-Wallis tests (for continuous variables) were used to compare the distributions of all variables by tinnitus status during the past 12 months. A modified Poisson regression model with robust error variances [28] to assess associations between cannabis use (any use and frequency of use) with tinnitus

status and tinnitus severity was used. Models for tinnitus severity were conducted only among those who reported tinnitus in the past 12 months. Separate models were performed for the overall sample and stratified analyses were conducted based on HIV status. Based on prior studies of risk factors for tinnitus [29-31], the model for the overall sample was adjusted for age, sex, race and ethnicity status, HIV status, loud noise exposure, self-rated hearing, smoking status and significant depressive symptoms, all of which were also associated with cannabis use in our sample. Models for the HIV-stratified analysis included the same set of covariates, with the HIV status variable excluded and HIV viral load suppression status and cumulate years of nucleoside reverse transcriptase inhibitors medication use (which have ototoxic effects) included as covariates. Missing data were substantial for current smoking (23%), cannabis use (23%), and significant depressive symptoms (25%), while all other variables had less than 5% missing data. Therefore, missing data for all variables were addressed using multiple imputations using chained equations [32]. Ten imputed data sets were generated for all variables, and modified Poisson regression models were conducted for each imputed dataset. The resulting prevalence ratios were combined according to Rubin's rules [33]. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

3. RESULTS

3.1. Sample Characteristics

The analytic sample comprised 3,437 participants, the majority of whom were female (55%), Black non-Hispanic individuals (54%), and PWH (63%) (Table **1**). The mean age was 55 years (SD=11). Thirty-one percent reported any cannabis use in the past 6 months. Additionally, 16% (n=545) of the sample reported experiencing tinnitus in the past 12 months (Table **1**). Tinnitus was reported by 14.4% of PWH and 18.1% of PWoH. Among participants with tinnitus (n=545), 65% (n=353) reported that their tinnitus was no problem or a small problem, while 35% (n=191) described it as a moderate to very big problem (Table **1**).

Table 1. Characteristics of the sample by tinnitus in the past 12 months.

	Tinnitus in the Past 12 Months						
	Overall (N=3,437)		Yes (n=545)		No (n=2,875)		
	n	%	n	%	n	%	*p*-value
Age in years (mean, standard deviation)	55 (11)		58 (11)		55 (11)		<0.01
Sex at birth							
Female	1803	54.8	230	43.8	1565	57.0	<0.01
Male	1486	45.2	295	56.2	1182	43.0	
Race and ethnicity							
Black, non-Hispanic	1783	54.3	194	37.0	1586	57.8	<0.01
White, non-Hispanic	890	27.1	240	45.7	643	23.4	
Hispanic	489	14.9	69	13.1	416	15.2	
Other	124	3.8	22	4.2	100	3.6	
HIV status							
Persons without HIV	1283	37.3	233	42.8	1041	36.2	<0.01
Persons with HIV	2154	62.7	312	57.2	1834	63.8	
Loud noise exposure‖							
No	2612	76.4	317	58.2	2294	79.8	<0.01
Yes	809	23.6	228	41.8	581	20.2	
Any trouble hearing							
No	2552	74.6	253	46.4	2298	79.9	<0.01
Yes	870	25.4	292	53.6	577	20.1	
Current smoking (past 6 months)							
No	1873	71.2	298	76.4	1570	70.4	0.01
Yes	756	28.8	92	23.6	660	29.6	
Significant depression symptoms‡							
No	1824	74.2	252	64.5	1570	76.1	<0.01
Yes	634	25.8	139	35.5	493	23.9	
Any cannabis use (past 6 months)							
No	1805	68.6	267	68.6	1533	68.6	0.99
Yes	827	31.4	122	31.4	701	31.4	

(Table 1) contd.....

	Tinnitus in the Past 12 Months						
	Overall (N=3,437)		Yes (n=545)		No (n=2,875)		
	n	%	n	%	n	%	*p*-value
Frequency of cannabis use (past 6 months)							
None	1805	68.2	267	67.8	1533	68.3	0.96
Occasional to moderate	469	17.7	70	17.8	396	17.7	
Heavy use	372	14.1	57	14.5	314	14.0	
Tinnitus problem severity†							
No significant problem	-	-	353	64.9	-	-	-
Significant problem	-	-	191	35.1	-	-	

Note: Frequencies do not always add up to the total due to missing data; ‖Self-reported as ever experiencing loud noise at a job for 4 hours or more per day and currently (past 12 months) loud noise exposure at work; †Among those with tinnitus in the past 12 months; ‡ Measured with the Center for Epidemiologic Studies Depression Scale (CES-D), significant depression symptoms defined as CES-D scores of 16 or more.

3.2. Association of Cannabis use with Tinnitus and Tinnitus Severity

Adjusted models for the overall sample revealed no significant association between cannabis use and the prevalence of tinnitus (adjusted prevalence ratio [aPR] = 1.03, 95% CI: 0.84, 1.25; Table 2). However, any cannabis use was associated with 29% lower prevalence of reporting tinnitus as a significant problem compared to non-users (aPR= 0.71, 95% CI: 0.54, 0.94; Table 2). Stratified analyses showed that among PWoH, cannabis use was similarly associated with lower prevalence of reporting tinnitus as a significant problem (aPR = 0.58, 95% CI: 0.37, 0.90; Table 2). Conversely, no significant associations between cannabis use and tinnitus outcomes were observed among persons with HIV.

Table 2. Association of cannabis use with tinnitus and tinnitus problem severity.

	Tinnitus Adjusted Prevalence ratios (95% CI)	Tinnitus problem severity‖ Adjusted Prevalence ratios (95% CI)
Overall Sample‡		
Cannabis		
No	Reference	Reference
Yes	1.03 (0.84, 1.25)	**0.71 (0.54 0.94)**
Frequency of cannabis use		
None	Reference	Reference
Occasional to moderate use	0.98 (0.76, 1.27)	0.69 (0.46, 1.02)
Heavy use	1.14 (0.88, 1.46)	**0.69 (0.50, 0.96)**
Among persons with HIV†		
Cannabis		
No	Reference	Reference
Yes	1.01 (0.71, 1.44)	0.62 (0.33, 1.13)
Frequency of cannabis use		
None	Reference	Reference
Occasional to moderate use	1.01 (0.69, 1.47)	0.85 (0.36, 1.98)
Heavy use	1.12 (0.72, 1.75)	0.44 (0.17, 1.09)
Among persons without HIV†		
Cannabis		
No	Reference	Reference
Yes	1.11 (0.85, 1.46)	**0.58 (0.37, 0.90)**
Frequency of cannabis use		
None	Reference	Reference
Occasional to moderate use	0.98 (0.66, 1.46)	**0.50 (0.27, 0.95)**
Heavy use	1.23 (0.82, 1.86)	0.61 (0.34, 1.10)

Note: ‡Models were adjusted for age, sex at birth, race/ethnicity, HIV status, loud noise exposure, self-rated hearing, smoking status, and significant depression symptoms; †The models for the HIV-stratified analyses were adjusted for the same covariates as the overall models, and HIV viral load suppression status and cumulative years of nucleoside reverse transcriptase inhibitors medication use;‖Among those with tinnitus in the past 12 months and defined as: "no significant problem (no problem or small problem)" *vs*. "significant problem (moderate, big, or very big problem). **Bold fonts** refer to statistically significant associations (p <0.05).

When considering the frequency of cannabis use, no significant associations with tinnitus prevalence were observed across the overall sample or in HIV-stratified analyses. However, heavy cannabis use was associated with reduced prevalence of reporting tinnitus as a significant problem in the overall sample (aPR = 0.69, 95% CI: 0.50, 0.96, Table **2**). Among persons PWoH, occasional-to-moderate cannabis use was significantly associated with lower prevalence of reporting tinnitus as a significant problem (aPR = 0.50, 95% CI: 0.27, 0.95). No significant associations were observed between the frequency of cannabis use and tinnitus outcomes among PWoH.

4. DISCUSSION

In this large, diverse sample of participants from the MWCCS cohort, we found no statistically significant association between cannabis use and tinnitus in the past 12 months compared to non-use. This lack of statistical association aligns with prior research finding no statistically significant link between cannabis use and tinnitus [22], yet contrasts with other reports, which reported a statistically significant association between cannabis use and an increased prevalence of tinnitus [20, 21]. These discrepancies may reflect differences in study populations, cannabis use patterns, tinnitus assessment methods, or the set of confounders adjusted in multivariable models. Further research using longitudinal designs and standardized measurements is necessary to clarify the relationship between cannabis use and tinnitus, as well as the underlying mechanisms that may explain these mixed findings.

Interestingly, in the overall sample and among persons without HIV, any cannabis use was significantly associated with a lower prevalence of reporting tinnitus as a moderate-to-very big problem. This finding is different from two prior studies that showed that among respondents with tinnitus, cannabis use was not associated with tinnitus severity [20, 21]. While we found no significant evidence that cannabis use was associated with a higher prevalence of reporting tinnitus, our findings suggest that among those who report tinnitus, cannabis use was associated with lower perceived severity of tinnitus. The mechanism by which cannabis may reduce tinnitus severity is unclear. However, it is possible that the anxiolytic properties of cannabinoids [34], may help patients manage stress and lessen the subjective impact of tinnitus on daily functioning. Additional research is needed to confirm these associations. Additionally, in a stratified analysis among those with HIV, the direction of the association between cannabis use and reporting tinnitus as a moderate-to-very big problem was similar to that in the overall sample and among those without HIV. However, confidence intervals around the prevalence estimates were wide, suggesting reduced precision. It is possible that this reduced precision might be due to differences in clinical burden and variability in the tinnitus symptom experience among persons with HIV. Additional studies are needed to further explore the association between cannabis and tinnitus severity in persons with HIV.

This study has some limitations that warrant consideration. First, because this analysis used cross-sectional data, it is not possible to determine the temporal relationship between cannabis use and tinnitus; the observed associations must be interpreted as correlational rather than causal. It also may be that individuals experiencing symptoms of tinnitus are using cannabis to reduce distress caused by their tinnitus, which could also contribute to the observed associations. Secondly, both tinnitus and cannabis use were self-reported and may be subject to misclassification bias. Specifically, misclassification of the cannabis and tinnitus prevalence-association, if non-differential, would likely bias estimates toward the null value, which likely explains, in part, our observed associations for tinnitus prevalence. On the other hand, the measurement of tinnitus problem severity is inherently subjective and may be influenced by several factors (*e.g.* psychological factors related to cannabis use). Therefore, the observed associations between cannabis use and tinnitus problem severity likely reflect either a true representation of tinnitus symptom burden or differences in perception and reporting. Further, our analysis did not capture other important cannabis parameters such as dosage, route of administration, or specific THC or CBD content of cannabis used, all of which could potentially impact tinnitus outcomes. Although we adjusted for established risk factors for tinnitus, residual confounding by unmeasured or imperfectly measured factors (including ototoxic medication exposures) and broader psychiatric comorbidities remains possible.

CONCLUSION

In this analysis of MWCCS data, cannabis use was not associated with a higher prevalence of tinnitus. However, cannabis use was associated with lower perceived severity of tinnitus. These findings raise the possibility that cannabis may be associated with lower perceived tinnitus burden. Given the cross-sectional design, potential for reverse causation, and residual confounding, these findings should be interpreted as hypothesis-generating. Additional research that leverages longitudinal designs, with better measurement of cannabis use and its constituents, is warranted.

LIST OF ABBREVIATIONS

PWH	=	Persons with HIV
PWoH	=	Persons without HIV
ART	=	Antiretroviral therapy
MACS	=	The Multicenter AIDS Cohort Study
WIHS	=	The Women’s Interagency HIV Study
MWCCS	=	The MACS/WIHS Combined Cohort Study

AUTHORS’ CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: C.O., M.P.: Study conception and design; D.W.:

Data analysis or interpretation; A.E., A.S., D.G., C.L., T.B., G.S., P.T., A.A., H.H., M.C.K., P.T., B.A., V.S., K.H., D.J., K.W., K.C., D.J.B.: Writing the paper. All authors reviewed the results and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All study procedures and protocols were reviewed and approved by the Institutional Review Boards for the respective MACS/WIHS Combined Cohort Study sites. (STUDY00002773 Emory University, 16882 JHBSPH IRB, Pro00055451 Advarra, BRANY File # 21-02-210-01E, 1544986-46 SUNY Downstate, 21-0857 UNC, BRANY File # 23-02-723-1540, 19071813 Rush, STU00022906 Northwestern University, 09-044 Cook County Health, 23015 JHSPH IRB, 1993-077 Georgetown University, INOVA-2024-142, IRB-20-2292 UCLA, 20210476 University of Miami, 2021H0423, The Ohio State University, STUDY21050072 University of Pittsburgh, 21-33925 UCSF, HS-21-00496 USC, 130607002 UAB, 2020-1120 UMMC).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

All participants provided written informed consent.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data of current study are available from corresponding author, [C.N.O], on a reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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