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Research article

Epidemiology and factors associated with cannabis use among patients with glaucoma in the *All of Us* Research Program

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A B S T R A C T

Purpose: To examine the epidemiology and factors of cannabis use among open-angle glaucoma (OAG) patients.
Methods: In this cross-sectional study, OAG participants in the *All of Us* database were included. Cannabis ever-users were defined based on record of cannabis use. Demographic and socioeconomic data were collected and compared between cannabis ever-users and never-users using Chi-Square tests and logistic regression. Odds ratios (OR) of potential factors associated with cannabis use were examined in univariable and multivariable models.
Results: Among 3723 OAG participants, 1436 (39%) were cannabis ever-users. The mean (SD) age of never-users and ever-users was 72.9 (10.4) and 69.2 (9.6) years, respectively ($P < 0.001$). Compared to never-users, Black (34%) and male (55%) participants were better represented in ever-users, while Hispanic or Latino participants (6%) were less represented ($P < 0.001$). Diversity was also observed in socioeconomic characteristics including marital status, housing security, and income/education levels. A higher percentage of ever-users had a degree ≥12 grades (91%), salaried employment (26%), housing insecurity (12%), and history of cigar smoking (48%), alcohol consumption (96%), and other substance use (47%) ($P < 0.001$). In the multivariable analysis, Black race (OR [95% CI] = 1.33 [1.06, 1.68]), higher education (OR = 1.19 [1.07, 1.32]), and history of nicotine product smoking (OR: 2.04–2.83), other substance use (OR = 8.14 [6.63, 10.04]), and alcohol consumption (OR = 6.80 [4.45, 10.79]) were significant factors associated with cannabis use. Increased age (OR = 0.96 [0.95, 0.97]), Asian race (OR = 0.18 [0.09, 0.33]), and Hispanic/Latino ethnicity (OR = 0.43 [0.27, 0.68]) were associated with decreased odds of use ($P < 0.02$).
Conclusions: This study elucidated the previously uncharacterized epidemiology and factors associated with cannabis use among OAG patients, which may help to identify patients requiring additional outreach on unsupervised marijuana use.

1. Introduction

Glaucoma is an irreversible disease and a worldwide leading cause of blindness [1,2]. Its most common form, open-angle glaucoma (OAG), affects at least 3 million people in the United States (US) [3,4], and reduction of intraocular-pressure (IOP) remains the only validated treatment [1]. Despite IOP-lowering treatments that are generally effective and safe, some patients self-medicate with non-prescription drugs or other unproven treatments for a variety of reasons [5,6].

Among substances with potential therapeutic effects for OAG, cannabis has garnered particular attention [6]. Some earlier studies have shown an IOP-reducing effect of cannabis [7–10]. However, its beneficial effects rely on the detailed components [11,12]. While some studies have shown neuroprotective effects of cannabis in animal models [13–15], evidence from humans remains lacking. The medical utility of cannabis is often limited by its psychoactive properties, short half-life, and patient tolerance [11]. Notably, its

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window between therapeutic effects and adverse effects is very narrow [6,16–18]. It is estimated that about 3 in 10 recreational cannabis users suffer from cannabis use disorder (CUD) [19], indicating the risk of abuse and health hazard in unsupervised cannabis use.

As the most accessible and commonly used federally illegal drug in the US [20], cannabis products are reported to be used by about 20% of Americans, and a more widespread use in the future is expected. The prevalence of past-year recreational cannabis use has increased from 10.4% in 2002 to 18.0% in 2019 [20], and as of July 2022, 19 states have approved recreational cannabis use. Recently, the Marijuana Opportunity Reinvestment and Expungement Act (MORE Act, H.R.3617), which proposed federal legalization of marijuana, was passed by the US House of Representatives. With increased access to recreational cannabis and information on the internet, more glaucoma patients may consider self-administering cannabis.

While an increased prevalence of cannabis use among OAG patients is anticipated [21], a substantial knowledge gap regarding the characteristics of cannabis use in this particular population remains. To fill the gap, in the current study, the epidemiology and factors associated with cannabis use in OAG were evaluated using the National Institutes of Health (NIH) *All of Us* database. For consistency, the term "cannabis" was used to refer to all types of cannabis products throughout this study.

2. Materials and methods

2.1. All of Us research program

This study adhered to the tenets of the Declaration of Helsinki. All data were obtained from the version 6 dataset of the NIH *All of Us* Research Program [22]. Participants of *All of Us* provided written informed consent at enrollment, which was approved by the *All of Us* Institutional Review Board (IRB). *All of Us* included a wide range of data from electronic health records (EHR), surveys, physical measurements, and biospecimen collection that can be accessed and analyzed using the cloud-based *All of Us* Researcher Workbench. All data are mapped to the Observational Health and Medicines Outcomes Partnership Common Data Model v5.2 maintained by the Observational Health and Data Sciences Initiative collaborative (https://www.ohdsi.org/). Prior to becoming available to researchers, *All of Us* data first underwent transformation and deidentification to protect participant privacy. Due to such processes, secondary analyses of the *All of Us* data, as performed in our study, was considered non-human subjects research by the University of California San Diego IRB.

2.2. Data processing

We defined our study cohort as participants aged $\geq$18 years with a diagnosis of OAG based on *All of Us* EHR condition codes (Supplemental t. 1). Definition for cannabis use was based on records indicating any cannabis use in any of the following data: (1) survey, (2) diagnosis condition, or (3) labs and measurements (details provided in Supplemental t. 2). Participants were then categorized as "cannabis ever-user" or "never-user".

After building the study cohort, demographic and socioeconomic survey data potentially relevant to cannabis use were identified from the *All of Us* database. Briefly, data items in the following dimensions were considered: (1) basic demographics (all items in the *All of Us* demographic package were included), (2) education level, (3) housing and living situations, (4) income level, (5) employment status, (6) marital status, (7) health insurance and type, (8) history of smoking, (9) history of alcohol consumption, and (10) history of other substance use (cocaine, hallucinogens, sedatives, opioids, etc.). Data items with survey response rate $<$30% were excluded, and data imputation (mode for categorical variables and mean for continuous variables) was performed for all included variables with missingness. Details of the socioeconomic survey data included in the final analysis are provided in Supplemental t. 3. The concept set including the aforementioned data items was then combined with the study cohort to create the final study dataset, which was analyzed using the *All of Us* Jupyter environment.

2.3. Statistical analysis

All statistical analyses were performed in an R notebook within the *All of Us* Workbench. The following R packages were used: ggplot2, tibble, tidyr, readr, purrr, dplyr, stringr, forcats. For comparison of the characteristics between OAG cannabis ever-users and never-users, Chi-square testing was performed for categorical variables and two-sample t-tests were performed for continuous variables after verifying that assumptions of t-tests were valid in this cohort. Any counts smaller than 20 (and their percentage) were censored when reported in the results, per *All of Us* policies to prevent re-identification of study participants. When the count of a data item was smaller than 20, it was re-coded as "$<$ 20" in the table, and its percentage was recoded to "x%" where "x" = 100*20/summary of the group. To identify factors associated with cannabis use among OAG patients, univariable and multivariable logistic regression modeling was performed. In logistic regression modeling, correlation coefficients were generated for each data variable, and bivariate analyses were performed to calculate the bivariate (crude/unadjusted) odds ratios (ORs), 95% confidence intervals (CIs), and associated P-values for determining statistically significant factors. Bidirectional stepwise feature selection with Akaike information criterion was used to select the most suited variables for multivariable analysis, while variables showing a high correlation coefficient $>$0.8 were removed to avoid multicollinearity. The adjusted ORs (95% CIs) and associated P-values of the potential factors were then reported using the best-performing multivariable model. To examine if factors associated with cannabis use differ between OAG and general public, a supplemental multivariable logistic regression modeling was performed on the general *All of Us* population, with the participants categorized into cannabis ever-users and never-users using the same method. Due to the issue of multiple comparison,

which is often observed in big-data studies, the cut-off P-value for statistical significance was adjusted to $P < 0.02$ in this study [23,24].

3. Results

3.1. General demographics

A total of 3723 OAG patients were identified in *All of Us*, of which 1436 (39%) were categorized as cannabis ever-users. The general demographic data of all participants are shown in Table 1. The two groups (cannabis ever-users vs. never-users) showed significant differences in age, gender, self-reported race and ethnicity ($P < 0.001$ for all). The mean (standard deviation [SD]) age of never-users and ever-users was 72.9 (10.4) and 69.2 (9.6) years, respectively. The majority of never-users were female (n = 1322, 58%), while there were more males (n = 790, 55%) among ever-users. Black participants represented 34% (n = 494) and 25% (n = 570) and White participants represented 56% (n = 803) and 48% (n = 1102) of cannabis ever-users and never-users, respectively. Asian participants were the least represented (<5% in both groups). The percentage of Hispanic or Latino participants was lower in ever-users (6%, n = 90), as compared to that of never-users (21%, n = 486).

The geographic distribution was also diverse ($P < 0.001$), with greater differences noticed in Illinois (ever-users = 15%; never-users = 9%), New York (ever-users = 12%; never-users = 20%), and a non-disclosed state (ever-users = 17%; never-users = 11%). Fig. 1 illustrates the prevalence of cannabis use among OAG participants by state based on *All of Us* data. Among states with available data, a higher prevalence of cannabis use among OAG participants was observed in the Midwest (particularly East North Central, e.g. Michigan and Illinois) and Northeast (particularly Middle Atlantic, e.g. New York and Pennsylvania) regions. States in the southern US generally have a lower prevalence of cannabis use.

3.2. Socioeconomic characteristics

Table 2 summarizes the socioeconomic characteristics of the two groups. Interestingly, significant differences were observed in most characteristics. Overall, cannabis ever-users had a higher education level ($P < 0.001$), with approximately 91% of the participants

Table 1
Demographic data of cannabis ever-users and never-users identified from the *All of Us* Research Program among participants diagnosed with open-angle glaucoma (OAG).

	OAG participants (N = 3723)		*P*-value
	Never-user, N = 2287 (61%)	Cannabis ever-user, N = 1436 (39%)	
Age (Mean, SD), yrs	72.9 (10.4)	69.2 (9.6)	**<0.001**
Gender (n, %)			**<0.001**
Male	965 (42%)	790 (55%)	
Female	1322 (58%)	646 (45%)	
Self-Reported Race (n, %)			**<0.001**
Black or African American	570 (25%)	494 (34%)	
White	1102 (48%)	803 (56%)	
Asian or Other	615 (27%)	139 (9%)	
Self-Reported Ethnicity (n, %)			**<0.001**
Not Hispanic or Latino	1801 (79%)	1346 (94%)	
Hispanic or Latino	486 (21%)	90 (6%)	
Geographic distribution (n, %)			**<0.001**
California	278 (12%)	175 (12%)	
Florida	190 (8%)	73 (5%)	
Illinois	216 (9%)	206 (14%)	
Arizona	44 (2%)	30 (2%)	
Pennsylvania	218 (10%)	151 (11%)	
Mississippi	<20 (1%)	<20 (1%)	
Massachusetts	169 (7%)	149 (9%)	
Georgia	<20 (1%)	<20 (1%)	
New York	450 (20%)	169 (12%)	
State Information Suppressed for Privacy	257 (11%)	242 (17%)	
Texas	40 (2%)	<20 (1%)	
Wisconsin	197 (8%)	102 (7%)	
Michigan	188 (8%)	118 (8%)	
Alabama	<20 (1%)	<20 (1%)	
Connecticut	<20 (1%)	<20 (1%)	
Louisiana	<20 (1%)	<20 (1%)	
Tennessee	<20 (1%)	<20 (1%)	

*P values of statistically significant variables were shown in bold.
Footnote: Per All of Us data policy, data collapse has been performed across cells for variables initially containing a single cell with a count of <20, in order to prevent data triangulation and deduction.
Abbreviation: SD = standard deviation; NA = not answered.

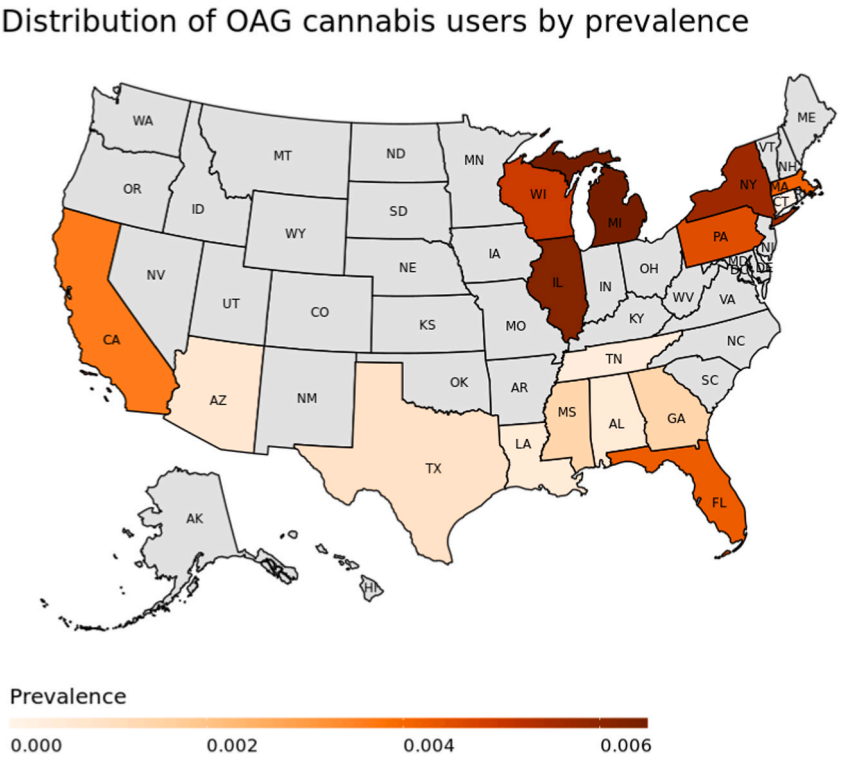

Fig. 1. The prevalence of cannabis use among open angle glaucoma (OAG) participants by state based on *All of Us* data. The prevalence was calculated by dividing the number of cannabis ever-users by the number of OAG participants in the state. The greyed area indicated states where data of cannabis use were not available or no OAG participants were enrolled in the *All of Us program*.

obtaining a degree higher than 12th grade or general education development (vs. never-users = 84%). The distribution of marital status was also different ($P < 0.001$). Most never-users were married (49%), divorced (18%), or widowed (14%), while 44% of ever-users were married, 20% divorced, and 20% never married. For living situation, no difference was found for the number of children and people living together in the household.

Regarding housing security, significantly more ever-users (12%) indicated stable home concern over the past 6 months, as compared to 8% in never-users ($P < 0.001$), although there was not significant difference in the percentage of home owners/renters between the two groups. A higher percentage of never-users were not currently employed for wages (77%, vs. ever-users = 73%; $P < 0.001$). For the annual income, although the percentage distribution was similar within the range of 25 k-150 k, more cannabis ever-users reported an annual income of >150 k (12%) or <25 k (26%), as compared to never-users (>150 k: 7%, <25 k: 21%). Of note, 30% and 18% of never-users and ever-users did not answer this question, respectively. In both groups, 96% of participants were medically insured; however, most did not provide information regarding the insurance type.

3.3. History of smoking, alcohol consumption, and other substance use

Overall, a higher prevalence of past smoking, alcohol consumption, and other substance use was observed in cannabis ever-users (Table 3). Approximately 9–10% of ever-users reported past use of smokeless tobacco, electronic nicotine products, and hookah (vs. never-users = 2–3%), and 48% reported past cigar use (vs. never-users = 22%) ($P < 0.001$ for all). For cigarette smoking, 42% and 10% of cannabis ever-users and 27% and 3% of never-users self-identified as non-current smokers and current daily smokers, respectively ($P < 0.001$). Nonetheless, 67% of never-users and 48% of ever-users did not answer about current cigarette use. No difference was found for the daily amount of current and average cigarette smoking and the mean duration of cigarette smoking.

Regarding past alcohol consumption, 96% of cannabis ever-users reported a positive history, while only 80% of never-users did. Additionally, around 31% of ever-users reported a drinking frequency greater than 2–3 times per weeks, while only 18% of never-users did ($P < 0.001$ for both). A higher average daily count of drink was also observed for ever-users, with 15–16% of participants reporting a daily count of >3–4 drinks (vs. never-users = 7–8%). Notably, a much higher percentage of never-users did not provide information on frequency and daily amount of alcohol consumption. As for history of other substance use, 47% of cannabis ever-users reported a positive history, as compared to 7% in never-users ($P < 0.001$).

Table 2
Socioeconomic characteristics of cannabis ever-users and never-users identified from the *All of Us* Research Program among participants diagnosed with open-angle glaucoma (OAG).

	Never-user	Cannabis ever-user	P-value
Education level (n, %)			<0.001
College graduate or advanced degree	994 (43%)	686 (48%)	
Highest grade: College year 1–3	531 (23%)	398 (28%)	
Highest grade: 12 or GED	412 (18%)	213 (15%)	
Less than a high school degree or equivalent	287 (13%)	113 (8%)	
NA	63 (3%)	26 (2%)	
Marital status (n, %)			**< 0.001**
Divorced	402 (18%)	287 (20%)	
Living with partner	44 (2%)	64 (4%)	
Married	1114 (49%)	629 (44%)	
Never married	301 (13%)	281 (20%)	
Separated	73 (3%)	44 (3%)	
Widowed	309 (14%)	109 (8%)	
NA	44 (2%)	22 (2%)	
Living situation (mean, SD)			
Number of people living together	1.2 (1.3)	1.1 (1.1)	0.04
Number of people younger than 18 years-old in the household	0.3 (0.7)	0.3 (0.7)	0.56
Housing situations (n, %)			0.02
Home owner	1282 (56%)	749 (52%)	
Home renter	844 (37%)	587 (41%)	
Other arrangement	95 (4%)	72 (5%)	
NA	66 (3%)	28 (2%)	
Stable home concern over past 6 months (n, %)			**< 0.001**
Yes	182 (8%)	169 (12%)	
No or NA	2104 (92%)	1267 (88.6%)	
Employment status (n, %)			**< 0.001**
Not currently employed for wages	1766 (77%)	1045 (73%)	
Employed for wages/self-employed or NA	521 (23%)	391 (27.3%)	
Annual income (n, %)			**0.005**
>200 k	103 (4%)	104 (7%)	
150 k-200 k	66 (3%)	73 (5%)	
100 k-150 k	210 (9%)	135 (9%)	
75 k-100 k	178 (8%)	124 (9%)	
50 k-75 k	217 (9%)	163 (11%)	
35 k-50 k	173 (8%)	94 (6%)	
25 k-35 k	171 (7%)	102 (7%)	
10 k-25 k	284 (12%)	203 (14%)	
Less than 10 k	218 (9%)	175 (12%)	
NA	667 (30%)	263 (18%)	
Health insurance (n, %)			**0.009**
Any health insurance	2206 (96%)	1372 (96%)	
Not insured	39 (2%)	44 (3%)	
NA	42 (2%)	20 (1%)	

*P values of statistically significant variables were shown in bold.
Footnote: Per All of Us data policy, data collapse has been performed across cells for variables initially containing a single cell with a count of <20, in order to prevent data triangulation and deduction.
Abbreviation: SD = standard deviation; GED = general education development; NA = not answered.

3.4. Factors associated with cannabis use

Potential factors associated with cannabis use in OAG are presented in Table 4. In the univariable analysis, many factors were significantly associated with increased odds of cannabis use, including male gender, higher education level, marital status being never married or living with partners, and having stable house concern ($P < 0.02$ for all). A positive history of smokeless tobacco, electronic nicotine product, hookah and cigar smoking, alcohol consumption, higher frequency of alcohol consumption, and any other substance use were also significant factors of cannabis use ($P < 0.001$ for all). In contrast, some other factors were found to be associated with decreased odds of cannabis use, such as increased age, Asian and other races, Hispanic or Latino ethnicity, marital status being married or widowed, not currently employed for wages, and having medical insurance ($P < 0.02$ for all).

In the multivariable analysis, Black or African American race (OR [95%CI] = 1.33 [1.06, 1.68]), higher education level (OR = 1.19 [1.07, 1.32]), and positive history of electronic nicotine product use, tobacco smoking in hookah, and cigar smoking (range of OR: 2.04–2.83) remained significantly associated with increased odds of cannabis use ($P < 0.02$ for all). The strongest risk factor was history of other substance use (OR = 8.14 [6.63, 10.04]), followed by history of alcohol consumption (OR = 6.80 [4.45, 10.79]) ($P < 0.001$ for both). As for factors associated with decreased odds of cannabis use, after adjusting for other variables, only increased age (OR = 0.96 [0.95, 0.97]), Asian race (OR = 0.18 [0.09, 0.33]), and Hispanic or Latino ethnicity (OR = 0.43 [0.27, 0.68]) remained

Table 3
History of smoking, alcohol consumption, and other substance use in cannabis ever-users and never-users identified from the *All of Us* Research Program among participants diagnosed with open-angle glaucoma (OAG).

	Never-user	Cannabis ever-user	P-value
History of smoking (n, %)			
History of smokeless tobacco use			**< 0.001**
No	2167 (95%)	1287 (90%)	
Yes	67 (3%)	129 (9%)	
NA	53 (2%)	20 (1%)	
History of electronic nicotine products use			**< 0.001**
No	2188 (96%)	1266 (88%)	
Yes	46 (2%)	142 (10%)	
NA	53 (2%)	28 (2%)	
History of tobacco smoking in hookah			**< 0.001**
No	2190 (96%)	1264 (88%)	
Yes	37 (2%)	137 (10%)	
NA	60 (3%)	35 (2%)	
History of cigar smoking			**< 0.001**
No	1709 (75%)	727 (51%)	
Yes	506 (22%)	685 (48%)	
NA	72 (3%)	24 (2%)	
Frequency of current cigar smoking			**0.006**
Not at all	491 (21%)	607 (42%)	
Some days or everyday	39 (1.5%)	79 (5.5%)	
NA	1757 (77%)	750 (52%)	
Frequency of current cigarette smoking			**< 0.001**
Not at all	628 (27%)	685 (48%)	
Some days	43 (2%)	83 (6%)	
Everyday	80 (3%)	149 (10%)	
NA	1536 (67%)	685 (48%)	
Current daily amount of cigarette smoking (mean, SD)	3.5 (8.0)	4.5 (9.9)	0.04
Years of cigarette smoking (mean, SD)	23.7 (15.7)	24.1 (15.4)	0.36
Average daily amount of cigarette smoking (mean, SD)	15.8 (13.6)	17.1 (14.0)	0.09
History of alcohol consumption (n, %)			
History of alcohol consumption			**< 0.001**
No	399 (17%)	27 (2%)	
Yes	1832 (80%)	1381 (96%)	
NA	56 (2%)	28 (2%)	
Frequency of alcohol consumption in the past year			**< 0.001**
Never	508 (22%)	287 (20%)	
Monthly or less	629 (28%)	381 (27%)	
2-4 times per month	299 (13%)	274 (19%)	
2-3 times per week	173 (8%)	200 (14%)	
4 or more times per week	223 (10%)	237 (17%)	
NA	455 (20%)	57 (4%)	
Average daily count of drink			**< 0.001**
1-2	1138 (50%)	848 (59%)	
3-4	126 (6%)	170 (12%)	
5-6	<20 (1%)	33 (3%)	
7-9	<20 (1%)	<20 (1%)	
10 or more	<20 (1%)	<20 (1%)	
NA	1002 (44%)	364 (25%)	
History of other substance use (n, %)			**< 0.001**
Yes	163 (7%)	672 (47%)	
No or NA	2124 (93%)	764 (52.9%)	

*P values of statistically significant variables were shown in bold.
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Abbreviation: SD = standard deviation; GED = general education development; NA = not answered.

significantly associated with decreased odds of use ($P < 0.02$ for all).

3.5. Supplemental analysis on the general All of Us population

For supplemental analysis on the general *All of Us* population, a total of 349,150 participants aged 18 or older were included, of which 180,917 (52%) were cannabis ever-users. The mean (SD) age of cannabis ever-users and never-users in this population was 53 (16.1) and 56 (17.2) years, respectively ($P < 0.001$). Factors associated with cannabis use in the general *All of Us* population are presented in Supplemental T. 4. Overall, race/ethnicities and substance use behaviors previously identified to be associated with cannabis use among OAG patients showed similar results. More socioeconomic factors, including marital, insurance, living and

Table 4
Potential risk factors associated with cannabis use among participants diagnosed with open-angle glaucoma (OAG) enrolled in the *All of Us* Research Program.

	Bivariate OR (95% CI)	P-Value	Multivariable OR (95% CI)	P-Value
Demographic factors				
Age	0.97 (0.96, 0.97)	**< 0.001**	0.96 (0.95, 0.97)	**< 0.001**
Male gender	1.68 (1.47, 1.91)	**< 0.001**	1.12 (0.94, 1.34)	0.21
Race: Black or African American	1.19 (1.02, 1.38)	0.02	1.33 (1.06, 1.68)	**0.013**
Race: Asian	0.25 (0.14, 0.40)	**< 0.001**	0.18 (0.09, 0.33)	**< 0.001**
Race: Others	0.32 (0.26, 0.40)	**< 0.001**	0.86 (0.56, 1.31)	0.49
Ethnicity: Hispanic or Latino	0.25 (0.20, 0.31)	**< 0.001**	0.43 (0.27, 0.68)	**< 0.001**
Socioeconomic factors				
Increased education level	1.18 (1.11, 1.26)	**0.013**	1.19 (1.07, 1.32)	**0.001**
Marital status: living with partner	2.04 (1.35, 3.09)	**0.001**	1.30 (0.78, 2.16)	0.31
Marital status: married	0.79 (0.66, 0.94)	**0.009**	0.81 (0.63, 1.05)	0.11
Marital status: never married	1.31 (1.05, 1.63)	**0.018**	1.02 (0.76, 1.35)	0.92
Marital status: separated	0.84 (056, 1.26)	0.41	1.00 (0.59, 1.68)	0.99
Marital status: widowed	0.49 (0.38, 0.64)	**< 0.001**	0.79 (0.57, 1.10)	0.16
Increased number of people living together	0.94 (0.89, 0.99)	0.03	0.96 (0.88, 1.04)	0.27
Home owner	0.76 (0.55, 1.05)	0.09	0.96 (0.63, 1.49)	0.85
Home renter	0.92 (0.67, 1.27)	0.60	1.24 (0.82, 1.91)	0.32
Stable house concern: yes	1.54 (1.24, 1.92)	**< 0.001**	1.14 (0.85, 1.53)	0.39
Not currently employed for wages	0.75 (0.64, 0.87)	**0.008**	1.11 (0.90, 1.37)	0.35
Increased annual income level	1.03 (1.00, 1.06)	0.05	1.01 (0.96, 1.06)	0.72
Medical insurance: yes	0.55 (0.35, 0.85)	**0.007**	1.18 (0.64, 2.17)	0.60
History of smokeless tobacco use: yes	3.27 (2.43, 4.45)	**< 0.001**	1.43 (0.99, 2.08)	0.06
History of electronic nicotine product use: yes	5.35 (3.84, 7.58)	**< 0.001**	2.34 (1.55, 3.56)	**< 0.001**
History of tobacco smoking in hookah: yes	6.41 (4.48, 9.41)	**< 0.001**	2.83 (1.84, 4.45)	**< 0.001**
History of cigar smoking: yes	3.21 (2.78, 3.71)	**< 0.001**	2.04 (1.68, 2.47)	**< 0.001**
History of alcohol consumption: yes	11.03 (7.54, 16.77)	**< 0.001**	6.80 (4.45, 10.79)	**< 0.001**
Increased frequency of alcohol consumption	1.25 (1.19, 1.32)	**< 0.001**	1.16 (1.09, 1.24)	**< 0.001**
History of any other substance use: yes	11.46 (9.50, 13.90)	**< 0.001**	8.14 (6.63, 10.04)	**< 0.001**

*P values of statistically significant variables were shown in bold.
Abbreviation: OR = Odds ratio.

housing status, demonstrated significant effects in this population ($P < 0.02$), potentially due to the greater sample size. Notably, a higher education level was significantly associated with lower odds of cannabis use (OR = 0.94 [0.94, 0.95], $P < 0.001$) among the entire *All of Us* population, in contrast to the greater odds among OAG patients.

4. Discussion

Based on our results, OAG cannabis ever-users and never-users differed demographically and socioeconomically. Black and male participants were better represented in ever-users, who are more likely to have a higher education level, employment with wages, stable home concern, and history of other addictive substance use. In the multivariable model, Black race, higher education level, and history of smoking, alcohol consumption, and other substance use were associated with cannabis use in OAG, while older age, Asian race, and Hispanic/Latino ethnicity were associated with decreased odds of use.

In the 2019 National Survey on Drug Use and Health (NSDUH), lifetime cannabis use was reported by 46% of US population $\geq$ 12 years [20]. In comparison, a lower prevalence was found among our OAG cohort, which is partially attributed to the lower prevalence of cannabis use in individuals age $\geq$ 65 years [25–27]. This is further supported by the higher rate (~52%) of cannabis ever-users found in the entire *All of Us* population, of which the mean age was younger. Consistent with prior works [25,27], older age was found protective of cannabis use in this analysis. Another demographic factor affecting substance use behavior is gender. As compared to females, males were more likely to use cannabis, and with a higher frequency and quantity of use [28–30]. Although gender was not a significant factor in our model, a higher percentage of males was still observed in OAG cannabis users.

With the diverse enrollment of *All of Us* [31], we were able to compare the racial/ethnic and geographic distribution of the two groups. Although data of some states were not available, a similar distribution of cannabis ever-users and never-users was observed in most states where cannabis has been fully legalized, including California, Michigan, and Massachusetts. While in New York, where recreational cannabis was only legalized in 2021, the percentage of never-users was much higher than that of ever-users. Considering the legality of cannabis might interact with other factors and affect the pattern of cannabis usage across states, we further examined its effect in the multivariable model. As expected, in comparison to medical legality (i.e., cannabis legalized only for medical use), full legality of cannabis was significantly associated with greater odds of use among OAG patients (OR = 1.32, P = 0.003). Unfortunately, there was no available patient-level geographic information from states where cannabis use is illegal. Given the limited data, these findings await confirmation. Nevertheless, it may be interesting to evaluate the state-level distribution of cannabis ever-users based on future changes in cannabis legality, which will also help understand the potential impact of cannabis legalization on a federal level.

In this study, Black race was found more associated with cannabis use in OAG, while Asians and Hispanic/Latino ethnicity were less

associated. Consistent with our findings, a lower prevalence of cannabis use and complications has been reported for Asian and Hispanic/Latino individuals [32–34], whereas Black/African Americans were reported with the highest prevalence [32–35]. Such racial/ethnic difference was also observed in the ways of cannabis use and purchase [32,36,37], expense on cannabis [37,38], and cannabis -associated medical conditions [34,39]. Notably, a higher risk was not found for Black race in other addictive substance use, such as alcohol and cocaine [33]. The stronger association between Black race and cannabis use is considered multifactorial, with factors like motives of use [40,41], age and emotion regulation [35], peer pressure [42], and disadvantaged financial/living condition invovled [35,43,44]. The higher prevalence of cannabis use among Black individuals is especially important in the context of OAG, which disproportionately impact Black individuals and has been associated with earlier disease onset, faster progression, and higher rates of visual impairment in this population [45–49]. More studies are needed to clarify the varying racial/ethnic diversities associated with different substances, including cannabis.

A comprehensive socioeconomic comparison between OAG cannabis ever-users and never-users was performed in this study. While differences were found in many characteristics, in the multivariable model, only a higher education level remained a significant factor associated with cannabis use. One possibility is that OAG participants of higher education are more likely to search for therapeutic information, thus more prone to self-medication with cannabis [7,8,50]. Another possibility is these patients may be more familiar with knowledge about cannabis, thus more confident in using it without supervision. Interestingly, a prior study using NSDUH data has shown an association between lower educational level and increased odds of cannabis dependence [51]. Some community studies have also linked early cannabis initiation to low education attainment [52,53]. In the supplemental analysis on the entire *All of Us* population (Supplemental T. 4), we found a higher education level to be protective against cannabis use. The discrepant results indicate the potentially distinctive patterns of cannabis use among OAG patients in relation to the general public. Furthermore, this suggests self-medication may be a possible mechanism of cannabis use among OAG patients, particularly the more well-educated ones, although further research would be needed to investigate this, given this was not specifically asked in *All of Us*.

Our analysis also demonstrated that cannabis use in OAG was associated with a positive history of smoking, alcohol consumption, and other substance use. This is unsurprising, as similar results have been reported in studies not limited to OAG [33,54–58], and the association between uses of different addictive substances has been well established [57–59]. Although expected, such association remains relevant. There has been growing literature indicating a negative effect of these lifestyle choices on glaucoma development and progression [60–65]. Moreover, studies on how different substances may interact and affect OAG remains lacking. It is unknown whether cannabis might mitigate or magnify the effects of other substances on OAG, and there has not been definite evidence on the effects of cannabis on the disease process of OAG. While more research is needed, our study shows a fairly high prevalence of cannabis use associated with past history of other addictive substance use among OAG individuals, which demonstrates the need for future investigation regarding polysubstance use and glaucoma risk.

From a public health perspective, demographic risk factors can be easily obtained in ophthalmic clinics, whereas socioeconomic and social history risk factors, particularly substance use history, are often neglected. In prior studies, the use of nicotine products, alcohol and illicit drugs was associated with not only cannabis use but also complications like CUD [30,33,66–69], which often require medical intervention [17–19]. Additionally, the psychoactive effects of cannabis could impair daily tasks performing such as driving [70,71]. Considering the higher risk of driving accidents in elder and visually-impaired individuals [72,73], OAG cannabis users might be at even greater risk [74]. Of note, patients self-administering cannabis may be less likely to seek professional help when needed. Therefore, it is important that ophthalmologists attend to these risk factors and provide patient outreach and education on the risk-benefit of unsupervised cannabis use when appropriate. If signs indicating potential cannabis or substance use disorder are present, a complete social history should be taken to evaluate the need for professional intervention.

4.1. Limitations

This study had a few limitations. First, cannabis ever-users were identified based on any positive survey or EHR data, so it is possible that data of some users were not available. Moreover, data regarding the forms (e.g. ingestion, inhalation) and time-horizon (current vs. former use/times/frequencies) of cannabis use were not available, although such information may help to better clarify the differing user characteristics and patterns of use among cannabis ever-users. Second, due to difficulty in determining the timing of first cannabis use, only the cross-sectional association was analyzed, but not the temporal or causal relationship. Third, since substance use is a complex issue, there might be residual risk factors not considered in this study, and the intent of cannabis use could not be clarified. Last, there are some inherent limitations of big-data studies, such as the possibility of incomplete, missing, or inaccurate data and sampling bias [75]. Additionally, while the data collection was confidential and de-identified, response bias in cannabis use might still be present due to possible social stigma and the inclusion of participants or collection of responses prior to cannabis legalization [76], which can result in an underestimated prevalence. As discussed earlier, a substantial knowledge gap exists regarding this topic. Despite the aforementioned limitations, as a pioneering study, our results may still provide insight into the characteristics of cannabis use in OAG.

In conclusion, using a diverse nationwide dataset, we elucidated the epidemiology and factors associated with cannabis use among OAG patients, which has not previously been characterized. As the prevalence of cannabis use increases, this study may help identify OAG patients requiring additional outreach on unsupervised cannabis use, and motivate future studies on the effects of cannabis on glaucoma development and progression.

Author contribution statement

Bharanidharan Radha Saseendrakumar, MS; Sally L. Baxter, MD, MSc; Jo-Hsuan Wu, MD: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Sasan Moghimi, MD; Robert N. Weinreb, MD: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Sophia Sidhu, MS; Alireza Kamalipour, MD, MPH: Analyzed and interpreted the data; Wrote the paper.

Data availability statement

The authors do not have permission to share data.

Additional information

Supplementary content related to this article has been published online at [URL].

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e15811.

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