Alcohol and Cannabis Use Associated with Cardiometabolic Biomarkers among "All of Us" Cancer Survivors

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ABSTRACT

Background: Cancer survivors are at increased risk for cardiometabolic comorbidities following cancer treatment, which may be further exacerbated by cannabis and alcohol use. We aimed to examine the direct relationships of cannabis, alcohol, and the co-use of both substances with cardiometabolic risk factors and to explore disparities by race/ethnicity and sex.

Methods: Cross-sectional data were extracted from adult cancer survivors in the "All of Us" from 2018 to 2022. Cannabis use was defined as occasional or frequent/regular cannabis use (vs. never) in the past 3 months and hazardous alcohol intake (AUDIT-C >3 for females; AUDIT-C >4 for males) versus nonhazardous in the past year, respectively. Co-use was defined as participants who engaged in regular cannabis and hazardous alcohol intake. We identified binary cardiovascular, immune, and metabolic system biomarkers, with high values defined by clinically established cutoffs or >75th percentile. We used multivariable logistic regression adjusting for sociodemographic and clinical factors.

Results: In our sample ($N = 7{,}054$), 7.6% were Hispanic, 6.2% were Black, and 86.2% were White cancer survivors. Less than 5% of Hispanic and White survivors reported substance co-use compared with 7% of Black survivors. Compared with never-users, co-users were 1.58 (95% confidence interval, 1.14–2.19) more likely to have high blood pressure. No significant associations were found between co-use and immune biomarkers or sex differences.

Conclusions: Co-use of cannabis and hazardous alcohol may worsen high blood pressure in survivors, who are at higher risk for cardiometabolic comorbidities.

Impact: The study investigates substance use and cardiometabolic biomarkers, urging much research on their effects on cancer survivors.

Introduction

By 2026, there will be more than 20 million cancer survivors in the United States (1, 2). Although the decrease in cancer mortality is a result of advancements in cancer treatment, evidence demonstrates that the leading cause of death among cancer survivors is cardiometabolism-related illnesses (3). Therefore, in this high-risk population, there is a critical need for identifying risk to prevent chronic cardiometabolic illnesses.

Cancer survivors have a higher risk for cardiovascular disease and type 2 diabetes risk compared with noncancer survivors (4, 5). Although there is evidence (6, 7) that some cancer treatments may increase risk for these comorbid conditions (8), there is limited evidence on the association between co-substance use, such as cannabis and alcohol usage, and cardiometabolic biomarkers among cancer survivor populations.

Cannabis and/or alcohol may contribute to existing cardiovascular and chronic conditions for cancer survivors. Cannabis use in the United States among cancer survivors varies between 8% and 25% (9, 10). Among cancer survivors undergoing treatment, cannabis use has been shown to help alleviate symptoms, including sleep, mental health, and physical problems (11–13). However, cannabis use may also affect cardiovascular health (14–17). For example, cannabis use may affect the cannabinoid receptors present in the central nervous system and adipose tissue, increasing the heart rate and cardiac contractility, elevating the myocardial oxygen demands, and leading to changes in blood pressure (BP) and vascular resistance (17, 18). According to the American Heart Association, cannabis users present with cardiometabolic risk factors such as high BP, type 2 diabetes or high cholesterol, and worse cardiovascular events than those who are non-cannabis users (16).

Increased alcohol consumption has also been linked to increased cardiometabolic events such as hypertension, dyslipidemia, type 2 diabetes, and obesity (19), as well as cancer reoccurrence, new cancers, and mortality (20, 21). Alcohol intake may affect the endothelium which is important in vascular functioning, and dysregulation from regular alcohol use may damage the blood vessels and influence future cardiovascular events (22). Alcohol intake is attributed to 4.8% of all cancer incidence and 3.2% of cancer mortality in the United States for those ages 30 years and older (23).

Given the limited evidence on the association between substance use and cardiometabolic biomarkers among cancer survivors, we explored the independent association in a large cancer survivorship cohort identified in the All of Us (AoU) Research Program. Finally, we assessed whether these independent associations differed by race/ethnicity and biological sex.

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Materials and Methods

Data collection and sample

The "AoU" is an NIH-funded program that is open to anyone of 18 years of age and older in the United States. Participants signed a consent form following the Declaration of Helsinki for data collection. Cross-sectional measurement, laboratory, and survey data collected from May 2018 to July 2022 for this study were de-identified and made available to approved researchers. The AoU program was approved by the NIH Institutional Review Board.

Our cohort included participants who were ever told by their healthcare provider that they had/have cancer (n = 37,146). We excluded participants who were missing any of our exposure variables (cannabis or hazardous alcohol use), those with multiple cancer sites, those with missing self-reported race/ethnicity, and those who reported skin cancer given that skin cancer is one of the most prevalent cancers in the United States, not often tracked on most cancer registries, and having more than 90% 5-year survival rate (24). Our final analytic sample size was n = 7,054 (**Fig. 1**), in which we saw no major differences in the distribution of those included and excluded in the outcome variables (Supplementary Table S1).

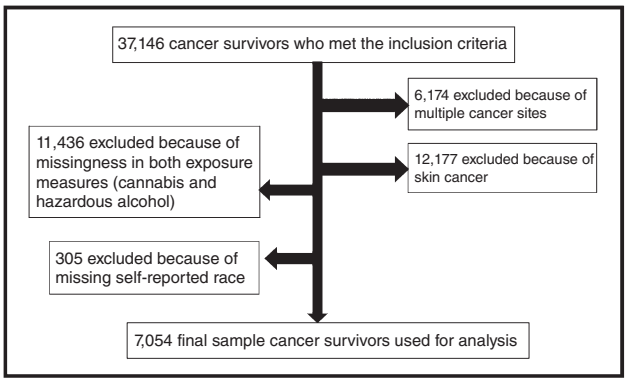

Figure 1.
Decision tree outlining the cohort's inclusion and exclusion criteria. The decision tree outlines the step-by-step process for the inclusion and exclusion of participants, detailing the number of cancer survivors retained in the final analytic sample. At each stage, specific exclusion criteria were applied, resulting in a sequential sample size reduction. The initial cohort size, exclusions at each step (e.g., multiple cancer sites and incomplete data), and final eligible sample size are displayed, illustrating the flow from the initial cohort to the final analytic group used in the analysis.

Measures

Demographics and covariates: Demographic characteristics included in our study were age in years (at survey completion), biological sex (male vs. female), race (White, Hispanic, or Black), marital status (married including living with a partner vs. single including single, divorced, widowed, and separated), active cancer treatment (yes vs. no), smoking status (never, former, or current smokers), nativity (US born vs. foreign born), and socioeconomic barrier index: composed of five socioeconomic status factors [education (≤ high school), income (≤35K), insurance (none), housing (rent/other), and employment status (unemployed)] dichotomized to create a composite that we truncated to 3+ because of sparsity as detailed in a previous study (25) with higher scores indicating higher socioeconomic barriers.

Exposure

Cannabis use frequency (cannabis use): To assess the level of cannabis usage, we utilized data from the following two questions: "In your LIFETIME, which of the following substances have you ever used?" if individuals selected "None of These Drugs," they were coded as having no usage of substances in a lifetime. For those that indicated cannabis (marijuana) as a substance used in their lifetime, we used the following question "In the PAST THREE MONTHS, how often have you used marijuana (cannabis, pot, grass, hash, etc.)?" We created a categorical variable including: (i) never-users and those who indicated never in the past three months, (ii) occasional users as those who selected once or twice and monthly, and (iii) frequent/regular users as those who selected weekly and daily or almost daily. Participants who selected prefer not to answer or skip the questions were set as missing.

Alcohol hazardous drinking status (hazardous drinking): The Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score was used to assess hazardous drinking. Among those who indicated as current drinking, we used the following three questions to create the AUDIT-C score: (i) drinking frequency: "How often did you have a drink containing alcohol in the past year?" (ii) drinking quantity: "On a typical day when you drink, how many drinks do you have?" and (iii) binge drinking: "How often did you have six or more drinks on one occasion in the past year?" To create the AUDIT-C composite score (ranging from 0 to 12), we added scores from the three questions scored from 0 (less alcohol consumption) to 4 points (more alcohol consumption) similar to other studies using cohorts from the AoU (26). Clinically hazardous drinking was defined as an AUDIT-C score of 3 or higher in women and AUDIT-C scores of 4 or higher in men (26).

Co-use: A co-use categorical variable was developed and assessed by using the hazardous drinking and cannabis use indicators. Co-use was defined as participants who were occasional or frequent/regular cannabis users and those who engaged in hazardous drinking. No co-use, those who selected to have never used cannabis in their lifetime, those who had no usage in the past three months, and those who did not engage in hazardous drinking and those who selected either having occasional or frequent/regular cannabis use or hazardous drinking were excluded when creating this variable.

Outcomes

AoU participants attended an in-person visit in which a trained staff person collected anthropometric and biospecimen data. Physical measurements collected in addition to biospecimens included height, weight, hip and waist measurements, and BP.

Cardiovascular markers: Using American Heart Association–established BP cutoffs (27), we calculated a normal/elevated BP variable as systolic BP values <130 mmHg and diastolic BP values <80 mm Hg. Systolic and diastolic pressure values of ≥130 or ≥80 mmHg, respectively, were considered high BP. High-density lipoprotein (HDL), low-density lipoprotein (LDL), hypertriglyceridemia: Males and females with HDL values of ≤50 and ≤40 mg/dL, respectively, were coded with low HDL (28). Those with LDL values of ≥130 mg/dL were coded as having elevated LDL versus normal (29). Participants with triglyceride values of ≥150 mg/dL (30) were coded with hypertriglyceridemia.

Metabolic markers: waist-to-hip ratio and hemoglobin A1c: Using waist-to-hip ratio cutoff (31), males and females with values of >0.95 and >0.80 were coded as elevated versus normal,

respectively. Lastly, elevated hemoglobin A1c (HbA1c) levels were coded as those with values ≥5.7% versus normal (32).

Immune markers: C-reactive protein and white blood cell count: Due to no established clinical cutoff, values falling in the >75% percentile for C-reactive protein and white blood cell count were coded as high versus those falling in the ≤75% percentile were coded as lower values for each indicator.

Statistical analysis

We used the χ^2 or Mann–Whitney *U* test to determine the association of all the variables by sex and race/ethnicity. Multivariable logistic regression models assessed the independent associations of cannabis, alcohol, and co-use with each cardiometabolic biomarker. To test whether these independent associations differed by sex or race/ethnicity, product interaction terms were included in the models, and subsequent stratified analyses were conducted for significant interaction terms. Models were adjusted for age, sex, nativity, socioeconomic barriers, marital status, smoking status, and active treatment status. Model assumptions were assessed and met. All statistical analyses were performed using R Jupyter Notebooks accessed via the AoU workbench and using a significance level at α >0.05. Adjusted ORs with 95% confidence intervals and *P* values were reported.

Data availability

Data from the AoU Research Program can only be accessed through the Researcher Workbench (https://workbench.researchallofus.org/login) as per the informed consent of program participants. The investigators are prohibited to share raw-level data of participants in accordance with the user agreement established by this program. Therefore, it is not possible to provide a de-identified dataset for this article. The interpretation and reporting of these data are the sole responsibility of the authors.

Results

In our sample, the median age of cancer survivors was 68.4 [IQR (Q1, Q3) = 58.6, 74.6] years. Most participants identified as White (86%) and reported their biological sex as female (66%; **Table 1**). In our exposure variables, 8.2% of our sample reported any cannabis use (i.e., frequent/regular or occasional), 31.4% engaged in hazardous drinking, and 3.2% engaged in co-use of both cannabis and hazardous alcohol use (**Table 2**).

Cannabis use

Results from our multivariable analyses showed no significant association between cannabis use and any of the cardiovascular, immune, and metabolic system biomarkers (**Table 3**, cannabis).

Hazardous drinking

We found statistically significant associations between hazardous drinking and metabolic system biomarkers (i.e., waist-to-hip ratio and HbA1c). Cancer survivors who were engaged in hazardous alcohol drinking had 0.75 (0.67, 0.86) and 0.56 (0.37, 0.83) times the likelihood of elevated waist-to-hip ratio and elevated HbA1c biomarkers, respectively, compared with those who did not engage in hazardous drinking. We did not observe statistically significant associations between hazardous alcohol drinking and any of the cardiovascular and immune system biomarkers (**Table 3**, Alcohol).

Substance co-use

Compared with survivors who were never co-users of cannabis and alcohol, cancer survivors who were co-users were 1.58 (1.14, 2.19) times as likely to have high BP and 0.57 (0.41, 0.81) times as likely to have an elevated waist-to-hip ratio. We found no statistically significant associations between co-use of substances and any of the immune system biomarkers (**Table 4**).

Race/ethnicity and biological sex differences

Our interaction term between cannabis*race/ethnicity in the cannabis and waist-to-hip ratio ($P_{\text{interaction}} = 0.03$) yielded significant results. Stratified models showed that only among Black cancer survivors, those who were frequent/regular cannabis users were 0.21 (0.08, 0.53) times as likely to have an elevated waist-to-hip ratio compared with Black cancer survivors who were not cannabis users. White and Hispanic cancer survivors had no statistically significant results in our stratified models (**Table 5**). Additionally, although there were statistically significant results from the interaction terms between the associations of cannabis and LDL cholesterol ($P_{\text{interaction}} = 0.03$) by race/ethnicity, we did not stratify our models by race/ethnicity for LDL because of our small sample size for Hispanic and Black cancer survivors. Lastly, for hazardous alcohol use and co-use, we found no statistically significant results in our race/ethnicity interaction product terms (all product terms $P_{\text{interaction}} > 0.05$). With regard to cannabis, hazardous alcohol, and co-use by sex, there were no statistically significant results in any of the outcomes assessed (all product terms $P_{\text{interaction}} > 0.05$).

Discussion

Using data from the AoU Research Program, we investigated the independent associations of cannabis use and hazardous drinking with cardiometabolic biomarkers among a large sample of cancer survivors. We further explored whether these associations differed by sex or race/ethnicity. We found that cannabis use was significantly associated with a lower waist-to-hip ratio among Black cancer survivors only. We also found that co-use was associated with higher BP and lower waist-to-hip ratio. Interestingly, there was also a significant inverse relationship between alcohol hazardous drinking and elevated HbA1c levels and waist-to-hip ratio.

We found that only the co-use of cannabis and alcohol was positively associated with high BP. Unlike findings in the general population, we did not find a significant association between cannabis use or hazardous drinking and any cardiovascular biomarkers (14–16, 19). Alcohol or cannabis use can independently increase BP through several mechanisms, including sympathetic nervous system activation and endothelial dysfunction (22, 33). Each substance can independently contribute to increased catecholamine release, altered baroreceptor reflexes, and reduced nitric oxide production, potentially leading to higher vascular resistance and elevated BP (22, 33). This suggests that co-use may have a synergistic effect, in which co-use has a greater effect on cardiovascular risk factors than the independent use of each substance among cancer survivors.

Additionally, it is plausible that cancer survivors in our study modified their health behaviors after cancer diagnosis, which could be an unaddressed confounder and possibly contribute to our null results. For example, cancer survivors could have decreased their substance usage (i.e., alcohol and cannabis) and improved their diet and physical activity (34, 35), potentially explaining our null findings for the independent associations between these substances and

Table 1. Demographic characteristics by race/ethnicity of the AoU sample of cancer survivors.

Characteristic	White (*N* = 6,082)	Hispanic (*N* = 535)	Black (*N* = 437)	Total (*N* = 7,054)	*P*
Sex					<0.001
Male	2,156 (35.4%)	140 (26.2%)	110 (25.5%)	2,406 (34.1%)	
Female	3,926 (64.6%)	395 (73.8%)	327 (74.8%)	4,648 (65.9%)	
Age					<0.001
Mean (SD)	66.8 (12.4)	58.3 (14.5)	61.4 (12.1)	65.8 (12.8)	
Median [Q1, Q3]	66.4 [60.2, 75.4]	59.6 [47.6, 69.3]	62.5 [53.4, 69.9]	68.4 [58.6, 74.6]	
Income					<0.001
Lowest quintile	1,160 (19.1%)	168 (31.6%)	182 (41.6%)	1,511 (21.4%)	
Rest	4,922 (80.9%)	366 (68.4%)	255 (58.4%)	5,543 (78.6%)	
Marital status					<0.001
Married	>4,000 (>76.0%)	>200 (>50.0%)	>100 (>30.0%)	4,793 (67.9%)	
Single	1719 (28.3%)	226 (42.2%)	261 (59.7%)	2,181 (31.3%)	
Missing	>25 (>0.1%)	≤20 (<5.0%)	≤20 (<5.0%)	55 (0.8%)	
Education					<0.001
Some college +	>5,000 (>90.0%)	>400 (>80.0%)	>300 (>75.0%)	6,422 (91.0%)	
≤High school	419 (6.9%)	87 (16.3%)	78 (17.8%)	584 (8.3%)	
Missing	>25 (>0.1%)	≤20 (<5.0%)	≤20 (<5.0%)	48 (0.7%)	
Insurance status					<0.001
Insured	6,051 (98.9%)	>400 (>90.0%)	>400 (>92.0%)	6,942 (98.4%)	
Uninsured	40 (0.7%)	>20 (>2.0%)	≤20 (<5.0%)	73 (1.0%)	
Missing	27 (0.4%)	≤20 (<5.0%)	≤20 (<5.0%)	39 (0.5%)	
Nativity					<0.001
United States	>5,000 (>90.0%)	>300 (>55.0%)	>350 (>90.0%)	6,472 (91.7%)	
Other	323 (5.3%)	212 (39.6%)	26 (5.9%)	561 (8.0%)	
Missing	≤20 (<5.0%)	≤20 (<5.0%)	≤20 (<5.0%)	21 (0.3%)	
Socioeconomic barriers					<0.001
0	4,355 (71.6%)	244 (45.6%)	184 (42.1%)	4,783 (67.9%)	
1	1,212 (19.9%)	151 (28.2%)	106 (24.3%)	1,469 (20.8%)	
2	365 (6.0%)	72 (13.5%)	75 (17.2%)	512 (7.3%)	
3+	150 (2.5%)	68 (12.7%)	72 (16.5%)	290 (4.1%)	
Housing status					<0.001
Own	5,072 (83.4%)	>250 (>50.0%)	>200 (>50.0%)	5,629 (79.7%)	
Rent/other arrangement	941 (15.5%)	208 (38.9%)	187 (42.8%)	1,336 (18.9%)	
Missing	69 (1.1%)	≤20 (<5.0%)	≤20 (<5.0%)	98 (1.4%)	
Employment status					<0.001
Employed	5,696 (93.7%)	>400 (>80.0%)	>300 (>75.0%)	6,497 (92.2%)	
unemployed	359 (5.9%)	75 (14.0%)	83 (19.0%)	517 (7.3%)	
Missing	27 (0.4%)	≤20 (<5.0%)	≤20 (<5.0%)	40 (0.6%)	
Treatment status					0.93
No	4,052 (66.6%)	>300 (>60.0%)	>200 (>60.0%)	4,628 (66.4%)	
Yes	2006 (33.0%)	180 (33.6%)	152 (34.8%)	2,338 (33.1%)	
Missing	24 (0.4%)	≤20 (<5.0%)	≤20 (<5.0%)	29 (0.4%)	

Note: Married includes those living with partner; single includes divorced, widowed, and separated.
P values were obtained using the χ^2 or Mann–Whitney *U* test.
Per "AoU" data use agreement policy, groups <20 participants are shown as ≤ 20 (%) with a corresponding > (%) category to prevent deriving counts <20 from other values.
No all percentages equal to 100.

the cardiovascular biomarkers. Moreover, in our sample, cancer survivors had a lower proportion of people with high BP (41.5% vs. 45.4%; ref. 36) and low HDL (4.6% vs. 18%; ref. 28) compared with the general US population. Our sample also had a lower proportion of people with a high waist-to-hip ratio (47.9% vs. 68.3%; ref. 37) compared with that of other cancer survivor populations in the United States, with these lower proportions potentially being attributed to the higher distribution of insured cancer survivors in our cohort (98.4%).

Among the immune risk factors, we did not find a significant association between hazardous alcohol or co-use and any immune risk factors. However, we found a significant relationship between hazardous alcohol and metabolic system biomarkers. Similar to studies in the general population, (38–42) we found that alcohol use was significantly associated with HbA1c levels and waist-to-hip ratio, with hazardous drinking being less likely to have elevated HbA1c levels and waist-to-hip ratio. This significant inverse association among alcohol use, HbA1c levels, and waist-to-hip ratio may be due to alcohol's direct effects on health behaviors, namely, dietary behaviors. For example, HbA1c levels and waist-to-hip ratio can be highly influenced by dietary patterns, which were not included in our models. A recent study in a representative sample of US adults shows that higher alcohol use influences the choice of dietary patterns that have a lower percentage of the total calories

Table 2. Descriptive characteristics by race/ethnicity of exposure and outcomes of the AoU sample of cancer survivors.

Characteristic	White (*N* = 6,082)	Hispanic (*N* = 535)	Black (*N* = 437)	Total (*N* = 7,054)	*P*
Exposures					
Cannabis use					<0.001
Never/no (in the last 3 months)	5,639 (92.7%)	484 (90.5%)	353 (80.8%)	6,476 (91.8%)	
Occasional	249 (4.1%)	25 (4.7%)	41 (9.4%)	315 (4.5%)	
Frequent/regular	194 (3.2%)	26 (4.9%)	43 (9.8%)	263 (3.7%)	
Hazardous drinking					<0.001
No	4,091 (67.3%)	415 (77.6%)	330 (75.5%)	4,836 (68.6%)	
Yes	1991 (32.7%)	120 (22.4%)	107 (24.5%)	2,218 (31.4%)	
Concurrent use					<0.001
Never	>3,500 (>60.0%)	>300 (>70.0%)	275 (62.9%)	4,485 (63.6%)	
Co-use	>150 (>1.0%)	≤20 (<5.0%)	29 (6.6%)	227 (3.2%)	
Missing	2072 (34.1%)	137 (25.6%)	133 (30.4%)	2,342 (33.2%)	
Outcomes					
Cardiovascular system					
BP					<0.001
Normal/elevated	2,449 (40.3%)	216 (40.4%)	143 (32.7%)	2,808 (39.8%)	
High BP	2,469 (40.6%)	230 (43.0%)	229 (52.4%)	2,928 (41.5%)	
Missing	1,164 (19.1%)	89 (16.6%)	65 (14.9%)	1,318 (18.7%)	
HDL					0.03
Normal	99 (1.6%)	≤20 (<5.0%)	≤20 (<5.0%)	122 (1.7%)	
Elevated	283 (4.7%)	≤20 (<5.0%)	>20 (>5.0%)	324 (4.6%)	
Missing	5,700 (93.7%)	512 (95.7%)	396 (90.6%)	6,608 (93.7%)	
LDL					0.13
Normal	297 (4.9%)	≤20 (<5.0%)	>20 (>5.0%)	343 (4.9%)	
Elevated	81 (1.3%)	≤20 (<5.0%)	≤20 (<5.0%)	93 (1.3%)	
Missing	5,704 (93.8%)	>450 (>90.0%)	>350 (>85.0%)	6,618 (93.8%)	
Hypertriglyceridemia					0.18
Normal	319 (5.2%)	≤20 (<5.0%)	>20 (>5.0%)	371 (5.3%)	
Elevated	89 (1.5%)	≤20 (<5.0%)	≤20 (<5.0%)	103 (1.5%)	
Missing	5,674 (93.3%)	>450 (>90.0%)	>350 (>85.0%)	6,580 (93.3%)	
Immune system					
CRP					0.12
Rest	316 (5.2%)	≤20 (<5.0%)	>20 (>5.0%)	360 (5.1%)	
>75th quantile	90 (1.5%)	≤20 (<5.0%)	≤20 (<5.0%)	111 (1.6%)	
Missing	5,676 (93.3%)	>450 (>92.0%)	>350 (>90.0%)	6,583 (93.3%)	
White blood cell count					0.86
Rest	248 (4.1%)	≤20 (<5.0%)	≤20 (<5.0%)	279 (4.0%)	
>75th quantile	75 (1.2%)	≤20 (<5.0%)	≤20 (<5.0%)	89 (1.3%)	
Missing	5,759 (94.7%)	>450 (>92.0%)	>350 (>92.0%)	6,689 (94.8%)	
Metabolic system					
Waist-to-hip ratio					<0.001
Normal	1,574 (25.9%)	127 (23.7%)	102 (23.3%)	1803 (25.6%)	
Elevated	2,838 (46.7%)	290 (54.2%)	254 (58.1%)	3,382 (47.9%)	
Missing	1,670 (27.5%)	118 (22.1%)	81 (18.5%)	1869 (26.5%)	
HbA1c level					0.02
Normal	355 (5.8%)	≤20 (<5.0%)	≤20 (<5.0%)	383 (5.4%)	
Elevated	191 (3.1%)	≤20 (<5.0%)	≤20 (<5.0%)	219 (3.1%)	
Missing	5,536 (91.0%)	>450 (>90.0%)	>350 (>90.0%)	6,452 (91.5%)	

Note: *P* values were obtained using the χ^2 or Mann–Whitney *U* test.
Per "AoU" data use agreement policy, groups <20 participants are shown as ≤20 (%) with a corresponding > (%) category to prevent deriving counts <20 from other values.
No all percentages equal to 100.
Abbreviation: CRP, C-reactive protein.

consumed were from carbohydrates and fat (42). It could be plausible that cancer survivors who engage in hazardous drinking behaviors may have poorer diet patterns, showing that increased alcohol consumption might have led to lower HbA1c levels and reduced abdominal adiposity because of their overall poor health. Moreover, key confounding (e.g., sleep and exercise) that might be associated with both HbA1c levels and waist-to-hip ratio was not available to adjust in this study.

Finally, we found that cannabis use was associated with a metabolic risk factor (i.e., waist-to-hip ratio) mainly among Black cancer survivors. Our findings are similar to a study assessing a sample of US Black noncancer survivors, which showed that current cannabis

Table 3. Multivariable association of substance use and cardiometabolic risk factors among cancer survivors from the AoU Research Program.

Variable	Cannabis		Alcohol
	Occasional	Frequent/regular	Hazardous drinking—yes
	aOR (95% CI)		
Cardiovascular system			
High BP (n = 5,513)	1.22 (0.93–1.60)	1.29 (0.95–1.74)	1.03 (0.91, 1.16)
Low HDL (n = 435)	1.33 (0.50–4.03)	0.56 (0.24–1.38)	1.43 (0.86, 2.43)
High LDL (n = 422)	1.43 (0.44–3.96)	1.50 (0.49–4.11)	1.45 (0.86, 2.44)
Hypertriglyceridemia (n = 464)	1.43 (0.48–3.86)	0.69 (0.23–1.78)	0.81 (0.47, 1.35)
Immune system			
CRP (n = 457)	1.92 (0.79–4.52)	0.83 (0.24–2.54)	1.12 (0.65, 1.90)
WBC (n = 357)	1.41 (0.43–4.11)	1.89 (0.60–5.73)	0.88 (0.49, 1.54)
Metabolic system			
High waist-to-hip ratio (n = 5,030)	0.86 (0.63–1.16)	0.71 (0.51–1.01)	**0.75 (0.67, 0.86)**
Elevated HbA1c level (n = 586)	1.08 (0.42–2.62)	1.42 (0.59–3.32)	**0.56 (0.37, 0.83)**

Note: Reference categories in cardiometabolic markers are either an established clinical cutoff or <75% percentile of the variable distribution (consider normal = 0).
Reference for exposures (cannabis: never; alcohol: hazardous drinking—no).
Logistic regression models were adjusted for race, age, sex, treatment status, nativity status, smoking usage, and socioeconomic barriers and/or cannabis use or hazardous alcohol use.
Bolded aOR and CI represent statistical significance.
BP ref = normal/elevated systolic (<130 mmHg) and diastolic (<80 mmHg). WBC count, CRP, HbA1c, HDL cholesterol, and LDL cholesterol.
n represents the sample size for each model for the exposure and outcome assessed.
Abbreviations: aOR, adjusted ORs; CI, confidence interval; CRP, C-reactive protein; WBC, white blood cells.

users had lower waist circumference compared with former and never-users (43). Given that the waist-to-hip ratio may be a better predictor to cardiovascular diseases (44) and that cannabis and waist-to-hip ratio associations are limited in the literature and more so among cancer survivors, it is crucial to continue exploring this relationship to better understand the impact of cannabis on metabolic health while assessing for important confounders this study was unable to adjust.

Table 4. Multivariable association of co-use of cannabis and hazardous alcohol with cardiometabolic risk factors among cancer survivors from the AoU Research Program.

Variable	Co-use
	aOR (95% CI)
Cardiovascular system	
High BP (n = 3,743)	**1.58(1.14–2.19)**
HDL (n = 278)	0.45(0.14–1.52)
LDL (n = 274)	2.39(0.75–7.05)
Hypertriglyceridemia (n = 295)	1.90(0.51–6.32)
Immune system	
CRP (n = 316)	2.68(0.79–8.93)
WBC (n = 230)	1.98(0.54–6.61)
Metabolic system	
Waist/Hip ratio (n = 3,383)	**0.57(0.41–0.81)**
HbA1c (n = 379)	0.91(0.32–2.37)

Note: Reference categories in cardiometabolic markers are either an established clinical cutoff or <75% percentile of the variable distribution (consider normal = 0)
Reference for exposure [co-usage (no cannabis and no hazardous alcohol use)].
Logistic regression models were adjusted for race, age, sex, treatment status, nativity status, smoking usage, and socioeconomic barriers.
Bolded aOR and CI represent statistical significance.
Blood pressure ref = normal/elevated systolic (<130 mmHg) and diastolic (<80 mmHg). WBC count, CRP, HbA1c, HDL cholesterol, and LDL cholesterol.
n represents the sample size for each model for the exposure and outcome assessed.
Abbreviations: aOR, adjusted ORs; CI, confidence interval; CRP, C-reactive protein; WBC, white blood cells.

The AoU Research Program allowed for the exploration of whether cannabis, alcohol, and co-use of these substances were independently associated with increased cardiometabolic risk using multiple objectively measured biomarkers in a large sample of US adult cancer survivors. However, there are some study limitations. The study's cross-sectional nature precludes the inference of a temporal or causal relationship. We were also unable to stratify our cannabis and LDL model by race/ethnicity because of our small sample of Hispanic and Black cancer survivors and the overall lower response rate for physical and biospecimen collection. However, in our sample, our substance use variables were similarly distributed between those who had biomarker data and those who did not, lessening the possibility of selection bias (Supplementary Table S2). Furthermore, solely relying on self-reported substance use may have led to nondifferential misclassification bias, as participants might underreport their consumption level because of recall errors or socially unacceptable levels. Thus, future studies should assess these associations longitudinally while incorporating both subjective and objective measures of substance use (e.g., saliva, urine, or hair follicle drug test results) to establish temporality, improve sampling of racial/ethnic minorities, and optimize biospecimen collection by testing for substance use among cancer survivors. Lastly, given that our sample median age is 66 years, it limits the generalizability of our findings. However, given that there are trends in the United States that alcohol (45) and cannabis (46) usage has increased among this age demographic population, continuing to explore these relationships among older cancer survivors is important.

Table 5. Multivariable association of hazardous alcohol with an elevated waist-to-hip ratio among cancer survivors from the AoU Research Program by race/ethnicity.

Variable	White (*N* = 4,287)	Hispanic (*N* = 403)	Black (*N* = 340)
		aOR (95% CI)	
Cannabis use			
Never/no (in the last 3 months)	Ref	Ref	Ref
Occasional	0.88(0.63, 1.25)	0.52(0.17, 1.60)	0.83(0.33, 2.26)
Frequent/regular	0.98(0.66, 1.47)	0.51(0,17, 1.60)	**0.21(0.08, 0.53)**

Note: Logistic regression models were adjusted for race, age, sex, treatment status, nativity status, smoking usage, socioeconomic barriers, and hazardous drinking.
Bolded aOR and CI represent statistical significance.
Abbreviations: aOR, adjusted ORs; CI, confidence interval.

Moreover, cannabis administration route (e.g., smoking or ingesting), alcohol beverage type (e.g., beer, wine, or spirit), and co-use classification (i.e., concurrent or simultaneous use) are additional moderators we were not able to assess given that these variables may play a role in clinical outcomes in the general population (39, 47, 48). Although we adjusted for smoking status, we were unable to account for additional confounders (e.g., diet, physical activity, or sleep) that may contribute to these relationships. Finally, we were not able to additionally adjust for existing conditions or current medication use as it significantly reduced our analytic sample size, statistical power, and the internal and external validity of the study. However, to mitigate potential confounding from comorbidities in our models, we adjusted for active cancer treatment status as it can affect cardiometabolic risk factors in cancer survivors.

This is one of the first studies to assess the direct relationships of cannabis, alcohol, and co-use of these substances with cardiovascular, immune, and metabolic biomarkers and explore race/ethnicity and sex differences in cancer survivors. The findings of this study showed that cannabis use was inversely associated with the waist-to-hip ratio among Black cancer survivors only and co-use was positively associated with high BP. Hazardous alcohol use was inversely associated with waist-to-hip ratio and HbA1c levels. Our findings suggest that substance use may play a role in inflammatory effects and hypertension risk in cancer survivors, who are already at higher risk of developing other chronic illnesses. Our results may guide future studies to continue exploring the relationship between these substances and their co-use and cardiometabolic biomarkers among cancer survivor populations while accounting for important confounders that we were not able to adjust in our study. Clinicians and researchers should consider the burden of substance use in cancer survivors when making clinical recommendations, interpreting findings, and communicating about health risks. Future studies should explore the longitudinal effects of cannabis, alcohol, and co-use on cardiometabolic risk factors, which are precursors to comorbidities.

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Authors' Contributions

A. Arizpe: Conceptualization, data curation, formal analysis, funding acquisition, methodology, writing–original draft, project administration, writing–review and editing. **T.M. Chapman:** Writing–original draft, writing–review and editing. **C. Rodriguez:** Writing–original draft, writing–review and editing. **A. Carvajal:** Writing–original draft, writing–review and editing. **K.J. Queen:** Formal analysis, writing–review and editing. **S. Navarro:** Writing–original draft, writing–review and editing. **C.Y. Ochoa-Dominguez:** Methodology, writing–review and editing. **S.E. Kim:** Methodology, writing–review and editing. **C.M. Toledo-Corral:** Supervision, methodology, writing–original draft, writing–review and editing. **A.J. Farias:** Conceptualization, resources, supervision, investigation, methodology, writing–original draft, writing–review and editing.

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Note

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