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Association of cannabis use with depression among cancer patients

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ABSTRACT

The rate of cannabis use by cancer patients is climbing. However, as the risk of mental illness caused by cannabis use in cancer patients has not been effectively evaluated, this study will analyze the association between cannabis use and depression in cancer patients. This study collected data from respondents to the National Health and Nutrition Examination Survey from 2005 to 2018. A total of 22,181 respondents self-reported information about cannabis use in questionnaire, of which 893 were diagnosed with cancer. We found that the rate of cannabis use among cancer patients increased each year from 2005 to 2018. We analyzed the association between cannabis use and depression in cancer patients by multivariable logistic regression. Results found that the current cannabis use had a significant positive correlation with increased risk of depression in cancer patients (OR = 2.135, 95% CI = 1.21–3.777, p = 0.009). In our stratified analysis, current cannabis use was associated with an increased risk of depression in cancer patients who were female, had a history of cocaine use, and initiated cannabis use after age 17. (OR = 1.981, 95% CI = 1.024–3.85, P = 0.043; OR = 3.19, 95% CI = 1.61–6.41, P < 0.001; OR = 2.236, 95% CI = 1.018–4.967, P = 0.045). In conclusion, the use of cannabis by cancer patients has an associated risk of depression and the cancer patients who currently use cannabis are more likely to have depression.

1. Introduction

Cannabis is one of the most widely used psychoactive substances in the world, with somewhere between three to five percent of the world's population having used cannabis at least once in their lifetimes (Hindley et al., 2020; Anthony et al., 2017). Cannabis is typically used for non-medical purposes. Indeed, in most countries, cannabis is still an illegal drug. In other countries, however, cannabis is gradually being decriminalized and legalized, making it easier to expand research on its medical potential (Degenhardt et al., 2018). In the United States, cannabis has become the most commonly used psychoactive substance after alcohol– about 8 million Americans use cannabis every day or almost every day (Weinberger et al., 2019). By 2022, 38 states in the US had approved the legalization of medical cannabis, and 19 states have even allowed the sale and non-medical use of cannabis (Jordan et al., 2022). Especially among adolescents, the prevalence of cannabis use has even exceeded smoking tobacco products in popularity, as 63% of first-time cannabis users are under age 18 (Hammond et al., 2022). With its increasing prevalence, there is rising concern that frequent cannabis use could bring about negative health and social consequences, such as an increase in mental illness, a rise in emergency counseling for cannabis-related emotional disorders, self-harm, and more (Gorfinkel et al., 2020).

Cannabis is a general term for the plant cannabis and bioactive preparations thereof. The most biologically active substance in cannabis-based metabolites is Δ9-tetrahydrocannabinol (THC), which acts on the cannabinoid receptor (CB receptor) of the central nervous system. Cannabis use is associated with an increased risk of cognitive dysfunction, psychotic symptoms and negative emotions (Wright et al., 2021). Previous studies have reported that compared with placebos, THC can significantly increase mental illness risk and general psychiatric symptoms, such as depression (Hindley et al., 2020; D'souza et al., 2004). Meta-analyses have also shown that heavy cannabis use is associated with users' anxiety and depression symptoms, although these

Abbreviations: BMI, body mass index; CB receptor, cannabinoid receptor; CSF, cerebrospinal fluid; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECS, endogenous cannabinoid system; FEV1, first forced vital capacity; FVC, forced vital capacity; IPR, income poverty ratio; NHANES, National Health and Nutrition Examination Survey; PET, positron emission tomography; PHQ-9, Patient's Health Questionnaire-9; THC, Δ9-tetrahydrocannabinol.

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Table 1
Baseline characteristics of cancer patients grouped by cannabis use status, NHANES 2005–2006 to 2017–2018.

Characteristics		Cannabis use status[c]			
		Never	Former	Current	P value
		n = 348	n = 415	n = 120	
Age, mean (SD)[a]		46.86 (9.86)	47.30 (10.00)	44.39 (10.90)	0.019
Gender, n(%)	Male	85 (24.4)	158 (38.1)	38 (31.4)	<0.001
	Female	263 (75.6)	257 (61.9)	82 (68.6)	
Marital, n(%)	Married	205 (58.9)	231 (55.7)	46 (38.0)	0.006
	Divorced	54 (15.5)	77 (18.6)	25 (20.7)	
	Living with partner	22 (6.3)	24 (5.8)	14 (11.6)	
	Never married	35 (10.1)	54 (13.0)	20 (16.5)	
	Others	32 (9.2)	29 (7.0)	16 (13.2)	
Ethnicity, n(%)	Hispanic	59 (17.0)	19 (4.6)	6 (5.0)	<0.001
	Non-Hispanic Black	44 (12.6)	52 (12.5)	17 (14.0)	
	Non-Hispanic White	166 (47.7)	304 (73.3)	89 (73.6)	
	Other	79 (22.7)	40 (9.6)	9 (7.4)	
Education, n(%)	Less than high school	81 (23.3)	51 (12.3)	15 (12.4)	<0.001
	High school or equivalent	72 (20.7)	82 (19.8)	33 (27.3)	
	Some college/technical or Bachelor's degree	195 (56.0)	282 (68.0)	73 (60.3)	
IPR, n(%)[b]	<1.35	114 (34.9)	107 (27.2)	54 (49.1)	0.001
	>1.85	186 (56.9)	250 (63.5)	47 (42.7)	
	1.35 ~ 1.85	27 (8.3)	37 (9.4)	9 (8.2)	
BMI, mean (SD)[b]		30.72 (7.54)	29.71 (7.15)	28.55 (7.79)	0.015
COPD, n(%)	NO	330 (94.8)	380 (91.6)	112 (92.6)	0.210
	YES	18 (5.2)	35 (8.4)	9 (7.4)	
Hypertension, n(%)	NO	206 (59.2)	247 (59.5)	79 (65.3)	0.464
	YES	142 (40.8)	168 (40.5)	42 (34.7)	
CVD, n(%)	NO	311 (89.4)	367 (88.4)	105 (86.8)	0.737
	YES	37 (10.6)	48 (11.6)	16 (13.2)	
DM, n(%)	NO	277 (80.8)	353 (85.9)	110 (90.9)	0.017
	YES	66 (19.2)	58 (14.1)	11 (9.1)	
Smoking, n(%)	Never	250 (71.8)	134 (32.4)	27 (22.3)	<0.001
	Current	51 (14.7)	146 (35.3)	65 (53.7)	
	Former	47 (13.5)	134 (32.4)	29 (24.0)	
Ever Used Cocaine, n(%)	NO	339 (98.0)	288 (69.4)	60 (50.0)	<0.001
	YES	7 (2.0)	127 (30.6)	60 (50.0)	
PHQ-9 > 4, n(%)	NO	237 (68.1)	262 (63.1)	58 (47.9)	<0.001
	YES	111 (31.9)	153 (36.9)	63 (52.1)	
PHQ-9 ≥ 10, n(%)	NO	298 (85.6)	334 (80.5)	89 (73.6)	0.009
	YES	50 (14.4)	81 (19.5)	32 (26.4)	

[a]Values are mean ± SD for continuous variables and percentage for categorical variables.
[b]Note the abbreviations: IPR: Income Poverty Ratio, BMI: body mass index, COPD: chronic obstructive pulmonarydisease, CVD: cardiovascular disease, DM: diabetes.
[c]Cannabis use status was divided into three groups: "Never", defined as the group who never used cannabis; "Former", defined as the group who used cannabis before and did not use cannabis in the past 30 days; "Current", defined as the group who used cannabis in the past 30 days.

studies have not made any causal inferences (Lev-Ran et al., 2014). Clinical studies have found that non-medical cannabis use in adults or adolescents and depression have a mutual promotion effect (Englund et al., 2016). Thus, further assessment of the potential psychological effects of cannabis is needed.

In recent years, the research and application of cannabis in the field of oncology has grown considerably, yielding new methods of utilizing the drug for reducing common adverse reactions related to tumor treatment, such as nausea, vomiting, loss of appetite, peripheral neuropathy, and pain (Abrams and Guzman, 2015). Especially for cancer pain management, the analgesic effect and availability of cannabis make it an effective substitute for opioids; according to a study of Medicaid beneficiaries in the United States, medical and adult-use cannabis can reduce the number of opioid prescriptions (Wen and Hockenberry, 2018). In Washington state, a cross-sectional survey of adult cancer patients showed that nearly 21 percent of cancer patients reported using cannabis in the past 30 days (Pergam et al., 2017).

These surveys may also reflect that over time, cancer patients have been exposed to more information about the potential benefits of cannabis in the management of cancer complications or adverse reactions to cancer treatment. Given the increasing prevalence of cannabis use among cancer patients, the potential risk of developing mental illness caused by cannabis requires attention. Therefore, in this study, the researchers used the national representative cancer patients' data from the National Health and Nutrition Examination Survey (NHANES, a program of studies designed to assess the health and nutritional status of adults and children in the United States.) database to analyze the relationship between cannabis use and depression in cancer patients. This study examines the association between different cannabis use statuses and depression in cancer patients, then goes on to evaluate the association between cumulative cannabis use and depression based on the correlation between age of initial cannabis use and depression in cancer patients.

2. Methods

The methods and materials can be found in the Appendix A.

3. Results

3.1. Characteristics of participants

Table 1 shows the baseline characteristics of cancer patients grouped by cannabis use status. Compared with females, males had higher cannabis use rates; simultaneously, non-Hispanic White participants had higher cannabis use rates than other racial/ethnic groups. Compared with patients who have never used cannabis, patients with a history of cannabis use – especially current cannabis users – had lower marriage rates, a lower income level, and a higher education level. There were significant differences in baseline age, BMI, diabetes prevalence,

smoking, combined cocaine use, and PHQ-9 scores between the groups ($P < 0.05$) (Table 1), but there were no significant differences in the rates of COPD, hypertension, and CVD ($P > 0.05$) (Table 1).

3.2. There was a positive correlation between cannabis use status and depression in cancer patients.

From 2005 to 2018, the prevalence of current cannabis use in cancer patients increased year by year (Fig. 1A and Table B.1). At the same time, we found that as cancer patients' cannabis use status changed, the incidence of depression among them also increased (Table B.2). Logistic regression analysis was used to further study the correlation between cannabis use status and depression in cancer patients – the results are shown in Fig. 1B and Table B.3. In the Crude Model, compared with "never" cannabis use, there was no significant correlation between former cannabis use and depression (OR = 1.247, 95% CI = 0.923–1.687, P = 0.151) (Fig. 1B). However, current cannabis use was significantly associated with depression in cancer patients (OR = 2.319, 95% CI = 1.522–3.544, P < 0.001) (Fig. 1B). In Model 3, after fully adjusting for all covariates, we found that current cannabis use in cancer patients was associated with a higher risk of depression (OR = 2.135,95% CI = 1.21–3.777, P = 0.009) (Fig. 1B). At the same time, using Model 3, we found that gender combined with a history of cocaine use were significantly correlated with depression in cancer patients, with an OR of 1.663 (95% CI = 1.157–2.407, P = 0.006) and 1.589 (95% CI = 1.023–2.466, P = 0.039) (Table B.3). With this background, we determined it was necessary to conduct a stratified analysis of the tumor patients.

3.3. Subgroup analysis

We also performed a subgroup analysis of cancer patients of different genders. In the fully adjusted Model 3, we found that there was a gender difference in the correlation between cannabis use status and depression in cancer patients: female cancer patients with current cannabis use were 98.1% more likely to develop depression than those who had never used cannabis (OR = 1.981, 95% CI = 1.024–3.85, P = 0.043) (Fig. 2A), while there was no significant correlation between cannabis use and depression in males (OR = 2.469, 95% CI = 0.72–8.514, P = 0.149) (Fig. 2B). Although there was a positive correlation between former cannabis use and depression in females in Model 1 (OR = 1.535, 95% CI = 1.023–2.316, P = 0.039) (Fig. 2A), there was no significant correlation after adjusting the model with additional variables. Cannabis use was often accompanied by cocaine use among these participants, so stratified analysis was conducted based on its presence or absence. In cancer patients without a history of cocaine use, current cannabis use was significantly positively correlated with depression (OR = 3.19, 95% CI = 1.61–6.41, P < 0.001) (Fig. 2C). However, in cancer patients with a history of cocaine use, there was no significant correlation between cannabis use and depression in either the Crude Model or the multivariable adjusted model ($P > 0.05$) (Fig. 2D).

We also performed a stratified analysis of cancer patients according to the age of their initial cannabis use. From this, we found that among cancer patients who first used cannabis at <17 years of age, current cannabis use was not significantly associated with depression ($P > 0.05$) (Fig. 2F). Conversely, in another group of cancer patients who first used cannabis at over than 17 years of age, current cannabis use was positively associated with a higher likelihood of depression in a model adjusted for all covariates (OR = 2.236, 95% CI = 1.018–4.967, P = 0.045) (Fig. 2E). This suggests that the correlation between the age of initial cannabis use and the onset of depression in participants may be affected by their individual cannabis use status. Tables B.4-B.6 show the detailed results in different models of association between cannabis use status and depression in cancer patients with different stratifications.

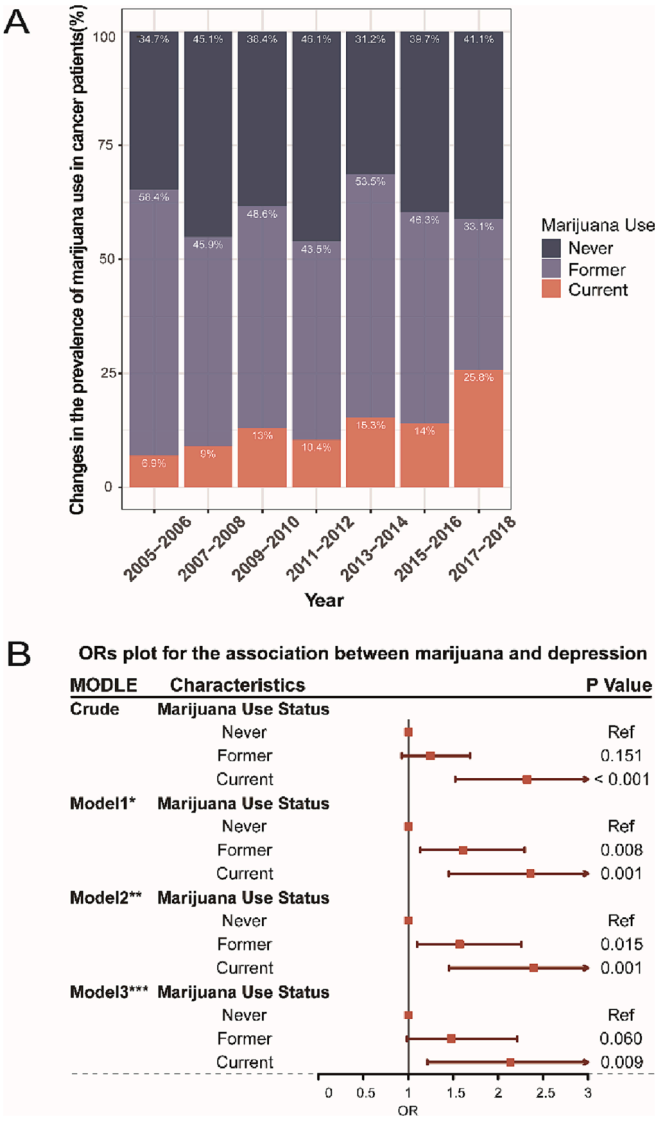

Fig. 1. Changes in the prevalence of cannabis use and the association of cannabis use status with depression in cancer patients. A. Changes in the prevalence of cannabis use among cancer patients in seven two-year cycles from 2005 to 2018. B. The relationship between different cannabis use statuses and depression in cancer patients.

3.4. Age of initial cannabis use is a risk factor for depression in cancer patients

We went on to further assess the association between age at first cannabis use and depression in cancer patients with a history of cannabis use. Restricted cubic spline regression revealed that there was a non-linear relationship between age of initial cannabis use and depression (P for non-linearity = 0.027). When the age of initial cannabis use was <17 years old, the lower the age of initial cannabis use, the higher the risk of depression; however, when the initial age of cannabis use was over 17 years old, the correlation was not significant (Fig. 3A). We divided these patients into an under 17 years old group (<17 group) and a 17 years old or older group (≥17 group), which we included as exposure factors. Compared with the ≥ 17 group, the < 17 group had no significant correlation with depression (P = 0.307) (Fig. 3B, and Table B.7). Based on the cannabis use status and the age of initial cannabis use, the cancer patients were further divided into new groups, each of which was called a "Joint Group" – these included a "Current" & <17 group, a "Current" & ≥17 group, a "Former" & < 17 group, and a

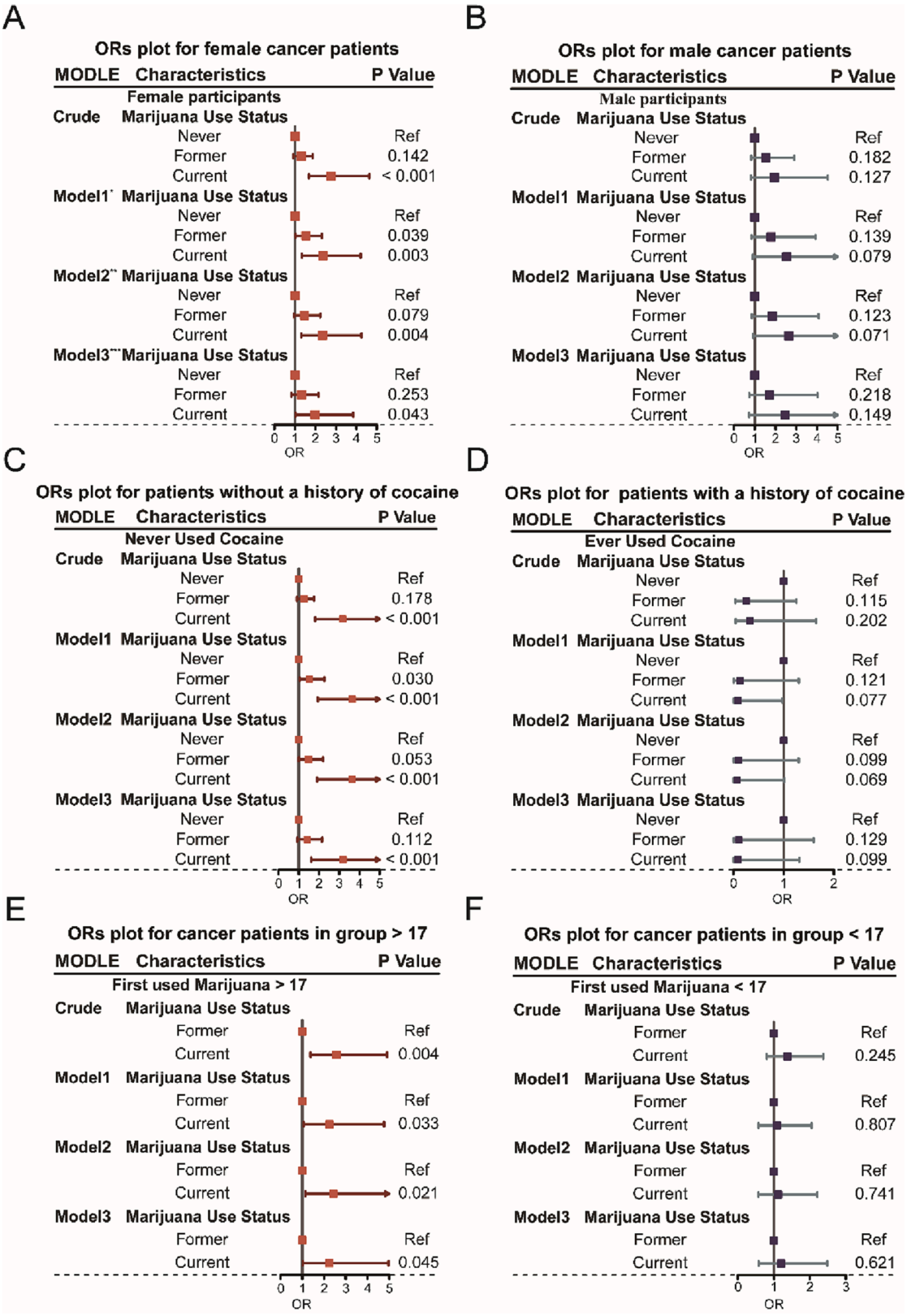

Fig. 2. Subgroup analysis. The correlation between cannabis use status and depression in cancer patients in different subgroups was illustrated using a forest map. Gender stratification: A. Correlation between cannabis use and depression in female cancer patients; B. Association between cannabis use and depression in male cancer patients; C. Stratification of cocaine use history: correlation between cannabis use and depression in cancer patients without history of cocaine use; D. Association between cannabis use and depression in cancer patients with a history of cocaine use. The "Never" group was taken as a reference. According to the age of initial cannabis use, cancer patients with a history of cannabis use were divided into the ≥17 group and <17 group with the age of initial cannabis use having a cut-off value of 17; E. Correlation of cannabis use status with depression in cancer patients with initial cannabis use age ≥17; and F. Association between cannabis use status and depression in cancer patients with the age of initial cannabis use <17. The "Former" group was taken as a reference.

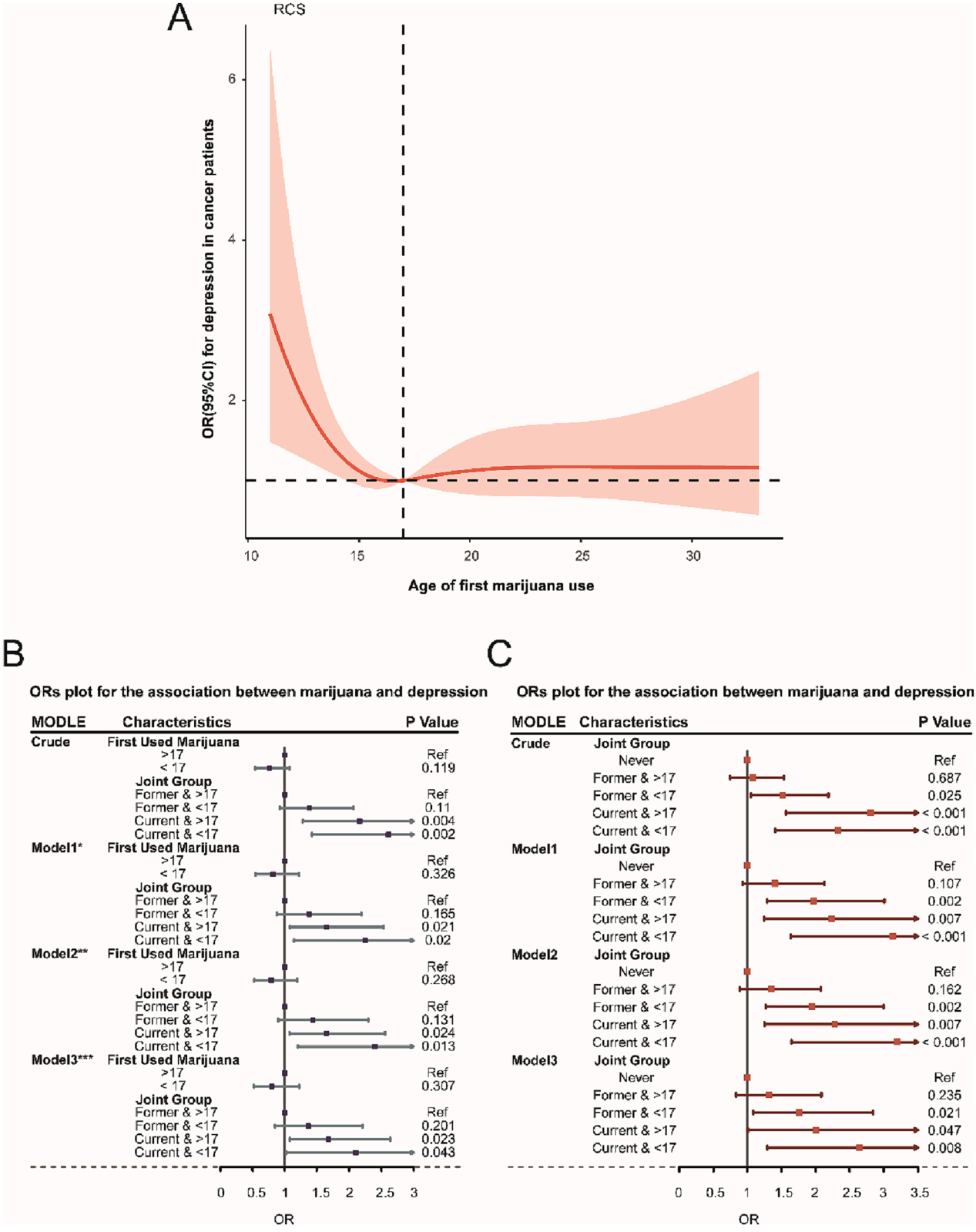

Fig. 3. Association between age of initial cannabis use with depression in cancer patients. A. Based on the logistic regression model, restrictive spline analysis showed the odds ratio between the age of initial cannabis use and depression; the cut-off value was determined according to the RCS curve; knots included the 5th, 35th, 65th, and 95th percentile of exposure factors; the model was fully adjusted according to social demographic factors, such as age and cannabis use status. B. The cancer patients who used cannabis were divided into the ≥17 group and <17 group, according to their age of initial cannabis use. Furthermore, cancer patients were grouped according to their cannabis use status and age of initial cannabis use. This was defined as the "Joint Group" and used as an exposure factor to analyze the correlation with depression. The ≥17 group and "Former" & ≥17 groups were taken as a reference, respectively. C. Taking cancer patients who have never used cannabis as a reference, the correlation between the "Joint Group" as an exposure factor and depression was analyzed.

"Former" & ≥ 17 group. The "Joint Group" was included in the analysis as an exposure factor. We found that among cancer patients using cannabis, those in the "Current" & ≥17 group, and the "Current" & <17 group were all significantly associated with depression, with ORs of 1.679 (95% CI = 1.076–2.639, P = 0.023) and 2.104 (95% CI = 1.023–4.35, P = 0.043), respectively (Fig. 3B, and Table B.7). Similarly, we found that in all cancer patients in the "Former" & <17 group, "Current" & ≥17 group, and "Current" & <17 group were all significantly positively correlated with depression as compared to the "Never" group. Their ORs were 1.759 (95% CI = 1.087–2.848, P = 0.021), 2.004 (95% CI = 1.008–3.990, P = 0.047), and 2.644 (95% CI = 1.296–5.432, P = 0.008), respectively (Fig. 3C, and Table B.8). In particular, cancer

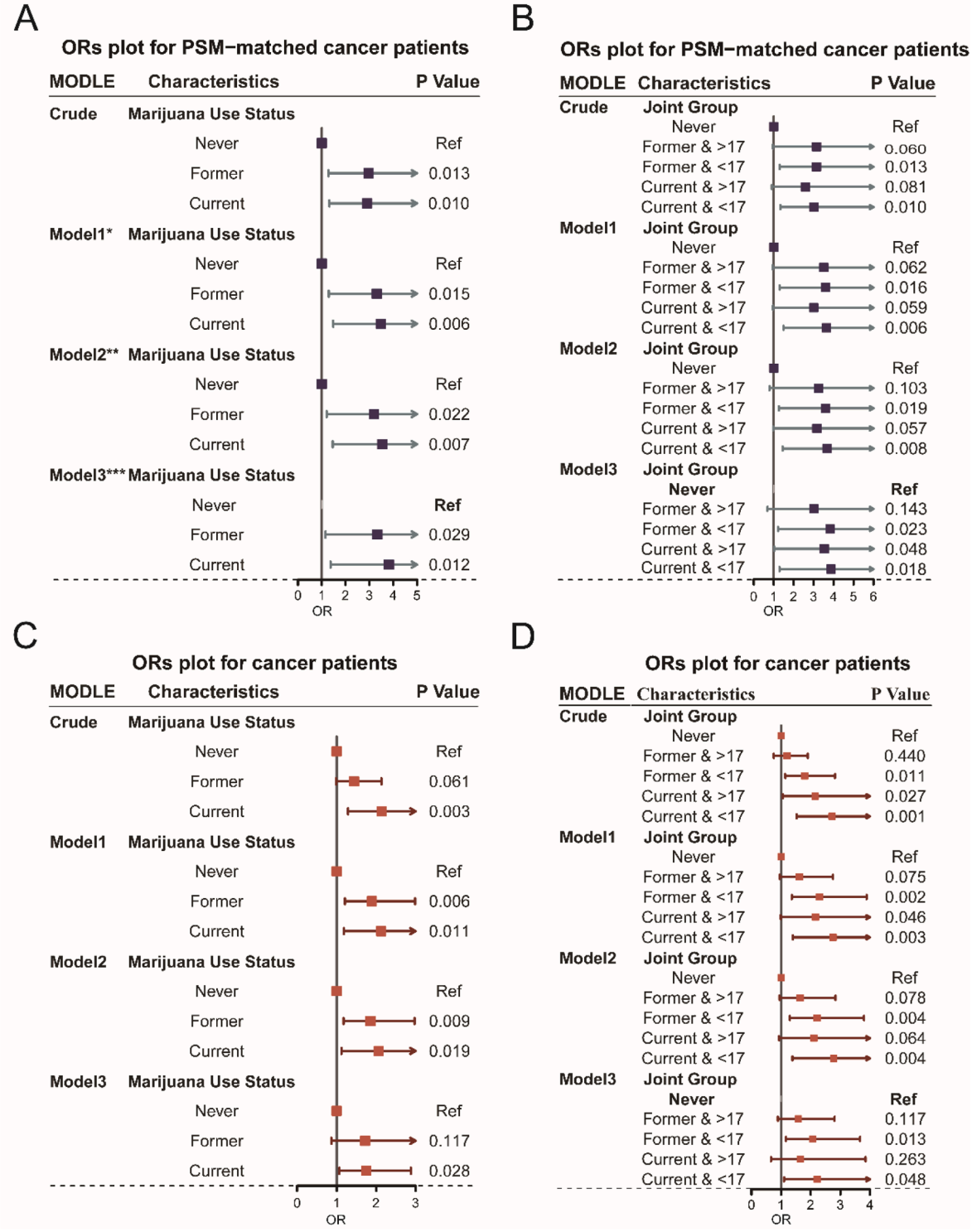

Fig. 4. Sensitivity analysis. A. The association between cannabis use and depression was assessed in cancer patients with similar baseline characteristics as obtained by PSM. B. Assessing the association of the "Joint Group" (cancer participants grouped by cannabis use status and age at first cannabis use) with depression in PSM-matched participants. C and D. To analyze the correlation between cannabis use status and severe depression in cancer patients; the exposure factors included the cannabis use status and the age of initial cannabis use. The "Never" group was taken as the reference.

patients whose age of initial cannabis use were younger than 17 years and were currently using cannabis were more likely to be depressed (OR = 2.644, 95% CI = 1.296–5.432, P = 0.008) (Fig. 3C and Table B.8).

3.5. Sensitivity analysis

We used PSM to select cancer patients with similar baseline characteristics for sensitivity analysis (Table B.9), then repeated our main analysis. Compared with cancer patients who had never used cannabis, the ORs of depression in cancer patients with both former and current cannabis use were 3.332 (95% CI = 1.154–10.125, P = 0.029) and 3.82 (95% CI = 1.367–11.326, P = 0.012), respectively (Fig. 4A, and Table B.10). Moreover, cancer patients with an age of initial cannabis use younger than 17 years old who were currently using cannabis were more likely to have depression (OR = 3.872, 95% CI = 1.292–12.239, P = 0.018) (Fig. 4B, and Table B.10). Similar results were obtained from the correlation analysis between cannabis use status and severe depression (PHQ-9 score $\geq$ 10) in cancer patients. Compared with cancer patients without a history of cannabis use, current cannabis use was significantly positively correlated with the risk of severe depression (OR = 1.746, 95% CI = 1.067–2.882, P = 0.028) (Fig. 4C, and Table B.11). Furthermore, cancer patients with age of initial cannabis use younger than 17 years old and who were currently using cannabis at the time of the study were more likely to develop depression than other groups (OR = 2.219, 95% CI = 1.099–4.857, P = 0.048) (Fig. 4D, and Table B.11).

3.6. Cannabis use is associated with depression in the "all participants" subset

We performed an analysis on the association between cannabis use and depression among the "all participants" subset. The "all participants" subset were grouped according to tumor diagnosis and their baseline characteristics were shown in (Table B.12). From 2005 to 2018, there was an upward trend in cannabis use among participants (Fig. 5A, and Table B.13). As their cannabis use statuses changed, there was also a gradual increase in the incidence of depression in the "all participants" group (Table B.14). We used the Crude Model and multivariable adjusted logistic regression model to examine the association between cannabis use and depression, the results of which revealed that cannabis use in the "all participants" subset increased the possibility of depression. Compared with the participants who never used cannabis, the ORs of depression for former cannabis use and current cannabis use were 1.290 (95% CI = 1.184–1.407, P < 0.001) and 1.663 (95% CI = 1.483–1.865, P < 0.001) (Fig. 5B), respectively. Sensitivity analysis was performed on the subset obtained by the PSM-matched "all participants" group (Table B.15), and the results were consistent with our main results. There was a significant positive correlation between current cannabis use and depression (OR = 1.595, 95% CI = 1.139–2.231, P = 0.006) (Fig. 5C).

4. Discussion

Cannabis is a commonly used psychoactive substance. With the ongoing expansion of cannabis's use in the field of oncology, it is increasingly important to evaluate its potential risks (Abu-Amna et al., 2021). Our study also draws conclusions consistent with previous studies that the use of cannabis in cancer patients may induce depression. In recent years, studies on the molecular mechanism of cannabis in the development of depression have also been carried out, and they have revealed that the endogenous cannabinoid system (ECS) is involved in the regulation of cognition, emotion, inflammation, appetite, pain, and the stress response of the body (Stampanoni Bassi et al., 2018). Decreased activity in the ECS may induce depression in humans (Hillard et al., 2012). The ECS system consists of two parts: endogenous cannabinoid and cannabinoid receptors (CB1 receptor and CB2 receptor). The CB1 receptor is widely expressed in the central nervous system. It is associated with reward and cognitive function, and it plays a major role in ECS-mediated pathophysiology of depression (Greydanus et al., 2013). There is also significant evidence to confirm the relationship between ECS and depression. For example, in rodent models, knockdown of CB1 receptor gene expression through gene modification is associated with an increase in depressive behavior and stress susceptibility (Jenkins and Khokhar, 2021). In animal models, it has been found that low-dose CB1 receptor agonists could stimulate 5-HT cells in the dorsal raphe nucleus and increase their discharge rate to achieve antidepressant effect. However, when the dosage of CB1 receptor agonist was continuously increased, it showed a significant inhibitory effect, which was the complete opposite of the effect on the low dose group (Cohen et al., 2019). The psychoactive effect of THC, the main active component of cannabis, comes from its active effect on the CB1 receptor. Continuous cannabis consumption, be it medical or non-medical, eventually leads to a decrease in CB1 receptor activity, thus inducing an inhibitory effect. This low activity in the ECS system then ultimately mediates the occurrence of depression (Wycoff et al., 2018). At the same time, THC can mediate the pathophysiological changes of depression by affecting the release of dopamine in the central nervous system, especially by regulating emotion and euphoria. Studies have shown that THC has a biphasic pattern in the release of dopamine in the central nervous system. A low dose of cannabis intake will increase the synthesis and release of dopamine, resulting in euphoria. If the cannabis dosage accumulates or the intake increases, the synthesis and release of dopamine are inhibited, which results in a loss of pleasure, low mood, and an increased risk of depression (Solowij et al., 2019). Our findings are consistent with previous studies in this regard. Compared with cancer patients who have never used cannabis, current cannabis use may increase their risk of depression. At the same time, for either compared with cancer patients who have never used cannabis or former users with an age of initial cannabis use >17 years old, current cannabis users with a younger initial cannabis use age show a higher possibility of developing depression. This illustrates the cumulative dose effect of cannabis. For our study population, therefore, frequent cannabis use may be an independent risk factor for the development of depression.

Our study found that there was a significant positive correlation between cannabis use and depression in female cancer patients, but not in male cancer patients. The difference may be related to gender differences in cannabinoid receptor expression. Gender differences in the endogenous cannabinoid system have been explored by researchers; in particular, the expression level of the CB1 receptor in different parts of the central nervous system has been found to have significant gender differences (Gorzalka et al., 2010; Craft et al., 2013). According to relevant research reports, women have higher levels of CB1 receptor mRNA transcription in the frontal cortex, hippocampus, amygdala, and cerebellum compared with men (de Fonseca et al., 1994). In the animal model, the density of CB1 receptors in the central nervous system of female animals, such as frontal cortex, hippocampus, amygdala, and midbrain, is higher and more widely distributed compared with male animals (Zamberletti et al., 2012). A human-based positron emission tomography (PET) study has shown that the availability of CB1 receptors in men is generally lower than that in women in most areas. Thus, this high expression of CB1 receptors in the central nervous system of women may increase women's susceptibility to cannabis (Normandin et al., 2015). The physiological effect and metabolism of cannabinoid may be different between males and females. Studies have shown that the direct physiological reactions to cannabis use by men are mainly sedation and vertigo. On the other hand, women's physiological response to cannabis was fatigue, drowsiness, and mental depression (Kaufmann et al., 2010). In another animal experiment, the researchers found that, in contrast to male cannabis users, THC was only metabolized into the primary metabolite 11-OH-THC in females, causing the THC concentration in their cerebrospinal fluid (CSF) to be higher than that in males. Furthermore, females had higher plasma THC levels after

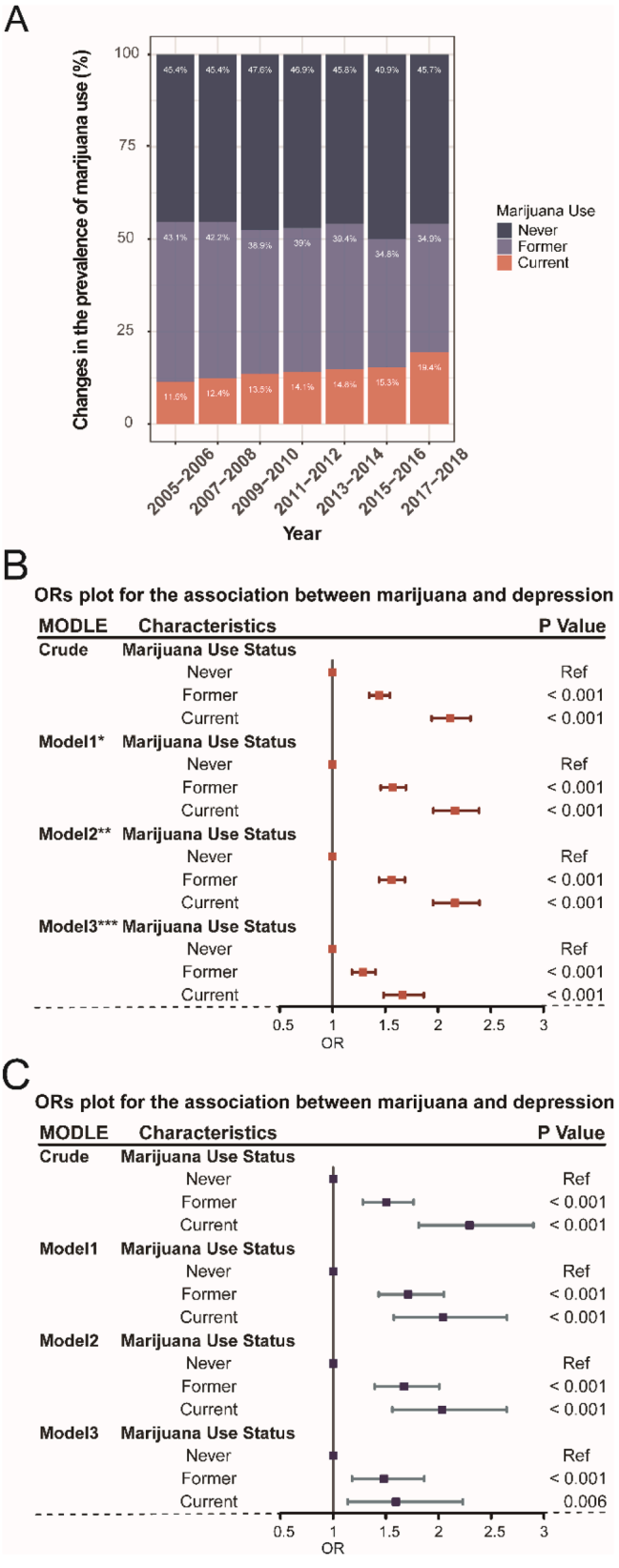

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Fig. 5. Changes in prevalence of cannabis use among all participants and the relationship between cannabis use status and depression in all participants. A. Changes in the prevalence of cannabis use in all participants in seven two-year cycles from 2005 to 2018. B. The relationship between cannabis use status and depression in all participants. The status of cannabis use was divided into three groups: "Never", defined as the group who never used cannabis; "Former", defined as the group who used cannabis before and did not use cannabis in the past 30 days; "Current", defined as the group who used cannabis in the past 30 days; The "Never" group was taken as the reference. C. All participants were matched by PSM to obtain a subset of participants with similar baseline characteristics, after which sensitivity analysis was conducted.

being given equal amounts of the drug as males (Wiley and Burston, 2014). These findings and theories may explain the fact that current cannabis use correlated with the increased risk of depression in the female cancer patients in our study. Of course, more evidence is needed for these findings to fully explain how cannabis use affects women and men differently. However, the experimental design of most current preclinical studies does not do a good job of differentiating between genders; furthermore, many clinical studies still do not include female subjects, and in those clinical studies that do include female subjects, gender is not usually discussed as a variable of interest. Our findings will hopefully shed light on future research, and we hope that more potential mechanisms leading to sex differences will be identified in future studies (Allick et al., 2021; Calakos et al., 2017).

In our results, we found that 17 years old is a cut-off value. Cancer patients with an initial cannabis use age of under 17 years old who were currently using cannabis were more likely to develop depression, which suggests that cannabis exposure in adolescence may increase the risk of depression in dulthood. According to an epidemiological survey in the United States, >1.6 million adolescents aged from 12 to 17 years old have reported cannabis use. According to the 2018 survey, 24% of U.S. high school students reported cannabis use in the past 30 days, of which 6.4% reported cannabis use almost daily (Hines et al., 2020). Numerous epidemiological studies have reported that adolescent cannabis use increases the risk of psychiatric disorders and complications, such as anxiety, and depression (Jacobus et al., 2013; van Winkel and Kuepper, 2014). Studies have also proposed that adolescent cannabis exposure can affect the expression of dopamine D2 receptor protein in both the striatum and the nucleus accumbens of the central nervous system (Morel et al., 2009). Indeed, animal experiments have shown that cannabis exposure during development is associated with the striatum of the central nervous system. In the youth model of THC exposure, the expression level of the dopamine D2 receptor in the striatum is significantly reduced in adulthood, and the decreased expression of the dopamine D2 receptor protein has long been a representative neurobiological feature of susceptibility to mental disorders (Ellgren et al., 2007; Tomasiewicz et al., 2012). The age of initial cannabis exposure was likewise a risk factor for depression in cancer patients. This finding suggests that premature cannabis exposure may have lasting neurological effects, especially during adolescence. Of course, large prospective longitudinal studies are still needed to further explore the relationship between cannabis exposure and adolescent neurological development. However, as the prevalence of marijuana among youth increases each year, we also need to pay more attention to this social phenomenon, and perhaps when we intervene early and limit youth access to cannabis, we may be better able to prevent the adverse effects of cannabis (Leadbeater et al., 2019; Subramaniam et al., 2018).

5. Conclusion

In this study, we explored the association between cannabis use and depression in all cancer respondents to NHANES surveys from 2005 to 2018. We observed a significant positive correlation between current cannabis use (within the last 30 days) and depression. We also observed that current cannabis use was an independent risk factor for depression

among female cancer patients, cancer patients with age of initial cannabis use older than 17 years, and cancer patients without a history of cocaine use. However, even though the age of initial cannabis use was not an independent risk factor for depression in cancer patients, early and ongoing cannabis use may be associated with a higher likelihood of depression in cancer patients. Although we have discussed the underlying mechanism of the correlation between cannabis use and depression, the causal relationship between cannabis and depression requires further research.

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CRediT authorship contribution statement

Shulu Hu: Writing - original draft. **Anqi Lin:** Writing - review & editing. **Peng Luo:** Conceptualization. **Jian Zhang:** Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102304.

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