

**Concept Paper Form**

<b>Provisional Paper Title:</b> Midlife Pain, Sleep, and Mood in Long-term Cannabis Users: Results of a Population-Representative Longitudinal Study
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<b>Today's Date:</b> 6/19/2024

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

**Objective of the study:**

Cannabis has been used to alleviate pain, sleep, and mood problems, but research shows that cannabis may actually worsen these symptoms over time. For example, several studies have shown:

- High-frequency cannabis use is associated with worse pain in the long term (Boehnke et al., 2020; Romero-Sandoval et al., 2018).
- Long-term, cannabis use is associated with negative effects on sleep, including reduced sleep duration and worse overall sleep (Edwards & Fibley, 2021; Winiger et al., 2021).
- Cannabis may worsen depression long-term, as well as anxiety, though research is more mixed for anxiety (Arendt, 2007; Lev-Ran et al., 2013; Gobbi et al., 2019; Crippa et al., 2009; Sideli et al., 2020).

These studies have all shed light on the association of cannabis with these negative outcomes, though most have multiple limitations that our study will address. Whereas many of these studies are cross-sectional and hence they were unable to determine temporal order of cannabis use and these outcomes, we will be able to establish this through the longitudinal Dunedin data. On top of this, most studies use retrospective reports for cannabis use, including yes/no questions for if a participant has ever used cannabis and lifetime reports of cannabis use. Measures for cannabis use in the Dunedin dataset are prospective and ascertained frequency of use and dependence repeatedly across numerous study waves, enabling a much richer characterization of cannabis use.

Our study will involve informative comparisons between long-term cannabis users and 4 groups on midlife pain, sleep, anxiety, and depression: (i) lifelong cannabis non-users, (ii) infrequent recreational cannabis users, (iii) cannabis quitters, (iv) long-term alcohol users.

We compare long-term cannabis users with lifelong non-users to replicate findings from case-control studies. We compare long-term cannabis users to midlife recreational users because most people who use cannabis use it infrequently, and it is necessary to understand whether pain, sleep, and mood problems are limited to frequent users or are apparent in infrequent users too. We compare long-term cannabis users with cannabis quitters to see if cessation is associated with better outcomes.

Furthermore, it is important to compare cannabis to alcohol because proponents of cannabis legalization claim that alcohol is far more harmful than cannabis. Moreover, like cannabis, people self-medicate with alcohol. Excessive alcohol use may be associated with greater pain severity (Zale et al., 2015), more sleep disturbances (He et al., 2019), and the presence of depressive disorders (Boden & Fergusson, 2011), though its relationship with anxiety is more mixed (D'Aquino et al., 2024; Schuckit & Hesselbrock, 2004). But, few studies have directly compared cannabis and alcohol on these outcomes. The proposed study will leverage the Dunedin Cohort to better understand associations between cannabis use and pain, sleep, and mood problems.

### **Data analysis methods:**

Analyses will use two complementary approaches: (1) a qualitative approach: comparison of long-term cannabis users with 4 informative subgroups on age-45 pain, sleep, anxiety, and depression, and (2) a quantitative approach: tests of dose-response associations between persistence of cannabis use from age 18-45 and age-45 outcomes. Tests of dose-response associations will be repeated using persistence of alcohol dependence as the exposure, for comparison with persistence of cannabis use.

1. Long-term cannabis users will be compared with 4 informative subgroups using t-tests.

*Long-term cannabis users:* study members who used cannabis weekly or more frequently in the past year at age 45, or were dependent on cannabis at age 45, and also used weekly or more frequently at one or more previous assessment waves.

The 4 comparison groups are defined as:

- (i) *Lifelong cannabis non-users:* study members who never used cannabis, never had a diagnosis of any substance-use disorder, and never used tobacco daily.
- (ii) *Midlife recreational cannabis users:* study members used cannabis between 6-51 days per year (i.e., used more than a few times but less than weekly) in midlife (age 32, 38, or 45), and had no history of weekly cannabis use or dependence.
- (iii) *Cannabis quitters:* study members did not use cannabis at age 45 but previously either diagnosed with cannabis dependence or used regularly (4+ days per week).
- (iv) *Long-term alcohol users:* study members who were weekly drinkers at age 45; had a diagnosis of alcohol dependence at 2+ waves; were mostly free from cannabis at age 45; and had no history of weekly cannabis use or dependence.

2. Dose-response associations will be tested using regression, with age-45 pain, sleep, anxiety, and depression as outcomes and with persistence of cannabis dependence, persistence of regular cannabis use, and persistence of alcohol dependence in adulthood between ages 18-45 as predictors.

*Persistence of cannabis dependence* will be defined by grouping study members according to those who (i) never used cannabis, (ii) used but never diagnosed, (iii) diagnosed at one wave, (iv) two waves, (v) three waves, and (vi) 4+ waves.

Sensitivity analysis will also examine persistence of regular cannabis use as the cannabis exposure. We will be doing analyses with both persistence of cannabis dependence and persistence of regular use as exposures in order to define cannabis use in two ways: dependence that captures problem use as defined by DSM diagnoses and regular use that captures overall frequency.

*Persistence of regular cannabis use* will be defined by grouping study members according to those who (i) never used cannabis, (ii) used but never regularly, (iii) used regularly at one wave, (iv) two waves, (v) three waves, and (vi) 4+ waves. Regular use is defined as using cannabis the majority of the days, i.e. at least 4 days per week.

*Persistence of alcohol dependence* will be defined by grouping study members according to those who (i) never used alcohol, (ii) drank alcohol at least weekly at one or more assessment waves but were never diagnosed with alcohol dependence, (iii) were diagnosed at one wave, (iv) were diagnosed at two waves, (v) were diagnosed at three waves, and (vi) were diagnosed at four or more waves.

*Quantitative exposure models for outcomes at age 45.*

- I. Pain: Analyses will use linear regression predicting pain, controlling for sex. Childhood SES and health will be added in as covariates. Then, persistent use of other substances will be added in. Lastly, the earliest measure for pain will be added as a covariate (SF-36 at age 26?).
- II. Sleep: Analyses will use logistic regression predicting sleep problems, controlling for sex. Childhood SES and health will be added in next as covariates. Then, persistent use of other substances will be added in. Lastly, sleep problems in childhood/adolescents will be added as a covariate.
- III. Anxiety: Analyses will use logistic regression predicting anxiety, controlling for sex. Childhood SES and health will be added in next as covariates. Then, persistent use of other substances will be added in. Lastly, anxiety in childhood/adolescents will be added as a covariate.
- IV. Depression: Analyses will use logistic regression predicting depression, controlling for sex. Childhood SES and health will be added in next as covariates. Then, persistent use of other substances will be added in. Lastly, depression in childhood/adolescents will be added as a covariate.

We acknowledge that the outcomes – pain, sleep, and mood problems -- are correlated. Analyses will address this by using a path analysis/structural equation modeling framework, which will allow the outcomes to correlate (Brand et al., 2010).

## **Variables needed at which ages:**

### Exposures:

1. Age-45 comparison groups: (i) long-term cannabis users, (ii) lifelong cannabis non-users with no other substance use problems, (iii) midlife recreational cannabis users, (iv) cannabis quitters, (v) long-term alcohol users.
2. Persistence of cannabis dependence ages 18-45, persistence of regular cannabis use from age 18-45, persistence of alcohol dependence

### Outcomes at age 45:

1. Pain composite score, consisting of musculoskeletal pain composite, musculoskeletal pain interference with life, and pain medication use (Brennan et al., 2023)
2. Sleep problems composite score, consisting of poor sleep quality (PSQI), sleep aid use, and social jetlag (Brennan et al., 2023)
3. Anxiety (dx)
4. Depression (dx)

### Covariates:

- I. Added to all cannabis models
  1. Childhood SES
  2. Childhood health
  3. Sex
  4. Persistence alcohol dependence
  5. Persistent illicit drug dependence
- II. Additionally added to models of Pain
  1. Find an earlier measure of pain (maybe SF-36 at age 26)
- III. Additionally added to models for Sleep
  1. Insomnia age 18 (dichotomous, Gregory et al. 2006)
  2. Persistent sleep problems from age 5, 7, 9 (dichotomous, Gregory et al. 2005)
- IV. Additionally added to models of Anxiety
  1. Anxiety (dx) – ages 11-18
- V. Additionally added to models of Depression
  1. Depression (dx) – ages 11-18

## **Significance of the Study (for theory, research methods or clinical practice):**

As stated in the grant application, this study has implications for research, prevention, treatment, and policy.

*Implications for future research:* An association between cannabis and the outcomes of pain, sleep, anxiety, and depression will attract attention to priority questions warranting further research investment. Understanding the effects of infrequent use (i.e., recreational use versus long-term use) will inform future research regarding the importance of distinguishing between different groups of cannabis users. If no associations are found, this will help the field identify hypotheses of cannabis harm that are unfruitful so that scientific resources can be directed elsewhere.

*Implications for prevention:* Knowledge of harms that do or do not characterize long-term users will inform substance-abuse prevention. Preventing adolescent cannabis use is a major focus now, but this study can inform whether cessation programs for midlife adults ought to be added to the prevention toolkit.

*Implications for treatment:* Further understanding the relationship between cannabis and pain, sleep, anxiety, and depression will call attention to the need for interventions, and whether interventions should target cannabis use specifically or substance use generally.

*Implications for policy:* Cannabis legalization is well underway, and findings of harm are unlikely to reverse this trend. But, new policies can be created to enhance the safety of cannabis use, including policies for medical marijuana. Due to the destigmatization of cannabis in recent years, information on potential harms of cannabis use, whether use is infrequent or long-term, needs to be disseminated to the public.

## **References**

- Arendt, M., Rosenberg, R., Fjordback, L., Brandholdt, J., Foldager, L., Sher, L., & Munk-Jørgensen, P. (2007). Testing the self-medication hypothesis of depression and aggression in cannabis-dependent subjects. *Psychological medicine*, 37(7), 935-945.
- Boden, J. M., & Fergusson, D. M. (2011). Alcohol and depression. *Addiction*, 106(5), 906-914.
- Boehnke, K. F., Scott, J. R., Litinas, E., Sisley, S., Williams, D. A., & Clauw, D. J. (2020). High-frequency medical cannabis use is associated with worse pain among individuals with chronic pain. *The Journal of Pain*, 21(5-6), 570-581.
- Brand, S., Gerber, M., Pühse, U., & Holsboer-Trachsler, E. (2010). The relation between sleep and pain among a non-clinical sample of young adults. *European archives of psychiatry and clinical neuroscience*, 260, 543-551.
- Brennan, G. M., Moffitt, T. E., Ambler, A., Harrington, H., Hogan, S., Houts, R. M., ... & Caspi, A. (2023). Tracing the origins of midlife despair: association of psychopathology during adolescence with a syndrome of despair-related maladies at midlife. *Psychological Medicine*, 53(16), 7569-7580.
- Capron, D. W., Allan, N. P., Norr, A. M., Zvolensky, M. J., & Schmidt, N. B. (2014). The effect of successful and unsuccessful smoking cessation on short-term anxiety, depression, and suicidality. *Addictive behaviors*, 39(4), 782-788.
- Castellanos-Ryan N, Morin É, Rioux C, London-Nadeau K, Leblond M. Academic, socioeconomic and interpersonal consequences of cannabis use: A narrative review. *Drugs: Education, Prevention and Policy*. 2021.1-19.
- Crippa, J. A., Zuardi, A. W., Martín-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., & Fusar-Poli, P. (2009). Cannabis and anxiety: a critical review of the evidence. *Human Psychopharmacology: Clinical and Experimental*, 24(7), 515-523.

- D'Aquino, S., Kumar, A., Riordan, B., & Callinan, S. (2024). Long-term effects of alcohol consumption on anxiety in adults: A systematic review. *Addictive Behaviors*, 108047.
- Edwards, D., & Filbey, F. M. (2021). Are sweet dreams made of these? Understanding the relationship between sleep and cannabis use. *Cannabis and Cannabinoid Research*, 6(6), 462-473.
- Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., ... & Mayo, N. (2019). Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: A systematic review and meta-analysis. *JAMA psychiatry*, 76(4), 426-434.
- He, S., Hasler, B. P., & Chakravorty, S. (2019). Alcohol and sleep-related problems. *Current opinion in psychology*, 30, 117-122.
- Lev-Ran, S., Roerecke, M., Le Foll, B., George, T. P., McKenzie, K., & Rehm, J. (2014). The association between cannabis use and depression: A systematic review and meta-analysis of longitudinal studies. *Psychological Medicine*, 44(4), 797-810.
- Lucatch, A. M., Kloiber, S. M., Meyer, J. H., Rizvi, S. J., & George, T. P. (2020). Effects of extended cannabis abstinence in major depressive disorder. *Canadian Journal of Addiction*, 11(3), 33-41.
- Meier, M. H. Cannabis use and psychosocial functioning: evidence from prospective longitudinal studies. *Current Opinion in Psychology*. 2021. 38: 19-24.
- Romero-Sandoval, E. A., Fincham, J. E., Kolano, A. L., Sharpe, B. N., & Alvarado-Vázquez, P. A. (2018). Cannabis for chronic pain: challenges and considerations. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 38(6), 651-662.
- Rooke, S. E., Norberg, M. M., & Copeland, J. (2011). Successful and unsuccessful cannabis quitters: Comparing group characteristics and quitting strategies. *Substance Abuse Treatment, Prevention, and Policy*, 6, 1-9.
- Schuckit, M. A., & Hesselbrock, V. (2004). Alcohol dependence and anxiety disorders: what is the relationship?. *Focus*, 151(3), 1723-453.
- Sideli, L., Quigley, H., La Cascia, C., & Murray, R. M. (2020). Cannabis use and the risk for psychosis and affective disorders. *Journal of dual diagnosis*, 16(1), 22-42.
- Winiger, E. A., Hitchcock, L. N., Bryan, A. D., & Bidwell, L. C. (2021). Cannabis use and sleep: expectations, outcomes, and the role of age. *Addictive behaviors*, 112, 106642.
- Zale, E. L., Maisto, S. A., & Ditre, J. W. (2015). Interrelations between pain and alcohol: An integrative review. *Clinical psychology review*, 37, 57-71.]