



Correspondence

Correspondence to “Which came first, the cannabis or the depression?”

Dear editors,

We greatly appreciate Dr. Theodore M. Brasky taking the time to provide thoughtful critique on our article. We welcome the chance to address his concerns in detail, as it provides an invaluable opportunity to improve the clarity and rigor of our work.

Firstly, a short review of our findings is given. 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.

Next, we will answer in detail the question posed by M. Brasky. Regarding the use of “risk”, Dr. Brasky makes an astute observation that this term is typically reserved for prospective studies denoting incidence, whereas our study design was cross-sectional. We should have instead used “association” to accurately reflect the nature of our statistical relationships. As Dr. Brasky notes, risk implies a predictive relationship over time that our data do not support. While some prior cross-sectional studies have employed “risk” in a looser sense, we agree with Dr. Brasky that precise terminology is critical for conveying the true meaning and limitations of findings. While some analyses have utilized the term “risk” when examining associations between exposures and outcomes in cross-sectional studies (Zhao et al., 2023; Zielińska et al., 2023; Zeng et al., 2023; Poursalehi et al., 2023); and we aimed to situate our work within this literature, it must be acknowledged that use of “risk” in this context has limitations. Cross-sectional data cannot establish temporal sequence between exposure and outcome. Consequently, observed statistical relationships, while suggestive, cannot isolate the impact of the exposure itself from numerous potential confounders that may also correlate with the outcome.

Regarding the characterization of cancer patients, we fully concede Dr. Brasky’s point. The NHANES survey did not collect granular data on patients’ cancer status and treatment timelines. Participants were simply asked to self-report a previous tumor diagnosis and type. There was no investigation into date of diagnosis, current treatment status, or remission status. As Dr. Brasky astutely states, this limitation means our cancer group likely represented a heterogeneous mixture of actively diagnosed patients as well as disease-free survivors across the continuum of care. Without medical chart validation, we had no means to accurately subclassify patients into clinically meaningful categories. This was a major oversight in our methodology that we should have

explicitly acknowledged. Dr. Brasky’s critique highlights the need for more rigorous capture of cancer status and treatment variables in epidemiological surveys examining this population. We sincerely appreciate this feedback, as it will significantly inform the design of future studies.

The third issue is the limitations of using the PHQ-9 with a 4-point threshold as the sole screening method for depression. The PHQ-9 is a widely recognized and scientifically supported tool, so we followed the common practice of using a score above 4 as indicative of depression (Kroenke et al., 2001). However, as Dr. Brasky noted, relying on a single PHQ-9 score has limitations. Subsequent studies should use a combination of screening methods to ensure scientific validity.

Regarding the relationship between cannabis use and depression, our analysis found a correlation but could not determine causation. Unfortunately, the NHANES data lacked details on cannabis use needed to establish a causal link. We can only posit a causal relationship based on previous studies showing links between cannabis and depression in animal models (Cohen et al., 2019); imaging studies (Barkus et al., 2011; Normandin et al., 2015); and clinical trials (Jordan et al., 2022; Harder et al., 2006).

There are still some confounding factors that affect our results in this study. First, our assessment and grouping of cannabis use status was based mainly on the time interval between the last use of cannabis in the self-report of the respondents and the interview. Therefore, it is difficult to assess the impact of long-term habitual cannabis use on the results. Second, in all the survey cycles of NHANES used in this study, the survey on the use of cannabis did not address the dosage, only its use or non-use. With this background, it was difficult to assess the specific dosage and daily frequency of cannabis use in cancer patients. Therefore, it was impossible for this study to assess whether a dose–response relationship exists between cannabis use and depression. Third, as an observational study, unknown confounding factors may exist.

This study also has some limitations. As an observational study, we could only support the positive association between cannabis use status and cancer patients’ depression using previous studies or theories, as our research was not able to explain the causal relationship. Moreover, we used PHQ-9 scores rather than clinical diagnoses to evaluate depression levels, possibly overestimating depression prevalence, especially among cancer patients. Follow-up clinical trials are needed to accurately diagnose depression.

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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

No data was used for the research described in the article.

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