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Manuscript Review: Investigating the Relationships Between Alcohol, Cannabis Use, and Circulating Cytokines: A Preliminary Analysis (Karoly et al., 2018).

Karoly et al.'s study aimed to investigate the associations between alcohol consumption, cannabis use, and aimed to explore the associations between alcohol consumption, cannabis use, and blood levels of three pro-inflammatory cytokines interleukin 6 (IL-6), IL-8, and IL-1β. Findings revealed a positive association between alcohol intake and IL-6 levels, indicating a potential link between alcohol use and inflammatory responses. Cannabis use showed a negative association with IL-1β, suggesting a potential dampening effect on inflammation. Additionally, an intriguing interaction emerged, indicating that among individuals who didn't use cannabis, higher alcohol consumption correlated strongly with increased IL-6 levels, but this link wasn't present in those who did use cannabis, hinting at a potential mitigating effect of cannabis on alcohol-related inflammation. The major strengths of this study is that it approached it from a comprehensive approach by analyzing multiple cytokines, providing a broader understanding of the immune response. The study also take consideration of moderation by exploring how cannabis use might moderate the relationship between alcohol and cytokines added depth to the findings. However, several limitations should be considered, including the cross-sectional design, which limits the ability to determine causal relationships between alcohol, cannabis use, and cytokine levels. Further research, including longitudinal studies and investigations into the specific mechanisms underlying the observed interactions, is needed to validate and extend these findings. The sample size, consisting of 66 participants (n = 66), might limit the generalizability of the findings. The reliance on self-reported substance use introduces potential biases and inaccuracies in data collection. Additionally, the sensitivity of the cytokine assays, with some concentrations below detection limits, could impact data analysis and interpretation. Additionally, there are several points which need to be addressed below:

Introduction:

1. The literature review is informative, but some key references lack specific details (e.g., Alfonso-Loeches and Guerri, 2011; Coller and Hutchinson, 2012). Request more specific information on these studies or suggest providing additional references to enhance the comprehensiveness of the literature review.
2. While the link between alcohol-induced inflammation and the study objectives is apparent, explicitly connecting how the proposed research addresses the identified gaps in the literature would strengthen the introduction. Ask the authors to explicitly state how their study bridges these gaps.

3. While discussing the impact of cannabinoid receptors on inflammatory signaling, it might be beneficial to briefly touch upon the potential translational implications of these findings. How might understanding these relationships influence AUD treatment or intervention strategies?

Method:

1. The demographic breakdown, including age, gender, and race, is informative. However, consider providing additional details on socioeconomic status and education to offer a more comprehensive understanding of the sample's characteristics.
2. The sample size of 66 participants is reasonable, given the exploratory nature of the study. However, consider justifying this sample size choice in relation to the study's objectives and the anticipated effect sizes.
3. The use of flyers and online advertisements, including platforms like Craigslist, is appropriate for recruiting participants from the greater Boulder-Denver area. However, consider discussing potential biases or limitations associated with this recruitment strategy, such as the potential exclusion of individuals without internet access or the potential bias of the regional nature of the participants' location.

Results:

1. The correlation section is well-structured, but a brief discussion on the magnitude of correlations and their potential implications for the study would strengthen the interpretation. For instance, the correlation between IL-8 and IL-6, though significant, has a relatively modest effect size.
2. The presentation of moderation results is thorough, but it would be beneficial to include additional information on the practical implications of the observed interactions. Consider discussing the potential real-world impact of the cannabis by drinks per drinking day interaction.
3. While the regression results are presented clearly, consider providing effect sizes for the significant main effects and interactions to enhance the interpretability of the findings.
4. The inclusion of TLFB total number of cigarettes and TLFB cigarettes per smoking day as covariates is appropriate. However, a more detailed explanation of the rationale behind their inclusion and their potential influence on the results would enhance the discussion.

Discussion:

1. Page 536, the second paragraph, first line, consider rephrasing the sentence "This cannabis by alcohol interaction suggests that more in-depth exploration..." for better clarity: "The interaction between cannabis and alcohol suggests that further exploration..."
2. Discuss potential reasons for the absence of significant relationships between alcohol or cannabis use and IL-8, considering the differences in sample characteristics compared to studies showing increased IL-8 in alcohol-dependent patients (Hill et al., 1993).