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Association of Alcohol With Cortical Thickness in Adolescents-Reply

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Letters

COMMENT & RESPONSE

In Reply We thank Kung et al for their thoughtful comments regarding the association of alcohol use with our findings.[1] The potential confounding or interactive associations of alcohol use when investigating cannabis associations is a perennial challenge with human research, but a number of analyses lead us to conclude that the cortical thinning we reported was most strongly associated with cannabis exposure.

First, we examined the association between AUDIT Alcohol Consumption (AUDIT-C) score and cortical thickness at 5-year follow-up in prefrontal regions we found to be associated with cannabis use (ie, regions shown in Figure 1 from our study[1]). Cannabis use was not included as a covariate in these analyses. There was no significant association between alcohol consumption and mean cortical thickness of left ($t_{786} = -1.32$, $P = .19$) or right prefrontal ($t_{786} = -1.91$, $P = .06$) regions of interest while controlling for age, total brain volume, sex, handedness, and site. When the same analyses were repeated, replacing alcohol consumption score with cannabis use, cannabis use was significantly associated with left ($t_{786} = -3.69$, $P < .001$) and right prefrontal ($t_{786} = -4.33$, $P < .001$) thickness. To assess whether alcohol exposure was exacerbating the cannabis associations, we tested for an AUDIT-C score by cannabis use interaction on cortical thickness in the same ROIs. No significant interactions were observed ($P > .19$).

We then conducted a vertex-level analysis examining the association between AUDIT-C score and cortical thickness at 5-year follow-up while controlling for the same nuisance variables. Cannabis use was not included as a covariate. No associations survived correction, even when lowering the initial height threshold to $P = .01$. Further, no evidence of a significant AUDIT-C score by cannabis use interaction was observed at the vertex level.

Next, we examined the association between AUDIT-C score and within-participant cortical thinning in the prefrontal regions shown in Figure 2 from our study.[1] Nuisance covariates but not cannabis use were included in models. AUDIT-C score at follow-up was only nominally associated with symmetrized percent change in left ($t_{786} = -2.20$, $P = .03$) and right prefrontal ($t_{786} = -2.05$, $P = .04$) regions of interest, and these associations did not

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survive correction for multiple comparisons. When cannabis use was entered into these models, alcohol use was no longer significantly associated with thinning in these regions of interest ($P > .20$). Moreover, while the cannabis use association was significant, there were no significant AUDIT-C score by cannabis use interactions.

To further address the possibility of other substances driving these cannabis-related associations, we used bayesian causal network (BCN) modeling[2] to explore potential causal relationships among prefrontal cortical thinning and adolescent nicotine, alcohol, and cannabis use. Using data from Albaugh et al,[1] we tested multiple network structure learning algorithms to build BCNs characterizing the potential relationship between prefrontal cortical thinning and substance use.[3] BCN models included tobacco and alcohol use at baseline and follow-up, in addition to cannabis use at follow-up (no participants had used cannabis at baseline). All BCN models strongly suggested a directional relationship of cannabis use between ages 14 and 19 years on accelerated thinning during that same period. They did not indicate a causal relationship of alcohol or tobacco on accelerated thinning. Our findings appear consistent with animal research on adolescent tetrahydrocannabinol exposure and prefrontal cortical maturation.[4]

Conflict of Interest Disclosures:

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