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Commentary on Kristjansson et al. (2018): Caffeine use during early adolescence as a possible risk factor for initiation of smoking and alcohol use

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In adolescents, caffeine intake strongly predicted later initiation of smoking and alcohol use, while there was no such association in the other direction. This suggests a possible causal pathway or shared risk factors. Triangulation – combining evidence from methods with different strengths and weaknesses – could elucidate the nature of this relationship.

Kristjansson et al. [1] present a well-designed study that followed adolescents from 6th to 7th grade, monitoring their intake of caffeine and their use of conventional cigarettes, e-cigarettes and alcohol. Using cross-lagged path models, the authors attempted to test causal effects from caffeine to other substance use, and from other substance use to caffeine. These analyses were adjusted for gender, family structure, ethnicity and maternal education.

While caffeine intake predicted later smoking and alcohol use, there was no such association of smoking or alcohol use with later caffeine intake. This suggests that caffeine may (causally) lead to the initiation of other substances. The mechanism underlying such a possible gateway effect remains unclear. One possibility, suggested by the authors, is a biological mechanism: exposing the brain to caffeine during early adolescence may affect striatal pathways associated with reward sensitivity, thereby increasing vulnerability to other substances. To further explore this possibility, it would be
interesting to test caffeine intake as a predictor of regular substance use and progression to substance use disorders (as opposed to lifetime use).

The study’s findings may also indicate shared risk factors that increase both caffeine intake and other substance use, instead of a causal pathway from one to the other. Adolescents with a high intake of caffeine may be more likely to be exposed to social environments in which smoking and alcohol use are also common. Caffeine intake would present itself first in the temporal sequence, simply because it usually begins to be consumed before smoking and alcohol-drinking are initiated. Another potential shared risk factor, noted by the authors, is personality. This aligns with extensive research showing that personality is strongly associated with smoking and alcohol use [2]–[5], as well as caffeine intake [6], [7]. Most notable are the personality traits impulsiveness, sensation seeking, and extraversion. It would be interesting to explore whether effects of caffeine intake on other substance use persist when individual differences in personality are accounted for.

It is worth noting that Kristjansson et al. [1] report a rather high intake of caffeine. In 6th grade (ages ~11-12 years) and 7th grade (ages ~12-13), the average caffeine intake was 253 mg/day and 236 mg/day, respectively. These estimates approach those from a recent study in adults from the UK and the Netherlands, where the average intake was 261 mg in English women and 240 mg in Dutch women and 324 mg in Dutch men [8]. While there is no consensus on safe levels of caffeine for children/adolescents, the threshold above which adverse health effect might occur in this age-group is 100 mg caffeine/day [9]. The average intake in this study easily surpasses that. The authors note that their sample includes communities where energy drink and soda consumption is high. Coffee consumption is also surprisingly common – 41% of young people in this study report that they drink coffee on a typical day. Since these characteristics may be specific to this particular sample, it would be good to attempt replication of Kristjansson et al.’s [1] findings in other (non-US-based) samples.

Evidence could be strengthened further by ‘triangulation’ – combining different research methods to come to robust conclusions [10], [11]. Longitudinal data-analysis is one way to infer causality, but it has its limitations. Another method, with different strengths and weaknesses, is
Mendelian randomization (MR). This is an instrumental variable approach that takes genetic variants robustly associated with an ‘exposure’ and uses those as a proxy to test causal effects on an ‘outcome’. In principle, it is better protected against biases from confounding and reverse causation [12]. A recent MR study explored causal effects between different substances (caffeine, smoking, alcohol, cannabis) [13] and found no clear evidence for causal effects. This was in an adult population, however, and MR may not be well-suited to detect effects acting during adolescence only, because genetic variants capture lifetime exposure. If well-powered genome-wide association studies of e-cigarette use become available, it would also be possible to explore the suggestive effect of e-cigarette use on caffeine intake found by Kristjansson et al. [1]. Another informative method for causal inference is the use of negative controls. By comparing the association between caffeine and other substance use to the association between caffeine and a negative control (with the same confounding structure as substance use but for which a causal effect is implausible), it could be determined whether there is residual confounding [14]. Triangulating evidence from these and other disciplines will provide a more definite answer to the question of whether caffeine intake promotes other substance use.

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