Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status

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Does cannabis use have substantial and permanent effects on neuropsychological functioning? Renewed and intense attention to the issue has followed recent research on the Dunedin cohort, which found a positive association between, on the one hand, adolescent-onset cannabis use and dependence and, on the other hand, a decline in IQ from childhood to adulthood [Meier et al. (2012) *Proc Natl Acad Sci USA* 109(40):E2657–E2664]. The association is given a causal interpretation by the authors, but existing research suggests an alternative confounding model based on time-varying effects of socioeconomic status on IQ. A simulation of the confounding model reproduces the reported associations from the Dunedin cohort, suggesting that the causal effects estimated in Meier et al. are likely to be overestimates, and that the true effect could be zero. Further analyses of the Dunedin cohort are proposed to distinguish between the competing interpretations. Although it would be too strong to say that the results have been discredited, the methodology is flawed and the causal inference drawn from the results premature.

marijuana | longitudinal

To what extent does cannabis use have permanent and substantial effects on neuropsychological functioning? The question has received renewed and worldwide attention with the recent evidence of correlations between, on the one hand, persistent cannabis use initiated in adolescence and, on the other hand, a decline in IQ-scores between the ages of 13 and 38 (1). Although Meier et al. (1) note the possibility of remaining confounders, they conclude that the findings are suggestive of a neurotoxic effect of cannabis on developing brains that permanently lowers IQ. This conclusion seems premature in light of likely confounding from socioeconomic status (SES). After a brief description and discussion of the Meier et al. study design, I present evidence regarding the relationship between IQ trajectories and SES. Simulation results indicate that SES-correlated cognitive decline is sufficient to reproduce the Meier et al. results. I conclude by sketching empirical analyses that can distinguish between the causal and confounding model.

Meier et al., 2012: Study Design and Methodological Issues

The Meier et al. (1) study uses data from the high-quality Dunedin cohort, a "prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y." As part of this study, participants were scored for use of—and dependence on—cannabis at ages 18, 21, 26, 32, and 38. Using these data, Meier et al. sort participants into cannabis-exposure groups: nonusers, users who never scored as dependent, and users who scored as dependent once, twice, or three or more times. Controlling for sex, ordinary least-squares regressions find IQ-declines increasing linearly with cannabis exposure (a dose–response relationship). The correlations persist within a number of subsets cleared of various possible confounders (e.g., subsamples with no alcohol dependence or no schizophrenia), and are driven by adolescent-onset users.

The causal interpretation of these results rests on the assumption that IQ-trajectories would have been equal across the different cannabis-exposure groups in the absence of cannabis use. The risk of selection bias is reduced through the use of a difference-in-difference estimator: because the outcome measure is IQ-change, the results will only be biased if omitted variables both correlate with adolescent-onset cannabis use and have a time-varying effect on IQ. Variables with potential relevance for IQ can be omitted provided their effects are both exhausted before age 13 and permanent, or provided exposure is always equal in childhood and adulthood. Although a number of confounders could conceivably remain, a natural and plausible candidate is SES.

Who Are the Adolescent-Onset Cannabis Users?

Although Meier et al. (1) do not present a table of background variables and average scores by cannabis-use groups, the extensive publications on the Dunedin cohort indicate that early-onset cannabis use is more common for those with poor self-control, prior conduct problems, and high scores on risk factors correlated with a low family SES (2, 3). Based on results from a similar cohort, a likely consequence of this is that Maori participants will be overrepresented (4).

In addition to predicting use, low-SES characteristics would also seem to predict dependence conditional on use for the Dunedin cohort (3, 5). Although the effect size in the Dunedin cohort is unknown, this effect can be sizeable, with young, low-SES cannabis users having an odds-ratio of 21.9 for transitioning into dependence in a German longitudinal study (6).

What Are Counterfactual IQ-Trajectories for Those at Risk for High Cannabis Exposure?

Predictions regarding the relationship between SES and IQ change can be derived from the recent Flynn–Dickens model of IQ (7–9). The model emphasizes a two-way causality between IQ and environment: A cognitively challenging environment raises an individual's IQ, and a higher individual IQ makes it more likely that an individual will self-select or be sorted into more cognitively challenging environments. This self-selection/sorting will also be affected by factors other than IQ that, following Heckman (10), I will refer to as "noncognitive factors." These factors are associated with future environments, and the future environment in turn affects future IQ. Over time, children with similar IQs but differing SES self-select or are sorted into environments with different cognitive demands. These differences in cognitive demands in turn, cause their IQs to diverge, generating SES-related differences in individual IQ trajectories. Similar

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reasoning holds for minorities, who may face cultural challenges, discrimination, and other issues raising the risk of poor outcomes.

This account rests on two assumptions. The first assumption is that noncognitive factors related to SES influence the future environment of an individual (education, occupation, and so forth). At a general level, this is known to be the case in that SES predicts educational attainment after controlling for individual IQ (11). Although IQ gains from early intervention programs tend to fade in the years following an intervention (11), the programs can nevertheless show large effects on long-term educational and occupational outcomes (10, 12). These effects consequently work through noncognitive factors, "hypothesized to be related to differences in motivation, perseverance, temperament, and other dimensions of social competence" (12). In a study on the Dunedin cohort, a measure of self-control closely related to these traits was positively correlated with childhood SES (5), and predicted both negative adolescent outcomes (e.g., school dropout, pregnancy) and adult outcomes (e.g., criminal convictions, health, wealth, and own SES).

The second assumption required is that these differences in future environments, caused by variation in noncognitive factors, in turn affect individual IQ. This influence seems to be the case for environments relevant at all stages of an individual´s life: adoption studies indicate that SES-related differences in a child's home environments causally affect IQs (13). Early-intervention studies can show substantial short-term effects on IQ (11, 12). Education has a substantial, positive causal effect on IQ (14–16). Employment supports cognitive skills in the elderly (17, 18).

Although cognitive demands influence IQs across the board, the heritability of childhood IQ varies from less than 0.2 for low-SES children to more than 0.7 for high-SES children (19). This finding means that environmental variation explains a larger share of childhood IQ variation in low-SES groups, suggesting that high-SES environments are sufficiently good that variation between them matters little for IQ (20). This finding would have three consequences in our context. First, schools will raise low-SES IQs more than high-SES IQs: the increase in cognitive demands facing a child entering school will be larger for low-SES children, whose home environment is less cognitively demanding. This difference is further amplified because, as noted, the baseline environment of low-SES children will be within a range where changes in environment have a large cognitive impact. Second, these gains will decline over time as children age and increasingly self-select environments and experiences in line with their genetic propensities and early-childhood influences. This reduction in forced environments raises the importance of the noncognitive factors, which correlate with SES, and which on average shift low-SES individuals toward environments and careers with lower cognitive demands. Third, heritable noncognitive factors will have little impact on the IQ of high-SES individuals, because these will tend to alter their environment within the range where environment has small IQ effects. As a consequence, the well-established increase in heritability of IQ with age (21, 22) will be driven by an even stronger increase in heritability of IQ within low-SES groups. This result would be consistent with the heritability measures for high-SES individuals being high already in childhood and adolescence (19, 23).

It is worth noting that the relationship between SES and IQ change is supported empirically and has validity independently of the Flynn–Dickens theory that led us to it. Empirical research on how IQ trajectories differ with individual characteristics indicates that age-related cognitive decline is higher for some minorities, those with low education, and those in jail (24,25). Such differences in trends cause substantial differences over time: IQ scores of black children in the United States fall 10 IQ points, equivalent to 0.67 of a SD, relative to white children between early childhood and young adulthood (26).

Indications of SES Confounding in the Meier et al. Study

A subanalysis of participants with high school or less in the Meier et al. (1) report provides indicative support of such confounding. Measures of SES typically use a combination of income, education, and occupation. Using own education as a noisy proxy for childhood SES, we can take the reported estimates from Meier et al. for those with high school education or less and calculate the (nonreported) effects on those with more than high school. Relative to nonusers in their own educational category, the IQ-loss of the most cannabis-exposed group (dependent 3+ times) is 0.45 SD units ($n = 26$) for those with high school education or less. The comparable effect for those with higher education is roughly half, at 0.24 SD units ($n = 12$). Similarly, the second-most cannabis-exposed group saw an IQ-drop of 0.22 SD units ($n = 20$) for the low-education subgroup, but only 0.14 SD units ($n = 35$) in the high-education subgroup. Two caveats should be noted: First, these estimates are based on small numbers. Second, as noted by the researchers, reduced schooling could be part of the causal path by which cannabis use lowers IQ.

Further strengthening the case for the confounding interpretation of the Meier et al. (1) results are prior studies on the same topic. A Canadian study of cannabis exposure on IQ change from ages 9–12 to ages 17–20 drew participants from a less socioeconomically diverse population ("largely middle-class families") (27). This study group implies less scope for SES-confounding, and, in line with this, the study reported no permanent effects of cannabis on IQ. A study of cognitive changes for a group of 1,318 participants over the course of a decade found no effects of cannabis use on cognitive decline (28). Cannabis users (light and heavy) "evidenced *less* cognitive decline than nonusers" ($P < 0.1$) in a univariate analysis, although the relationship disappeared after controlling for education, age, minority status, and other confounders. A third study included substance abuse in a multivariate analysis of the risk of experiencing cognitive decline over a 1-y period (25). For those below 65 in age, the authors found beneficial effects of education and negative effects of minority status and jail residence (all statistically significant), but no effects of substance use (lifetime status). Again, some caveats are in order: Meier et al. suggest that the IQ effects are seen for the subset of users who began using in adolescence and also persisted with high levels of cannabis use over several years. The study period and the intensity of use may be too low in the Canadian sample for this effect to be discernible, and the other studies did not estimate models that would allow the effect of cannabis use on IQ to differ with age of first use.

Comparing and Contrasting the Causal and Confounding Model

The correlational patterns produced by the SES confounder were examined using a simulation model that contained no causal effect of cannabis on adult IQ. Instead, the simulation model assumes that: (*i*) SES predicts cannabis exposure, and (*ii*) low-SES groups receive a temporary IQ boost from compulsory schooling that averages 4 IQ points or ~0.25 SD units. This boost is undone over time as individuals age out of forced environments and the environment-shaping influence of noncognitive factors increases. The simulation model establishes that the confounder was sufficient to reproduce the effects found in the Meier et al. (1) study: Fig. 1 shows the mean and 95% confidence intervals of the effects produced by the simulation model (based on 500 runs, each with $n = 875$), with the actual estimates from Meier et al. ($n = 894$) plotted in. The stochastic variation implied by the simulation model places the actual Meier et al. results well within the feasible set of results. Although the large uncertainty bands (caused in part by the small number of participants in high-exposure groups) would seem to imply that the effects are not statistically significant, this is not the case: Meier et al. report only *t* test and associated *P* values from an

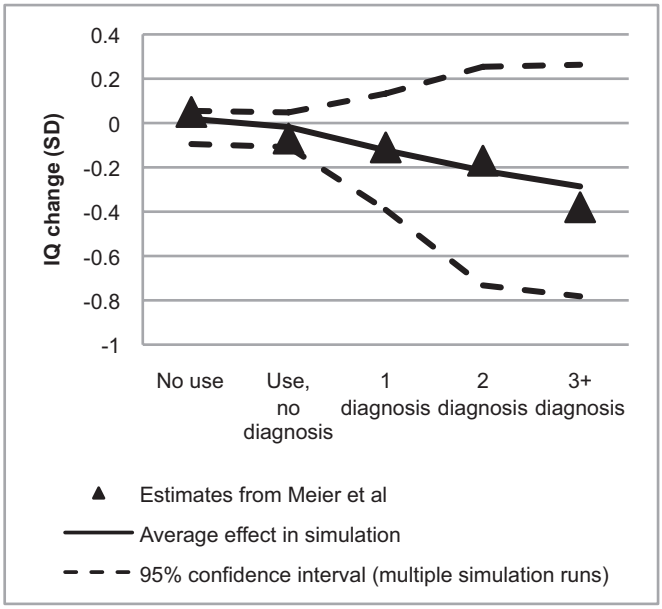

Fig. 1. Estimated effects from the main table of the Meier et al. (1) study compared with average effects in baseline specification of simulation model, with confidence intervals based on 500 runs.

ordinary least-squares regression with a linear trend. In the simulation model, this test is significant at the 10% level in ∼60% of simulations, at the 5% level in ∼50% of the simulations, and at the 1% level in ∼30%.

Although the Flynn–Dickens model suggests a number of interesting hypotheses regarding SES and IQ change that could be explored within the rich Dunedin cohort data, I will restrict myself to noting some analyses that could help distinguish between the causal and confounding model.

Descriptive Statistics for Background Traits and Early Environment by Adolescent-Onset Cannabis-Exposure Group. Such a table would highlight possible confounders, by indicating the extent to which SES and SES-related noncognitive traits have determined placement in different cannabis-exposure groups. If this sorting is very weak, the case for confounding interpretation is weakened.

Confounders. The reported estimates in Meier et al. (1) only controlled for sex in their analyses, examining potential confounders individually in separate subanalyses. The risk with this approach is that it overestimates the effect of cannabis use if cannabis use is correlated with a number of confounders that have small individual, but large collective, impact. For example, the researchers could run a regression of adult IQ on childhood IQ, cannabis exposure, childhood traits and environmental characteristics, educational level, occupational status (as a proxy for a job's cognitive demands), and employment history.

Marked Differences Between Adolescent-Onset and Adult-Onset Cannabis Users. The permanent IQ-declines in Meier et al. (1) were observed almost exclusively in adolescent-onset users. The confounding model would then predict that adult-onset users on average had higher family SES and exhibited fewer risk factors predicting low education, conduct problems, and unemployment.

Alternative Methods for Correcting for Selection Bias. The confounding model implies that adolescent-onset users are a group that (independently of cannabis use) would tend to self-select or be sorted away from cognitively demanding environments, and consequently experience IQ-declines after childhood. A number of methods exist to deal with selection bias in observational data, and there are specification tests available that help assess their appropriateness (29). We know that participant IQ in the Dunedin cohort was measured at ages 7, 9, and 11 (5). The assumption used in Meier et al. (1) of time-invariant individual heterogeneity can be tested using these multiple preexposure measurements of IQ: Did the different exposure groups have identical IQ trajectories before their cannabis use? Alternatively, if sorting into cannabis-exposure groups correlates with preexposure IQ-trajectories, a random-growth estimator would use this additional data on preexposure IQs to extrapolate linear individual IQ trends and identify the causal effects of cannabis.

Consistency with IQ Heritability Results. The increasing heritability of IQ with age (particularly in low-SES groups) implies that the change in IQ from childhood to adulthood is determined more by heritable than by environmental factors. This implication places some constraints on the plausible size of environmental effects, such as cannabis. What is the share of variation in adult IQ explained by cannabis use in the Dunedin cohort, and how does this compare with the share of variation in adult IQ that we should expect to be explained by environmental factors based on established studies on IQ?

Conclusion

Meier et al.'s (1) estimated effect of adolescent-onset cannabis use on IQ is likely biased, and the true effect could be zero. It would be too strong to say that the results have been discredited, but fair to say that the methodology is flawed and the causal inference drawn from the results premature. Furthermore, should a direct effect of adolescent-onset cannabis use remain after controlling for confounders, the Flynn–Dickens model suggests an alternative causal path through which this may occur. This model, too, would predict reduced IQ in so far as heavy, persistent, adolescent-onset cannabis use involves a culture and norms that raise the risk of dropping out of school, getting entangled with crime, and other such behaviors. Unlike a neurotoxic effect, however, this effect would be nonpermanent and mediated by the cognitive demands of different environments. Because the effect in this case would be a result of culture rather than pharmacology, it would also have different policy implications.

Methods

Based on the confounding interpretation of the Meier et al. (1) estimates, a simulation model was built using Mathematica (v6) to generate simulated data samples of similar size. The model has three SES levels, draws adult and childhood IQs that differ by SES, assumes that lower-SES individuals have higher risk for cannabis exposure than high-SES individuals at all levels, and that the sorting intensifies with exposure level. Details and robustness checks are available in *SI Methods*.

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