VIEWPOINT

Use of Genetically Informed Methods to Clarify the Nature of the Association Between Cannabis Use and Risk for Schizophrenia

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Cohort studies and meta-analyses have documented a robust association between cannabis use, heavy use, and misuse with future risk of schizophrenia.[1-3] Despite adjusting for covariates, including current psychotic symptoms, other psychopathology, and social integration,[1] the ability of these models to determine the degree to which cannabis causes schizophrenia is limited and dependent on their ability to capture all relevant confounders. When evaluating efforts to reduce cannabis use as a means of preventing schizophrenia, the proportion of this association that is causal is critical.

Given the high heritability of schizophrenia, we reviewed reports that relied on 4 genetic methods (**Table**) capable of addressing the nature of the cannabis-schizophrenia association. We evaluated 3 hypotheses: (1) it is entirely causal, (2) it is partly causal and partly confounded by genetic/familial effects and/or reverse causation, or (3) it is entirely noncausal. (We are unable to review the literature regarding short-term psychiatric effects of cannabis administration.[9]) Confounding here refers to genetic risks that increase the probability of both using/misusing cannabis and schizophrenia, thereby explaining at least part of the association. In this example, reverse causality refers to a theoretical underlying mechanism in which schizophrenia liability or symptoms increase the risk of using cannabis. The first 2 methods are natural experiments, discordant relative designs, and mendelian randomization, that directly evaluate each hypothesis. The 2 other methods, linkage disequilibrium score regression (LDSR) and polygenic risk scores (PRSs), measure genetic associations, which, although less definitive, provide evidence of correlated genetic risks that undermine the plausibility of hypothesis 1. Each hypothesis generates distinct expectations under each method (Table). Therefore, our approach determines which of the hypothetical expectations best fit the aggregate results. By examining multiple methods with different strengths and limitations, we attempt to triangulate the observed results hoping thereby to increase confidence in our conclusions.

Natural Experiments

Discordant relative designs examine declines in exposure-outcome associations while systematically increasing control over confounding genetic or environmental risks shared between relatives of increasing closeness.[4] If hypothesis 1 is correct, then the expected odds ratio (OR) for the cannabis-schizophrenia association should be the same for unrelated pairs in the general population and in relative pairs including full sibling pairs and monozygotic twin pairs discordant for cannabis exposure, ie, OR for unrelated pairs = full sibling pairs OR = monozygotic twin pairs OR (Table). In contrast, when ORs decline as relatedness increases but remain significantly greater than unity in close relatives (OR for unrelated pairs > full sibling pairs OR > monozygotic twin pairs OR > 1), hypothesis 2 is supported. Under the entirely noncausal hypothesis, ORs decrease rapidly in discordant pairs of relatives and are not significantly different from unity in monozygotic twin pairs (OR for unrelated pairs > full sibling pairs OR $\geq$ 1; monozygotic twin pairs OR = 1). We are aware of only 1 such analysis examining the cannabis-schizophrenia association. Giordano et al[4] reported a significant increase in schizophrenia among individuals with cannabis misuse. However, as genetic relatedness increased, the ORs declined. The change in ORs from 10.44 in the general population to 3.52 for discordant monozygotic twin pairs, a 66% decline, is consistent with hypothesis 2 and suggests substantial confounding.

Mendelian randomization is a type of instrumental variable analysis for approximating randomization to experimental and control conditions. Using single-nucleotide variants as instrumental variables, Vaucher et al[1] found that the genetic liability to lifetime cannabis use was associated with a significant increase in the risk of schizophrenia by 37%. In contrast, Gage et al[5] and Pasman et al[6] found much stronger evidence that genetic liability to schizophrenia was associated with an increase in the risk of lifetime cannabis use, ie, reverse causality. These mendelian randomization studies rely on single-nucleotide variant instrumental variables associated with lifetime cannabis use, not heavy use or misuse. However, in aggregate, results from available mendelian randomization studies are most consistent with hypothesis 2.

Measures of Genetic Association

Evidence of pleiotropy or correlated genetic risks between cannabis use and schizophrenia is incompatible with hypothesis 1. Expectations under LDSR and PRS methods cannot distinguish hypothesis 2 from 3 (Table). However, they are valid for estimating the size of correlated genetic risks. Critically, an LDSR genetic correlation or schizophrenia PRS regression coefficient greater than 0 (ie, genetic $r > 0$ or schizophrenia PRS $\beta > 0$) is incompatible with hypothesis 1. Two LDSR studies[6,8] have reported significant genome-wide genetic correlations between lifetime cannabis use/misuse and schizophrenia (genetic r range, 0.22-0.25). Among PRS reports, 1 regressed cannabis misuse onto a PRS for schizophrenia in a restricted sample and found no effect.[7] In contrast, 4 large population-based studies, including Verweij et al,[8] found that high PRSs for

Table. Four Genetic Methods to Address the Cannabis-Schizophrenia Association and Expected Results Under 3 Hypotheses

	Natural experiments		Measures of genetic association	
Hypothesis	Discordant sibling pair[a]	MR[b]	LDSR[c]	Regression of cannabis on schizophrenia PRS[d]
1. Entirely causal	OR for unrelated pairs = full sibling pairs OR = monozygotic twin pairs OR	Lifetime cannabis use β > 0; schizophrenia β = 0	Genetic r = 0	Schizophrenia PRS β = 0
2. Partly causal and confounded	OR for unrelated pairs > full sibling pairs OR > monozygotic twin pairs OR > 1	Lifetime cannabis use β > 0; schizophrenia β > 0	Genetic r > 0	Schizophrenia PRS β > 0
3. Entirely noncausal	OR for unrelated pairs > full sibling pairs OR > 1; monozygotic twin pairs OR = 1	Lifetime cannabis use β = 0; schizophrenia β > 0		
Summary of published results	OR for unrelated pairs, 10.44 > full sibling pairs OR, 5.07 > monozygotic twin pairs OR, 3.92[4,e]	Stronger evidence of reverse causality[5-7,f]	Modest pleiotropy genetic r range, 0.22-0.25[6,8]	Schizophrenia PRS predicts multiple cannabis phenotypes[8]
Results consistent with	Hypotheses 2	Hypotheses 2	Hypotheses 2 and 3	Hypotheses 2 and 3

Abbreviations: LDSR, linkage disequilibrium score regression; MR, mendelian randomization; OR, odds ratio; PRS, polygenic risk score.

[a] In discordant sibling pair analyses, if the association is entirely causal, then the OR for unrelated pairs, regular sibling pairs, and monozygotic twin pairs should all be significant and statistically indistinguishable. Hypothesis 2 is supported if ORs decline as relatedness increases but remain significantly greater than unity in close relatives (ie, monozygotic twin pairs OR > 1). Hypothesis 3 is supported if ORs decrease rapidly in discordant pairs of relatives and are not significantly different from unity in monozygotic twin pairs (OR = 1).

[b] MR: Under hypothesis 1, regression coefficients associated with the genetic liability to cannabis exposure and schizophrenia are greater than 0 and indistinguishable from 0, respectively. Hypothesis 2 is supported when cannabis β and schizophrenia β are greater than 0. Hypotheses 3 is supported if genetic liability to cannabis exposure is indistinguishable from 0 and schizophrenia is greater than 0. A schizophrenia β greater than 0 indicates reverse causality.

[c] LDSR genetic correlations between cannabis and schizophrenia are indistinguishable from 0 under hypothesis 1. Correlations greater than 0 indicate pleiotropy or noncausal, correlated genetic risks between cannabis and schizophrenia, consistent with hypotheses 2 and 3.

[d] Hypothesis 1 is supported if the coefficient associated with the regression of cannabis use on schizophrenia polygenic risk scores is indistinguishable from 0. A regression coefficient greater than 0 is consistent with hypotheses 2 and 3.

[e] Tests of significance were unavailable for monozygotic twin pairs.

[f] All 3 MR studies found no evidence of pleiotropic effects for single-nucleotide variants used as genetic instrumental variables.

schizophrenia significantly predict more cannabis and comorbid substance use/misuse. Although the LDSR genetic correlations were modest and effect sizes for schizophrenia PRSs were small, these results provide evidence of significant confounding inconsistent with hypothesis 1.

Conclusions

As summarized in the Table, when triangulating across 4 genetically informative methods, the findings, with considerable but not complete consistency, argue against hypothesis 1. Although the number of available studies is modest, there is relatively reliable evidence across multiple methods that the cannabis-schizophrenia association stems partly from shared familial/genetic risk factors and/or reverse causation. We also have good evidence against hypothesis 3, ie, familial/genetic risk factors explaining all of the association. The 1 study that directly estimated the degree of familial confounding[4] suggests that it is substantial and accounts for more than half of the observed association. Results from LDRS and PRS methods suggest more modest degrees of confounding while raising the possibility of reverse causation. A prudent conclusion is that the observed cannabis-schizophrenia association in the general population may arise from some potential causal effect of cannabis on the risk of schizophrenia, while an appreciable proportion of the association is not causal. When based on associations observed in the population (ie, without control for confounders), claims made about the changes in risk for schizophrenia stemming from changing levels of cannabis use are very likely to be exaggerated and potentially substantially so. Before definitive conclusions can be reached, further research is needed on this important public health question that should include genetic strategies (eg, further corelative or mendelian randomization designs) and nongenetic approaches (eg, controlled pre-post designs examining changes in incidence rates of schizophrenia in states with a rise in cannabis consumption associated with decriminalization).

ARTICLE INFORMATION

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