Review

Biological Psychiatry

Association Between Cannabis and Psychosis: Epidemiologic Evidence

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ABSTRACT

Associations between cannabis use and psychotic outcomes are consistently reported, but establishing causality from observational designs can be problematic. We review the evidence from longitudinal studies that have examined this relationship and discuss the epidemiologic evidence for and against interpreting the findings as causal. We also review the evidence identifying groups at particularly high risk of developing psychosis from using cannabis. Overall, evidence from epidemiologic studies provides strong enough evidence to warrant a public health message that cannabis use can increase the risk of psychotic disorders. However, further studies are required to determine the magnitude of this effect, to determine the effect of different strains of cannabis on risk, and to identify high-risk groups particularly susceptible to the effects of cannabis on psychosis. We also discuss complementary epidemiologic methods that can help address these questions.

Keywords: Cannabis, Epidemiology, Longitudinal studies, Marijuana, Psychosis, Schizophrenia

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Population studies consistently show that cannabis use is associated with psychotic experiences and disorders, including schizophrenia, but whether associations are causal is difficult to ascertain from observational designs. Randomized controlled trials (RCTs) in laboratory conditions provide evidence that delta-9-tetrahydrocannabinol (THC), the main active compound in cannabis, can induce transient psychotic-like experiences (1). However, these experiences resolve within a few hours and rarely cause distress, in contrast to psychotic disorders where experiences are prolonged and impairment often substantial.

It is important to establish whether the association between cannabis and psychotic disorder is causal and to accurately estimate the magnitude of this effect, as cannabis might represent the most potentially modifiable risk factor for psychosis. Noncausal explanations for associations arising from observational studies include reverse causation (where associations reflect psychosis increasing risk of using cannabis), bias (where problems with measurement or sample selection lead to incorrect estimates), and confounding (where other variables that increase risk of both cannabis use and psychosis lead to spurious associations) and are discussed further below.

RCTs of cannabinoid use or interventions to reduce cannabis use tend to have follow-up periods too short to yield useful information about psychosis risk arising from long-term use (2) and are not discussed further here. Nor do we review case studies or studies relying on a diagnosis of cannabis-induced psychotic disorder, as such diagnoses are dependent on assumptions of a causal role of cannabis in specific cases by a clinician, and there is no robust evidence as far as we are aware of clinical characteristics that allow the distinction of this disorder to be made (3).

EVIDENCE FROM CASE-CONTROL AND CROSS-SECTIONAL STUDIES

Evidence from most case-control and cross-sectional studies support an association between cannabis use and schizophrenia (4–6) and psychotic symptoms (7–9). A potential problem of case-control studies is selection bias arising from inadequate sampling of a control group, and in both these designs reverse causation cannot be excluded. Longitudinal or cohort studies provide a stronger design to examine evidence in support of a causal association.

EVIDENCE FROM COHORT STUDIES

A 2007 systematic review identified seven cohort studies investigating the association between cannabis use and schizophrenia, psychotic disorders, or psychotic experiences (10). Since this publication, three more have been published. These 10 studies are described below and in Table 1.

Studies Investigating Psychotic Disorder

The Swedish Conscript Study found a dose-response relationship between cannabis use by age 18 and incident schizophrenia by age 45 (11,12), with a threefold increase in risk in those who reported using cannabis more than 50 times by age 18 (95% confidence interval [CI] 1.7, 5.5).

In the Dunedin birth cohort study (13), cannabis use by age 15 was associated with an increase in schizophreniform disorder at age 26 (odds ratio [OR] 11.4, 95% CI 1.8, 70.5), with a weaker association in those first using between ages 15 and 18 (OR 2.0, 95% CI .8, 5.0), although confidence intervals were wide and overlapping.

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Table 1. Description of the Longitudinal Studies on Cannabis and Psychotic Outcomes Published to Date

Cohort	Sample Size (and with Outcome)	Exposure	Outcome	Results (Adjusted) OR (95% CI)	Strengths	Limitations
ECA (20)	2295 (477)	Daily use of cannabis (binary)	Psychotic experiences (binary)	2.0 (1.25, 3.12)	Large sample size, interview-based psychotic experiences measure	No attempt to account for intoxication
NEMESIS (14)	4045 (38)	Ever use and frequency of use	Psychosis symptoms (severity)	2.76 (1.18, 6.47)	Legality of cannabis use in Netherlands; investigation of self-medication hypothesis; attempt to remove intoxication effect; large sample size; repeated measures of exposure and outcome	Sample size too small to examine psychotic disorders robustly
Swedish Cohort (12)	50087 (362)	Cumulative cannabis use	Schizophrenia diagnosis	Linear trend 1.2 (1.1, 1.4)	Large sample size, attempt to remove intoxication effect, schizophrenia measure	Only male subjects included, therefore results may not be generalizable; large temporal gap between exposure and outcome, could miss variation in cannabis use; low levels of cannabis use at baseline
Dunedin (13)	759 (25)	Ever use of cannabis by age 15/18	Schizophreniform diagnosis	2.91 (1.20, 7.04)	Strong cohort retention, minimizing possibility of attrition bias; schizophreniform disorder measure	Small sample size, exacerbated by dividing sample into cannabis before/after 15; limited adjustment for confounding
Christchurch (17,18)	1265	Cannabis use; dependence	Psychotic experiences	1.8 (1.2, 2.6)	Thorough consideration of confounders; use of fixed-effects regression to minimize confounding by time invariant confounders	Lack of clinical measure of psychosis; small sample size
EDSP (19)	2437 (424)	Used at least five times	Psychotic symptoms	1.2 (1.1, 1.3)	Investigation of reverse causation hypothesis	Sample size too small to examine psychotic disorders robustly?
NPMS (21)	1795 (134)	Dependence (three-level measure)	Self-reported psychotic symptoms	1.5 (.6, 3.9)	Thorough consideration of confounders	Few cannabis users; sample selected due to pre-existing mental health problems so may not be generalizable
Rossler *et al.* (22)	591 [2200 (221) records]	Heaviness of use (three-level measure)	Schizophrenia nuclear symptoms (self-report)	Adjusted results not reported—unadjusted 1.77 (.96, 3.24)	Many repeated measures over long follow-up	Small sample size; limited consideration of confounders
California (16)	41670 (174)	Hospitalization for cannabis abuse	Hospitalization for schizophrenia	8.2 (5.1, 13.1)	Large sample size	Extreme exposure measure; limited consideration of confounders
ALSPAC (23)	1756 (97)	Cumulative use (four-level)	Psychotic experiences severity (four-level)	1.12 (.76, 1.65)	Thorough consideration of confounders	Small sample size; correlation of covariates; young age of participants; lack of clinical measure of psychosis

ALSPAC, Avon Longitudinal Study of Parents and Children; ECA, Epidemiologic Catchment Area; EDSP, Early Developmental Stages of Psychopathology; NEMESIS, Netherlands Mental Health Survey and Incidence Study; NPMS, National Psychiatric Morbidity Survey.