Early Cannabis Use and Estimated Risk of Later Onset of Depression Spells: Epidemiologic Evidence From the Population-based World Health Organization World Mental Health Survey Initiative

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Early-onset cannabis use is widespread in many countries and might cause later onset of depression. Sound epidemiologic data across countries are missing. The authors estimated the suspected causal association that links early-onset (age <17 years) cannabis use with later-onset (age ≥17 years) risk of a depression spell, using data on 85,088 subjects from 17 countries participating in the population-based World Health Organization World Mental Health Survey Initiative (2001–2005). In all surveys, multistage household probability samples were evaluated with a fully structured diagnostic interview for assessment of psychiatric conditions. The association between early-onset cannabis use and later risk of a depression spell was studied using conditional logistic regression with local area matching of cases and controls, controlling for sex, age, tobacco use, and other mental health problems. The overall association was modest (controlled for sex and age, risk ratio = 1.5, 95% confidence interval: 1.4, 1.7), was statistically robust in 5 countries, and showed no sex difference. The association did not change appreciably with statistical adjustment for mental health problems, except for childhood conduct problems, which reduced the association to nonsignificance. This study did not allow differentiation of levels of cannabis use; this issue deserves consideration in future research.

cannabis; depression; mental health; world health

Recreational cannabis use occurs across the globe (1). In recent decades, the age of initiation has declined, and concern about the public health impact has mounted (1, 2). Largely based on evidence from Western countries, various reviews have concentrated on a suspected association between cannabis use and psychosis (3–5). Statistically significant associations between cannabis use and anxiety and major depressive symptoms or disorders have been found in some high-income countries (6–14), although several studies have failed to identify such a relation (15–22). Brook et al. (23) proposed that the risk of depression increases when cannabis use starts early. Schneider (24) suggested a mechanism for this potential age-specific association, namely that cannabis onset during puberty exacerbates morphologic and behavioral disturbances not seen with adult-onset cannabis use.

Here, with community samples from diverse countries, we estimated whether cannabis onset by the middle of adolescence (before age 17 years) is followed by greater risk of first onset of a depression spell, with due attention to sex and age variations. We used a local area matching approach (25) to constrain the effects of geographic variation in
enforcement of cannabis laws, local jurisdictional variation in subnational law, and other socially shared local area variations that might confound cannabis-depression estimates and which also account for potential geographic variation in odds of exposure to cannabis use (26). Furthermore, we considered an array of possibly confounding mental health problems, including childhood conduct problems. Childhood conduct problems and early rule violations have been described to precede early peer rejection, affiliation with drug-using peers, early-onset cannabis use, and subsequent low self-esteem and mood disturbances (27, 28) and thus are important confounding variables.

To our knowledge, this study is the largest study of this issue to date and the first to examine the association between early-onset cannabis use and risk of later depressive spells across 17 countries with varied economic, social, and cultural norms.

**Table 1.** Cross-sectional Survey and Sample Characteristics for Cases With a Depression Spell, Noncases, and Local Area Risk Sets, World Health Organization World Mental Health Survey Initiative, 2001–2005a

<table>
<thead>
<tr>
<th>Region and Country</th>
<th>Survey Characteristic</th>
<th>Field Dates</th>
<th>Response Rate, %</th>
<th>Survey Sample Size, no.</th>
<th>No. of Cases</th>
<th>No. of Noncases</th>
<th>No. of Risk Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
<td>NSMH</td>
<td>2003</td>
<td>88</td>
<td>4,426</td>
<td>483</td>
<td>3,748</td>
<td>32</td>
</tr>
<tr>
<td>Mexico</td>
<td>M-NCS</td>
<td>2001–2002</td>
<td>77</td>
<td>5,782</td>
<td>468</td>
<td>5,125</td>
<td>58</td>
</tr>
<tr>
<td>United States</td>
<td>NCS-R</td>
<td>2002–2003</td>
<td>71</td>
<td>9,282</td>
<td>1,299</td>
<td>3,695</td>
<td>42</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>ESEMeD</td>
<td>2001–2002</td>
<td>51</td>
<td>2,419</td>
<td>388</td>
<td>588</td>
<td>23</td>
</tr>
<tr>
<td>France</td>
<td>ESEMeD</td>
<td>2001–2002</td>
<td>46</td>
<td>2,894</td>
<td>613</td>
<td>683</td>
<td>27</td>
</tr>
<tr>
<td>Germany</td>
<td>ESEMeD</td>
<td>2002–2003</td>
<td>58</td>
<td>3,555</td>
<td>381</td>
<td>868</td>
<td>33</td>
</tr>
<tr>
<td>Italy</td>
<td>ESEMeD</td>
<td>2001–2002</td>
<td>71</td>
<td>4,712</td>
<td>496</td>
<td>1,161</td>
<td>42</td>
</tr>
<tr>
<td>Spain</td>
<td>ESEMeD</td>
<td>2001–2002</td>
<td>79</td>
<td>5,473</td>
<td>717</td>
<td>1,266</td>
<td>48</td>
</tr>
<tr>
<td>Ukraine</td>
<td>CMDPSD</td>
<td>2002</td>
<td>78</td>
<td>4,725</td>
<td>642</td>
<td>860</td>
<td>38</td>
</tr>
<tr>
<td>Middle East and Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>INHS</td>
<td>2002–2004</td>
<td>73</td>
<td>4,859</td>
<td>298</td>
<td>4,141</td>
<td>61</td>
</tr>
<tr>
<td>Lebanon</td>
<td>LEBANON</td>
<td>2002–2003</td>
<td>70</td>
<td>2,857</td>
<td>317</td>
<td>636</td>
<td>29</td>
</tr>
<tr>
<td>Nigeria</td>
<td>NSMHW</td>
<td>2002–2004</td>
<td>79</td>
<td>6,752</td>
<td>238</td>
<td>1,798</td>
<td>53</td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>WMHJ</td>
<td>2002–2003</td>
<td>51</td>
<td>2,436</td>
<td>222</td>
<td>1,029</td>
<td>39</td>
</tr>
<tr>
<td>China</td>
<td>B-WMH, S-WMH</td>
<td>2002–2003</td>
<td>75</td>
<td>5,201</td>
<td>191</td>
<td>1,390</td>
<td>46</td>
</tr>
<tr>
<td>Oceania</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>NZMHS</td>
<td>2004–2005</td>
<td>73</td>
<td>12,992</td>
<td>2,038</td>
<td>10,079</td>
<td>166</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td>85,088</td>
<td>9,647</td>
</tr>
</tbody>
</table>

Abbreviations: B-WMH, Beijing World Mental Health Survey; CMDPSD, Ukrainie Comorbid Mental Disorders during Periods of Social Disruption; ESEMeD, European Study of the Epidemiology of Mental Disorders; INHS, Israel National Health Survey; LEBANON, Lebanese Evaluation of the Burden of Ailments and Needs of the Nation; M-NCS, Mexico National Comorbidity Survey; NCS-R, US National Comorbidity Survey Replication; NSMH, Colombian National Study of Mental Health; NSMHW, Nigerian Survey of Mental Health and Wellbeing; NZMHS, New Zealand Mental Health Survey; S-WMH, Shanghai World Mental Health Survey; SASH, South Africa Health Survey; WMHJ, World Mental Health Japan Survey.

a Estimates were based on data obtained from 17 countries participating in the World Mental Health Surveys Consortium.

**MATERIALS AND METHODS**

**Participants**

Data were obtained from cross-sectional surveys carried out at 18 sites within the World Mental Health Survey (WMHS) Consortium during 2001–2005: the Americas (Colombia, Mexico, the United States), Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Ukraine), the Middle East and Africa (Israel, Lebanon, Nigeria, South Africa), Asia (Japan and 2 separate surveys carried out in Beijing and Shanghai, China), and Oceania (New Zealand). The minimum age of subjects was generally 18 years. Table 1 provides an overview of each site’s sample, methods, and recruitment results. Details about consistent use of standardized interview translation protocols, training procedures, and field quality control monitoring for reduction of between-site variation in data quality and institutional review.
board approval of the participation of human subjects can be found elsewhere (29; http://www.hcp.med.harvard.edu/wmh). Sample sizes ranged from 2,372 (the Netherlands) to 12,992 (New Zealand), with a total of 85,088 participants. Response rates averaged 70%, ranging upward to 88% (Colombia).

**Local area matching within each site**

The WMHS sampling design makes it possible to form matched local area risk sets based upon how a country’s multistage area probability sample was constructed. For example, at the Beijing site, sampling was done from lists of neighborhoods organized around local area committees of the Communist Party. In the United States, some sampling strata were counties or combinations of counties (30). Via conditioning on these strata, this “matching” within a local area risk set holds constant shared local area variables that otherwise might confound cannabis-mood associations and might be difficult to measure directly (e.g., prevailing cannabis smoking norms, levels of cannabis availability, police presence, levels of socially shared anomie, socioeconomic status).

**Measures**

**Composite International Diagnostic Interview.** All assessments were from the WMHS Composite International Diagnostic Interview (CIDI), version 3.0, a fully structured diagnostic interview for evaluation of psychiatric conditions (31, 32). Within this assessment, participants were asked whether they had ever smoked cannabis and whether they had ever experienced mood disturbances, including first onset of a depression spell as described below. The CIDI 3.0 starts with a screening section, with key questions for most disorders. The reason for this is to reduce interview duration, because of the large number of disorders evaluated and the large number of questions per section, and to minimize the possibility that respondents will learn how to shorten the interview by answering key questions negatively if these questions are asked each time at the beginning of a disorder section. Participants responding affirmatively to a key question in this screening section are administered the section of the CIDI pertaining to that disorder.

Except for Israel and South Africa, where all respondents were administered the full interview, investigators in all WMHS countries conducted subsampling for a 2-part CIDI that reduced respondent burden, such that 100% completed part I (core standardized item sets) but a smaller probability subsample completed part II (noncore item sets) (29). For survey analysis purposes and to account for differential selection probabilities, each participant is assigned a weight based on the inverse of the probability of selection for the survey sample and for each part of the CIDI.

**Assessment of first depression spell at or after age 17 years.** A “depression spell” refers to a negative and distressing change in mood, manifest as feeling sad, discouraged, or unresolved, that is present throughout most of each day and nearly every day for at least 2 weeks, accompanied by at least 1 other mood problem (problems with sleep, appetite, energy, ability to concentrate and remember, or self-worth). This definition of a depression spell is less strict than the criteria used for major depressive disorder and major depressive episode in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (33). Furthermore, for the depression spell, no diagnostic hierarchies or exclusion rules can thwart attempts to understand cannabis-induced mood disturbances, as occurs when current major depression diagnostic criteria with exclusion rules are fully implemented. Indeed, variations in the handling of diagnostic hierarchies may account for some observed variability in estimates regarding the cannabis-major depression association (34).

Based on the CIDI assessment, participants experiencing such a depression spell were asked about age of onset; 9,647 qualified as having experienced onset at or after age 17 years. These “cases” were matched within 821 local areas to a total of 41,071 noncase “controls” who had never experienced such a spell (Table 1). Respondents whose first depression spell occurred before age 17 years and respondents younger than age 17 years were excluded.

**Assessment of early-onset cannabis use.** Valid estimation of the cannabis-depression hypothesis requires earlier onset of cannabis use and later onset of a depression spell. Prior publications helped to set the age of initiation of cannabis use at a threshold of 16 years (34–38). The assessment asked, “Have you ever used either marijuana or hashish, even once?” and “How old were you the first time you used marijuana or hashish?” Cannabis onset age before 17 years was set by responses to these CIDI items.

**Assessment of other mental health problems.** Other mental health problems or behaviors, such as persistent adult cannabis use and tobacco smoking, might be related to the first onset of a depression spell, temporally subsequent to early-onset cannabis use. Therefore, in analysis of the association between early-onset cannabis use and first onset of a depression spell, we took these variables into account. The resulting estimates of the association between early-onset cannabis smoking and an adult-onset depression spell might well be downwardly biased in these exploratory analyses, as would be the case if persistent adult cannabis smoking or adult tobacco smoking actually lay on mediational pathways leading from early cannabis use to a later depression spell. Data on all covariates of interest were taken from CIDI standardized items, including tobacco smoking, which almost always preceded first use of cannabis in these data (1).

Persistent adult cannabis use was measured via assessment of cannabis use during the 12 months prior to assessment. Adult cannabis use was not assessed in the European countries, except for Ukraine. Other mental health problems were measured by means of the lifetime symptoms in the CIDI screening section: fear and panic attack; other panic symptoms; manifestations of manic spells; excessive irritability, grumpiness, or bad mood; worry; nervous or anxious feelings; miscellaneous phobia-like fears (e.g., an irrational fear of crowds, animals, insects, blood, closed spaces, high places, or flying); shyness; childhood problems with attention; childhood restlessness/fidgetiness; anger in childhood or adolescence; and separation anxiety. Furthermore, lifetime alcohol use was assessed from the CIDI alcohol section.
Precannabis violations of social norms and conduct problems might confound estimation of any cannabis-depression association. Therefore, we created an “early conduct problems” index (sum score) from the multiple-item assessment of childhood/early adolescent conduct problems from CIDI part II (see Appendix Table 1). These problems were assessed in all countries except Israel, South Africa, Japan, and New Zealand.

Data analysis

Associations linking early-onset cannabis use and a later-onset depression spell were estimated via odds ratios from conditional logistic regression analyses with local area-matched cases and controls, with and without statistical adjustment for covariates, using STATA, version 10, “clogit” commands (Stata Corporation, College Station, Texas) that yield regression slope coefficients. After exponentiation, odds ratios estimate risk ratios. The complex survey sample structure is accommodated by local area matching within risk sets (25).

RESULTS

Association between early-onset cannabis use and later depression spells

Early-onset cannabis use was moderately associated with later onset of a depression spell at a bivariate level (risk ratio (RR) = 1.2, 95% confidence interval (CI): 1.1, 1.3; P < 0.001; Table 2). Females were more likely than males to have experienced a depression spell after age 16 years (RR = 1.9, 95% CI: 1.8, 2.0; P < 0.001). Age was also associated with a later-onset depression spell, with an age-squared term being required to address residual nonlinearity (both P’s < 0.05; higher-order polynomials of age were not required). Tobacco smoking and a depression spell after age 16 years were associated too modestly for tobacco to function as an important confounder here (RR = 1.2, 95% CI: 1.1, 1.2; P < 0.001).

Crude and sex- and age-adjusted risk ratios for the association between early-onset cannabis use and a later spell of depression are shown in Table 3, according to country. The overall sex- and age-adjusted risk ratio estimate (hereafter called the adjusted RR (aRR)) was 1.5 (95% CI: 1.4, 1.7; P < 0.001). Germany, Ukraine, Nigeria, South Africa, and New Zealand had statistically robust aRR estimates, with the strongest associations being seen in sub-Saharan Africa (in South Africa, aRR = 3.9, 95% CI: 2.0, 7.5 (P < 0.001); in Nigeria, aRR = 3.2, 95% CI: 1.2, 8.5 (P = 0.02)). Estimations for Lebanon, Japan, and China failed because early-onset cannabis use was rare there.

Figure 1 depicts the site-specific estimates in a horizontal summary plot inspired by the meta-analytic vertical “funnel plot.” The horizontal line shows the overall meta-analytic risk ratio summary estimate, derived as if each site had published its own sex- and age-adjusted risk ratio estimate and 95% confidence interval, with a rather narrow 95% confidence interval for this covariate-adjusted risk

Table 2. Estimated Association Between Early-Onset (Age < 17 Years) Cannabis Use and Later Onset (Age ≥ 17 Years) of a Depression Spell Before Adjustment for Covariates, World Health Organization World Mental Health Survey Initiative, 2001–2005

<table>
<thead>
<tr>
<th>Depression Spell Status</th>
<th>Casesb (n = 9,647)</th>
<th>Noncase Controlsb (n = 41,071)</th>
<th>Estimated Risk Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main covariates under study</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Early-onset cannabis use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes 904 9</td>
<td>2,955 7</td>
<td>1.2</td>
<td>1.1, 1.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No (referent) 8,743 91</td>
<td>38,116 93</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female 6,551 68</td>
<td>22,295 54</td>
<td>1.9</td>
<td>1.8, 2.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male (referent) 3,096 32</td>
<td>18,776 46</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and age squaredc</td>
<td>9,647 100</td>
<td>1.0</td>
<td>1.0, 1.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Primary additional covariate under study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of tobacco smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes 5,040 52</td>
<td>18,968 46</td>
<td>1.2</td>
<td>1.1, 1.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No (referent) 4,605 48</td>
<td>22,083 54</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Estimates were based on data obtained from 17 countries participating in the World Mental Health Surveys Consortium.

b The mean age of cases was 46.2 years (standard deviation, 15.3); the mean age of controls was 43.0 years (standard deviation, 17.0).

c After age was centered on its mean value for the sample, the estimated age-related log odds difference changes in relation to the following equation with each 1-year increase in age: 0.0121918 + (age) + (−0.0009107) + (age^2).

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The possibility of different associations between the sexes and between different age categories deserves attention. In an age-adjusted model with a product term for early cannabis use and sex (male vs. female), the product term \( P \) value was 0.084, and we estimated the aRR for the cannabis-depression association as 1.6 for males (95% CI: 1.4, 1.8; \( P < 0.001 \)) and 1.4 for females (95% CI: 1.2, 1.6; \( P < 0.001 \)), indicating no difference in the association according to sex. There was a tendency for the cannabis-depression association to be stronger in older participants (age 17–24 years: aRR = 1.6, 95% CI: 1.2, 2.1 (\( P < 0.001 \)); age 25–34 years: aRR = 1.3, 95% CI: 1.1, 1.6 (\( P = 0.001 \)); age 35–44 years: aRR = 1.5, 95% CI: 1.3, 1.7 (\( P < 0.001 \)); and age \( \geq 45 \) years: aRR = 1.8, 95% CI: 1.4, 2.2 (\( P < 0.001 \)); the aRR was controlled for sex).

The aRR estimates did not vary appreciably across strata defined by tobacco smoking history (data not shown).

### Controlling for other mental health problems

The cannabis-depression association was reestimated with statistical adjustment for persistency of cannabis use
and other mental health problems that might be functioning as confounding variables. Persistency of cannabis use into the 12 months prior to assessment did not appear to alter the size of the cannabis-depression association. Moreover, statistical adjustment for a broad array of pre-cannabis, concurrent, and post-cannabis mental health problems in a conditional logistic regression model did little to attenuate the originally observed association (Figure 2).

To study the possibility of confounding by a propensity to commit early violations of social norms, we created an index of childhood conduct problems as described in Appendix Table 1 and reestimated the cannabis-depression association with this index in the model, along with terms for age, age squared, and sex. This was possible for all but 4 countries, which did not administer this assessment. Based on data from the 13 countries that administered the childhood conduct problems assessment, and prior to statistical adjustment for this index of early norm violations, the aRR for the estimated cannabis-depression association was modest at 1.18 (95% CI: 1.02, 1.37; \(P = 0.02\)). With statistical adjustment for the index of early norm violations, the estimated cannabis-depression association dropped towards the null value and lacked statistical significance (aRR = 1.08, 95% CI: 0.93, 1.25; \(P = 0.32\)).

**DISCUSSION**

**Key findings**

The general summary evidence from this cross-site research with representation of all world regions suggests that there might be a modest but statistically robust sex- and age-adjusted association linking early-onset cannabis use with later occurrence of a depression spell. In most prior research on the hazards of cannabis use, the “controls” have been drawn from the total population, without taking into account the fact that in many places cannabis smoking is a violation of social norms. Unless early propensity for norm violations of this type can be taken into account, or unless norm violation has no association with the hazards of interest, other research teams may find what has been observed here—namely, an initial statistically robust signal of cannabis-related harm that would disappear when cases and controls were selected with attention to the norm-violation distribution or when the propensity toward norm violation was held constant.

Other studies on the relation between cannabis use and major depression symptoms or disorders have also found moderate associations, but no significant association was reported in some studies (21, 39). According to the review...
by Degenhardt et al. (15) on the association between cannabis use and depression, a number of studies found a modest association between early regular cannabis use and later depression, which persisted after controlling for potentially confounding variables.

Of course, the cannabis-depression association touches upon only 1 possible cannabis-associated psychiatric hazard. The world literature now references an array of possibilities, as recently reviewed by Hall and Degenhardt (40). As they noted in that review, the range of suspected hazards of this type is broad and encompasses anxiety disturbances as well as schizophrenia or schizophrenia-like psychosis reactions. Readers can judge for themselves whether the published evidence justifies a claim that early-onset or later-onset cannabis smoking might represent a generalized vulnerability to psychiatric disturbances (e.g., with the form of the disturbance being shaped by individual-level propensities in addition to the cannabis smoking), whether it might be a causal influence with adverse mental health consequences, or whether the observed associations might be a manifestation of something else (e.g., substantive or methodological possibilities mentioned elsewhere in this discussion).

We found evidence for an association between early cannabis use and later depression spells for 5 individual countries (Germany, Ukraine, Nigeria, South Africa, and New Zealand), representing both developed and developing countries. It is difficult to explain why in some countries the association was significant, while in others it was not. A high prevalence of early cannabis use in a particular country was not a clear explanation for a significant relation. For example, the United States and New Zealand had the highest prevalences of early cannabis use (1), but only in New Zealand was the association significant. On the contrary, in South Africa and Nigeria, the prevalence of early cannabis use was low (1), while the aRR was large and significant. It might be that in these countries the deviancy of cannabis use influences the incidence of a later depression spell.

We found no difference between females and males in the association linking early-onset cannabis use with later occurrence of a depression spell. In addition, the study by Poulin et al. (13) did not find clear sex differences, while Patton et al. (14) reported females to be more at risk. The cannabis-depression association was highest in the oldest age group. This might be explained by the fact that the oldest age group had more time to develop depressive symptoms. Another explanation might be the higher prevalence of cannabis use in younger age cohorts (1), which makes early cannabis use more normative in younger cohorts and therefore less deviant, with fewer negative consequences (e.g., discrimination, criminalization, use in segregated subcultures), thereby lowering the likelihood of deleterious mental effects such as depressive symptoms. In addition, a shorter duration of cannabis exposure among the younger cohorts could explain this finding, although controlling for persistence of cannabis use in this study did not alter the association.

**Strength and limitations**

A major strength of this study was its coverage of multiple global regions, with multisite standardized sampling,
assessment, and risk-set matching approaches that con-
strained methodological and local area variations to a large extent.

Limitations included the limited capacity of cross-
sectional surveys to shed light on suspected causal associ-
atios, although some of these limitations were constrained
via the use of specific ages of onset of cannabis use and
depression spells to assure temporal sequencing. Retrospec-
tive reports on age at first cannabis use can be questioned,
although these have been found to be more reliable than
reports on tobacco and alcohol use (41). Repeated measure-
ments over time show that reported age of first substance use
tends to increase as people age (42–44). Thus, it might be
possible that in our study, some older subjects inaccurately
estimated their age at first cannabis use as older and were
misclassified as later-onset cannabis users. Therefore, the
greater cannabis-depression association found in older co-
horts might be even larger than was estimated here. Sym-
toms of depression and their age of onset were also assessed
by means of retrospective reports, which might be biased by
the reconstruction of memories based on current affective
states (10). Subjects who incorrectly reported onset of their
depression symptoms as occurring at a later age (i.e., after
their 17th birthday) would have been inadvertently included
in the analyses as cases.

A limitation that might have affected this study’s esti-
mates is the level of survey nonresponse. This is a likely
source of underestimation of illegal drug involvement but
not necessarily a source of bias with respect to estimated
associations with other variables (45). Furthermore, under-
reporting of cannabis use might have occurred, because
some respondents may be unwilling to disclose an illegal
behavior, and this might vary across countries. This bias
might have resulted in underestimation of the association
between early cannabis use and depression spells. However,
we assume that the assurance of anonymity, as was done
clearly before and at the start of the interview, will have
helped to limit this.

The data did not allow differentiation between levels of
cannabis use as reported elsewhere (9, 14). Degenhardt et al.
(15) concluded that infrequent cannabis use has no associ-
ation with depression. Perhaps our study’s estimates can be
attributed to what generally is a low level of cannabis in-
volved among persons who start to use this drug. Possi-
bly, if the study focus had been on early onset of regular
cannabis use, the observed cannabis-depression association
might have been stronger. On the other hand, the youngest
cannabis users may be most at risk, simply because their
cannabis use is more likely to become long-standing (21).

Multiple covariates were considered, but there remain
possible model misspecifications, with some suspected con-
founding variables not being measured at all or not being
measured with sufficient accuracy and precision. Because
ages of onset of the reported symptoms were not assessed, in
some cases onset might have happened after the occurrence
of the depression spell. The influences of family and parent-
ing factors and childhood trauma were not studied; their
confounding effects could be studied in future research. This
study’s control of precannabis norm violations is a case in
point. The assessment of alleged cannabis toxicity will de-
pend upon more complete attention to this source of con-
founding, when the toxic outcome is in the domain of mood
disturbances or other mental health problems known to vary
with premorbid norm violations and conduct problems.

Finally, in a prospective study of the cannabis-depression
association, one might be able to match cannabis users and
nonusers at the time of a baseline assessment, with subse-
quent follow-up for ascertainment of later depression and
with formation of area-matched risk sets based on neighbor-
hood of residence at the time of initiation of cannabis use.
This approach was not possible in the present context but
could be used in future prospective studies.

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Appendix Table 1 continue.
Appendix Table 1. Items Included in the Early Conduct Problems Index and the Screening Section of the World Mental Health Survey Composite International Diagnostic Interview, World Health Organization World Mental Health Survey Initiative, 2001–2005

Conduct problems in childhood or early adolescence
- Telling lies to trick people
- Getting out of doing things by fooling people or lying
- Staying out later than your parents wanted
- Skipping school
- Shoplifting
- Stealing from people you lived with
- Breaking into a car, home, or building
- Setting a fire to try to cause damage
- Damaging property
- Running away from home
- Bullying, threatening, or frightening others
- Often getting involved in physical fights
- Using a weapon on another person
- Being physically cruel to an animal and hurting it on purpose
- Being physically cruel to a person and hurting them on purpose
- Forcing someone to give you something like money, jewelry, or clothing by threatening them or causing them injury
- Stealing someone’s purse, wallet, luggage, package, or bag by grabbing it from them
- Making anyone do something sexual by forcing, intimidating, or threatening them
- Ever being suspended or expelled from school as a result of your behavior or aggression
- Being fired from a job because of your behavior or aggression
- Getting in trouble with the police as a result of your behavior or aggression
- Being arrested because of your behavior or aggression
- Being sent to jail, prison, or a juvenile correction facility because of your behavior or aggression

Screeners items on lifetime mental problems and alcohol status
- Alcohol drinking status: ever/never
- Tobacco smoking status: ever/never
- Attack of fear/panic during one’s lifetime
- Ever feeling panic symptoms
- Ever having a period of manic behavior
- Irritability, grumpiness, or bad mood for several days or longer
- Period of excessive worry
- Being more nervous/anxious than most people
- Being anxious/worried for 1 month or longer
- Phobia
  - Animals/insects
  - Water
  - Blood/injury/medical setting
  - Closed spaces
  - High places
  - Flying
- Ever feeling really shy
- Feeling afraid in crowds, in public, or while traveling
- Attention difficulty before age 7 years for 6 months or longer
- Restlessness/fidgetiness before age 7 years for 6 months or longer
- Being angry or in trouble during childhood/adolescence for 6 months or longer
- Separation anxiety at age 5 years or older for 1 month or longer
- Separation anxiety in adulthood for 1 month or longer

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