

# Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review



Theresa H M Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R E Barnes, Peter B Jones, Margaret Burke, Glyn Lewis

## Summary

**Background** Whether cannabis can cause psychotic or affective symptoms that persist beyond transient intoxication is unclear. We systematically reviewed the evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes.

**Methods** We searched Medline, Embase, CINAHL, PsycINFO, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, and MEDCARIB from their inception to September, 2006, searched reference lists of studies selected for inclusion, and contacted experts. Studies were included if longitudinal and population based. 35 studies from 4804 references were included. Data extraction and quality assessment were done independently and in duplicate.

**Findings** There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1.41, 95% CI 1.20–1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2.09, 1.54–2.84). Results of analyses restricted to studies of more clinically relevant psychotic disorders were similar. Depression, suicidal thoughts, and anxiety outcomes were examined separately. Findings for these outcomes were less consistent, and fewer attempts were made to address non-causal explanations, than for psychosis. A substantial confounding effect was present for both psychotic and affective outcomes.

**Interpretation** The evidence is consistent with the view that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects, although evidence for affective outcomes is less strong. The uncertainty about whether cannabis causes psychosis is unlikely to be resolved by further longitudinal studies such as those reviewed here. However, we conclude that there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

## Introduction

Cannabis, or marijuana, is the most commonly used illegal substance in most countries, including the UK and USA.<sup>1–3</sup> About 20% of young people now report use at least once per week or heavy use (use on >100 occasions).<sup>4,5</sup> Use has increased particularly during early adolescence, when the developing brain might be especially susceptible to environmental exposures.<sup>6</sup> Experimental studies<sup>7–10</sup> and surveys of users<sup>11–13</sup> provide strong evidence that cannabis intoxication can produce transient, and usually mild, psychotic and affective experiences. Of greater concern are chronic symptoms that persist beyond, or occur independently of, intoxication effects.

Whether cannabis increases the incidence of established syndromes such as schizophrenia or depression is unclear, but this question is important because these disorders lead to substantial distress for individuals and their families, and to public burden from health-care costs. Randomised controlled trials (RCTs) of cannabis for medical use<sup>14</sup> are unlikely to be helpful in addressing the question of causality because there are substantial differences between the pharmacokinetic profiles of such preparations and of cannabis used as a recreational drug. The typically short follow-up periods of such trials also substantially hinder interpretation of results.

Previous reviews in this field have not been very systematic, have examined broad psychosocial outcomes rather than mental illness, or have included cross-sectional

data.<sup>15–19</sup> We have systematically reviewed longitudinal studies of cannabis use and subsequent psychotic or affective mental health outcomes, and we have assessed the strength of evidence that cannabis use and these outcomes are causally related.

## Methods

### Study selection and data collection

Studies were included if they were population-based longitudinal studies, or case-control studies nested within longitudinal designs. We excluded cohorts of people with mental illness or substance-use-related problems, studies of prison populations, and RCTs of cannabis for medical use.<sup>14</sup>

Diagnostic outcomes for psychosis included schizophrenia, schizophreniform, schizoaffective, or psychotic disorders, non-affective or affective psychoses, psychosis not otherwise specified, psychotic symptoms, delusions, hallucinations, or thought disorder. Presence of delusions, hallucinations, or thought disorder was a requirement for all psychosis outcomes. Affective, mood, or bipolar disorder, affective disorder not otherwise specified, depression, suicidal ideation or suicide attempts, anxiety, neurosis, and mania were included for affective outcomes.

We searched the following databases from their inception to Sept 5, 2006: Medline, Embase, and the Cumulative Index to Nursing and Allied Health Literature

*Lancet* 2007; 370: 319–28

See [Editorial](#) page 292

See [Comment](#) page 293

Academic Unit of Psychiatry

(T H M Moore MSc, S Zammit PhD, A Lingford-Hughes PhD, G Lewis PhD) and Department of Social Medicine (M Burke MSc), University of Bristol, Bristol, UK; Department of Psychological Medicine, Cardiff University, Cardiff, UK (S Zammit); Department of Psychological Medicine, Imperial College, London, UK (T R E Barnes DSc); and Department of Psychiatry, Cambridge University, Cambridge, UK (P B Jones PhD)

Correspondence to:

Dr Stanley Zammit, Department of Psychological Medicine, Cardiff University, Cardiff CF14 4XN, UK  
zammits@cardiff.ac.uk

(CINAHL) on OVID; PsycINFO on WebSPIRS; ISI Web of Knowledge and ISI Proceedings; ZETOC (a British library database of journal and conference contents); BIOSIS on EDINA; and Latin American and Caribbean Health Sciences (LILACS) and Caribbean Health Sciences Literature (MEDCARIB). We searched using the format “([psychosis or schizophrenia or synonyms] or [affective disorder or depression or synonyms]) and (cannabis or synonyms)”, using text words and indexing (MeSH) terms (full details are available on GL’s departmental website).

The search was restricted to studies on human beings but was not limited by language or study design. We searched reference lists of included studies, and wrote to experts in the field and researchers responsible for studies to find other published and unpublished studies of relevance. We examined all titles and abstracts, and obtained full texts of potentially relevant papers. Working independently and in duplicate, we read the papers and determined whether they met inclusion criteria using eligibility record forms (available on the corresponding author’s departmental website). We resolved disagreements by consensus, and extracted data independently and in duplicate.

We assessed study quality by recording how potential non-causal explanations, particularly bias and confounding factors, were accounted for in each study. We assessed information on sampling strategy, response rates, missing data, attrition, and attempts to address reverse causation, intoxication effects, and confounding factors.

**Data synthesis**

Where study characteristics were judged reasonably homogeneous, we grouped studies together and pooled data in a meta-analysis; otherwise, we present a narrative synthesis of data. We pooled studies using the DerSimonian and Laird random-effects model<sup>20</sup> and the metan command in Stata (9.0). Where studies presented data only in subgroups, these were incorporated as separate studies. We assessed heterogeneity using the *I*<sup>2</sup>

statistic.<sup>21</sup> Presence of publication bias was investigated by use of funnel plots and Egger’s Test.<sup>22</sup> A summary of compliance with MOOSE guidelines<sup>23</sup> is available on GL’s departmental website.

**Role of the funding source**

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

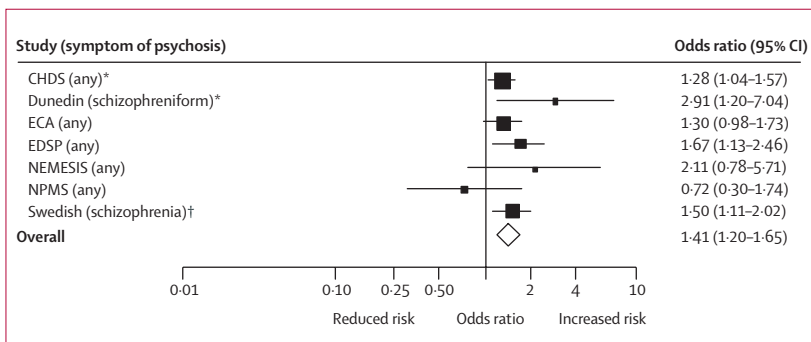
Searches of electronic bibliographic databases, expert advice, and searches of reference lists of included studies and other reviews yielded 4804 references. On the basis of their titles and abstracts, we judged that 175 (3.6%) of these references potentially contained enough detail to be relevant. 143 of these references were excluded as not relevant when we had read the whole paper. Details of the studies that were excluded at this stage, including those that we regarded as near misses, are available on GL’s departmental website.

We found 11 studies of psychosis; these reports presented data from seven cohort studies. There were five adult population-based cohorts: the Epidemiological Catchment Area (ECA) study based in the USA;<sup>24</sup> the Early Developmental Stages of Psychopathology (EDSP) study based in Germany;<sup>25</sup> the Netherlands Mental Health Survey and Incidence Study (NEMESIS);<sup>26</sup> the National Psychiatric Morbidity Survey (NPMS) based in the UK;<sup>27</sup> and the 1969 Swedish Conscript Cohort.<sup>28–30</sup> There were also two birth cohorts, from Dunedin<sup>31,32</sup> and Christchurch (CHDS)<sup>33,34</sup> in New Zealand. For the Swedish conscripts and CHDS cohorts, data from the most recent reports<sup>29,34</sup> were included in each case because these had longer follow-up to cover more events, and had more comprehensive analyses to keep reverse causation and confounding effects to a minimum. Omission of individuals with schizophrenia simplex made no difference to results for schizophrenia in the study of Swedish conscripts (Zammit S, unpublished). However, results for non-schizophrenia psychoses from this cohort were not included because the diagnostic codes that were used potentially included many people without psychosis as defined in this study.

Three of the eligible studies examined psychotic disorders, which were defined as the presence of psychotic symptoms with concurrent evidence of impaired functioning (Dunedin,<sup>31</sup> NEMESIS,<sup>26</sup> and Swedish conscripts<sup>29</sup>), and six studies used the broader outcome of psychotic symptoms with no requirement for impaired functioning (CHDS,<sup>34</sup> Dunedin,<sup>31</sup> ECA,<sup>24</sup> EDSP,<sup>25</sup> NEMESIS,<sup>26</sup> and NPMS<sup>27</sup>).

For affective outcomes, 24 reports were identified from 15 cohort studies: two birth cohorts from New Zealand (CHDS<sup>35–37</sup> and Dunedin<sup>31,32,38</sup>); six adult population-based

For Glyn Lewis’s departmental website see [bristol.ac.uk/Depts/Psychiatry/research/psychotic.html](http://bristol.ac.uk/Depts/Psychiatry/research/psychotic.html)



**Figure 1: Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to ever use of cannabis in individual studies**  
 Exposure was ever use of cannabis in all studies except for the NPMS, in which the measure was ever use over the past 1 year only. \*Additional data were provided by investigators in these studies.<sup>31,34</sup> †Results were unaltered when the 4% of cases with simplex schizophrenia were omitted.

cohorts, from the USA (Berkeley,<sup>39</sup> ECA,<sup>40,41</sup> and NY state<sup>42,43</sup>), the UK (NPMS [Haynes J, University of Bristol, personal communication]), Australia (Northern Rivers Mental Health Study, NoRMHS<sup>44</sup>), and Colombia;<sup>45</sup> and seven school-based cohorts, from Australia (Victoria<sup>46</sup>) and the USA (AddHealth,<sup>47,48</sup> Baltimore,<sup>49</sup> Chicago,<sup>50</sup> LA schools,<sup>51,52</sup> LAT,<sup>53</sup> and NY schools<sup>54,55</sup>). Various outcomes were examined, including depression (ten studies), depressive symptoms (six studies), suicidal ideation or suicide attempts (six studies), anxiety disorders (five studies), and anxiety symptoms (one study). We identified one study that had data on mania, though there was only one event in the whole sample.<sup>44</sup>

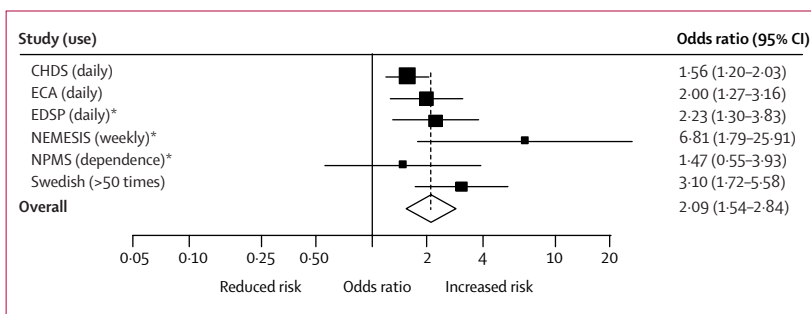
**Results for the seven studies included for psychosis are summarised in webtable 1 and figure 1.** There was no evidence to support the presence of publication bias (Egger test,  $p=0.48$ ). The unadjusted results of all studies reported evidence of an increased risk of psychosis in people who used cannabis compared with non-users. These associations were reduced, but nevertheless persisted, in six of the studies after adjustment for confounding factors.

Estimates were pooled under the assumption that measures of psychosis were on a continuum of symptoms from mild (self-report of psychotic symptoms) to severe (clinical diagnosis of schizophrenia). **There was an increased risk of a psychotic outcome in individuals who ever used cannabis (adjusted odds ratio=1.41, 95% CI 1.20–1.65; heterogeneity  $p=0.28$ ;  $I^2=19.2\%$ ).**

Of the six studies that either examined a linear trend across cannabis use frequencies<sup>25,26,29,34</sup> or compared higher with lower frequency categories,<sup>24,27</sup> all reported findings that were consistent with a dose-response effect. **Figure 2 shows the associations reported for people with most frequent cannabis use compared with non-users of cannabis in each study where such data were available. In the pooled analysis, there was an increased risk of a psychotic outcome in individuals who used cannabis most frequently (adjusted odds ratio=2.09, 1.54–2.84; heterogeneity  $p=0.11$ ;  $I^2=44.1\%$ ).**

We also examined the specific relation between cannabis use and risk of developing a psychotic disorder. The narrowest definition of psychotic disorder was in the Swedish conscripts study,<sup>29</sup> which reported an increased risk of schizophrenia in individuals who used cannabis. Studies of schizophreniform disorder from Dunedin<sup>31</sup> (additional data unstratified by age at first use were supplied by the researchers) and needs-based diagnosis of psychotic disorder from NEMESIS<sup>26</sup> also showed associations with cannabis use. Pooled data from these studies show an increased risk of psychotic disorders in individuals who had ever used cannabis (adjusted odds ratio=2.58, 1.08–6.13; heterogeneity  $p=0.049$ ;  $I^2=66.9\%$ ).

We repeated the pooled analyses for most frequent cannabis use and for psychotic disorders but omitted the results from NEMESIS because this had the greatest effect on heterogeneity. In these sensitivity analyses,



**Figure 2: Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to most frequent use of cannabis in individual studies**

\*Results were not adjusted for other drug use.

there remained an increased risk of a psychotic outcome in people who used cannabis most frequently (odds ratio=1.92, 1.50–2.47; heterogeneity  $p=0.26$ ;  $I^2=25.0\%$ ), and also an increased risk of psychotic disorders in people who had ever used cannabis (odds ratio=1.82, 1.01–3.30; heterogeneity  $p=0.16$ ;  $I^2=48.3\%$ ).

Two studies have examined differential effects of cannabis on psychosis according to age of first use of this drug. **In the Dunedin study, a stronger effect of cannabis on psychotic symptoms was reported for individuals who first used cannabis before, as opposed to after, 16 years of age.<sup>31</sup>** There was much weaker evidence for this age effect for schizophreniform disorder, although the CIs were very wide. In the Swedish conscripts study, there was no evidence that the effect of cannabis on risk of schizophrenia differed for people who first used cannabis before, as opposed to after, age 16 years.<sup>30</sup>

Other putative interactions were also reported. A further report on the Dunedin cohort<sup>32</sup> described a strong effect of cannabis on risk of schizophreniform disorder in people homozygous for the valine allele at Val158Met within the catechol-O-methyltransferase (COMT) gene (crude odds ratio=10.9, 2.2–54.1), with no apparent effect in methionine homozygotes (crude odds ratio=1.1, 0.21–5.4) and an intermediate effect in heterozygotes. This potential interaction was observed only in people who first used cannabis before age 18 years, with no evidence of interaction in those who first used it after this age.

In the EDSP study, the effect of cannabis on psychosis outcome was stronger in groups described as psychosis prone than in non-prone groups.<sup>25</sup> However, psychosis-prone individuals already had evidence of psychotic features at baseline, and this study was therefore not examining differences in the effects of cannabis on psychosis incidence between these groups.

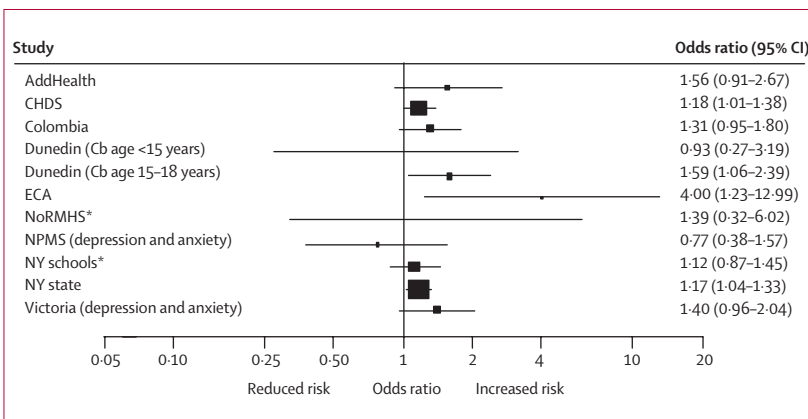
We assessed the quality of the studies included for psychosis. Because reverse causation, intoxication effects, and confounding factors could have led to overestimation of the true causal association between cannabis use and psychosis, we assessed the degree to which the potential effect of these was kept to a minimum within each study (table 1).

See Online for webtable 1

	Attempt to limit reverse causation	Attempt to limit intoxication effects	Approximate change from crude to adjusted OR (%)*
CHDS <sup>33,34†</sup>	Adjusted for psychotic symptoms at previous assessment and used SEM to address direction of causation	Used SCL-90 to measure outcome. This does not allow identification of symptoms caused by drug intoxication	65% ↓
Dunedin <sup>31†</sup>	Adjusted for psychotic symptoms at age 11 years (cannabis measures at age 15 and 18 years)	Used DIS to measure outcome. Excluded symptoms caused solely by drug use	10% ↓
ECA <sup>24</sup>	Excluded people with psychotic diagnosis at baseline	Used DIS to measure outcome. Excluded symptoms caused solely by drug use	30% ↓
EDSP <sup>25</sup>	Adjusted for predisposition to psychosis measured at baseline	Used M-CIDI to measure outcome. Stated that no symptoms were due to acute effects of drug use	15% ↓
NEMESIS <sup>26</sup>	Excluded people with psychotic symptoms at baseline	Used CIDI to measure outcome. Excluded symptoms caused by drug use	50% ↓
NPMS <sup>27</sup>	Excluded people with psychotic symptoms at baseline	Used PSQ to measure outcome. This does not allow identification of symptoms caused by drug intoxication	80% ↓
Swedish conscripts <sup>29,30</sup>	Excluded people with psychotic diagnosis at baseline	Used ICD clinical diagnosis of schizophrenia as outcome, suggesting intoxication effects unlikely	60% ↓

OR=odds ratio. SEM=structural equation modelling. SCL-90=symptom checklist 90. DIS=diagnostic interview schedule. M-CIDI=Munich version of CIDI. CIDI=composite international diagnostic interview. PSQ=psychosis screening questionnaire. ICD=International classification of diseases. ↓=decrease. \*Change between crude OR and that after adjustment for confounding factors was calculated as (crude OR-adjusted OR)/(crude OR-1). †Additional data, to allow estimation of change between crude and adjusted estimates, kindly provided by the researchers.

**Table 1: Information on possible alternative causes for associations reported between cannabis use and psychosis outcomes in seven cohorts**



**Figure 3: Forest plot showing adjusted odds ratios and 95% CI for any depression outcome according to cannabis exposure in individual studies**

Depression outcome measures: centre for epidemiological studies (CES-D) score >22 (AddHealth); diagnostic and statistical manual of mental disorders (DSM; CHDS, Dunedin, and NY state); WHO international classification of diseases 10th revision (ICD-10; NoRMHS); DSM symptom lasting ≥2 weeks (ECA); clinical interview schedule—revised (CIS-R) score ≥12 (NPMS, Victoria); symptom checklist 90 assessment (SCL-90) upper quartile (Colombia); and SCL-90 >median score (NY schools). Subgroup data from the Dunedin study were incorporated as separate studies. Exposure to cannabis (Cb): ever use (AddHealth, Dunedin, NPMS); current use (NY schools); use less than once per week in the past 6 months (Victoria); use at least once per month (Colombia); frequency of use (a linear trend across frequency categories; CHDS, NY state); cannabis misuse disorder (ECA, NoRMHS). The point estimates of odds ratios (squares) are not visible for studies in which the variance was very high. \*Unadjusted results calculated from data in tables in the original studies.<sup>44</sup>

Four studies<sup>24,26,27,29</sup> excluded participants who had experienced psychosis at baseline. In the Swedish conscripts study,<sup>29</sup> reverse causation was limited further by analysis restricted to patients admitted for schizophrenia at least 5 years after conscription; this analysis produced similar results to the main analysis. Three studies<sup>25,31,34</sup> adjusted in the analysis for psychotic symptoms at baseline. Although this approach partly addresses the problem of reverse causation, it averages the association between cannabis and psychosis incidence with that between cannabis and symptom chronicity or relapse. In CHDS,<sup>34</sup> structural equation modelling results suggested that cannabis use was significantly associated with subsequent increase in risk of psychotic symptoms rather than vice versa.

Intoxication effects were not specifically mentioned in reports of the ECA<sup>24</sup> and NEMESIS<sup>26</sup> studies, but the outcome assessment (also used in Dunedin<sup>31</sup> and EDSP<sup>25</sup>) instructs the interviewer to exclude psychotic symptoms that arise solely from drug use. The questionnaires used in CHDS<sup>34</sup> and NPMS<sup>27</sup> do not allow intoxication to be assessed. However, exclusion of intoxication effects in those who use cannabis every day is likely to be very difficult. In the Swedish conscripts study,<sup>29</sup> use of WHO International Classification of Diseases criteria suggests that misclassification of a cannabis-intoxication psychosis was unlikely; the same is probably true for the Dunedin study,<sup>31</sup> in which psychosis was defined by the presence of symptoms of schizophreniform disorder for longer than 1 month.

The studies listed in table 1 adjusted for about 60 different confounding factors, including other substance use, personality traits, sociodemographic markers, intellectual ability, and other mental health problems. For all studies, fully adjusted estimates were attenuated, compared with crude results, by an average of about 45% (range 10%–80%). In the CHDS, use of fixed-effects regression to adjust further for unmeasured non-varying confounding factors made little difference to results.<sup>34</sup> Adjustment for other substance use led to a substantial attenuation of effect in the ECA study<sup>24</sup> and NEMESIS,<sup>26</sup> whereas in the Swedish conscripts study<sup>29</sup> the strongest confounding factors were IQ score, urban upbringing, and other mental health disorders.

Loss to follow-up occurred for between 4%<sup>31</sup> and 32%<sup>27</sup> of the cohorts we included for psychosis. No data on attrition were available from the Swedish conscript study.<sup>29</sup> Sensitivity analyses from two of the studies<sup>26,34</sup> suggest that attrition might have had small effects on results, although reclassification of outcome in NEMESIS did not differentiate between people with different cannabis use at baseline.

Depressive outcomes were examined in 15 cohorts (webtable 2). There was no evidence to support the presence of publication bias (Egger test, ten studies;  $p=0.13$ ). Of ten studies that examined a diagnosis of depression or above-threshold rating scores (figure 3),



five reported evidence of an association with cannabis use that persisted after adjustment.<sup>31,37,40,43,46</sup> However, in two of these,<sup>31,46</sup> significant associations were observed only in subgroup analyses, and in the Dunedin study<sup>31</sup> no baseline measures of depression were accounted for. Weak evidence for association was reported by two further studies,<sup>45,48</sup> and an association observed in NPMS (Haynes J, personal communication) was eliminated after adjustment. In view of the heterogeneity across these studies in relation to measures of cannabis exposure (which included ever use, frequency of use, and cannabis misuse disorder), we did not think a meta-analysis of these data would be appropriate. Using average values from these studies—of 35% having ever used cannabis and 15% having developed depression—we estimated that a sample with more than 230 events would be required for 80% power to detect an odds ratio for depression of 1.5 (a larger effect than was observed in most studies). Thus, about half the studies probably had insufficient power to observe an association of this size.

Six studies<sup>32,38,51–54</sup> from five cohorts examined depressive symptoms on a continuous scale. Evidence of association was observed in the Berkeley<sup>38</sup> and LA schools<sup>51,52</sup> cohorts (webtable 2). However, in the Berkeley study only crude results were presented, and the association was observed in men but not women,<sup>39</sup> whereas in the LA schools cohort an increased risk observed in an early part of the study<sup>51</sup> was not replicated in a later wave.<sup>52</sup>

Of the studies that examined a linear trend across cannabis use frequencies<sup>37,41,51,52</sup> or that compared higher with lower frequency groups<sup>46</sup> (Haynes J, personal communication), four reported findings that were consistent with a dose-response effect on depression outcomes (webtable 2). Figure 4 shows the associations reported for participants with most frequent cannabis use compared with non-users, with some evidence for an increased risk of depression in a pooled analysis (adjusted odds ratio=1.49, 1.15–1.94; heterogeneity  $p=0.192$ ;  $I^2=29.6\%$ ).

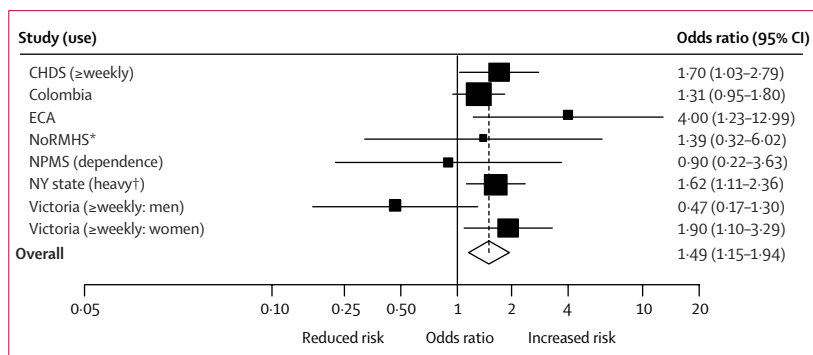
Seven studies assessed suicidal ideation or suicide attempts. Four of these<sup>10,37,47,49</sup> reported an association between cannabis use and increased risk in adjusted analyses and one<sup>50</sup> showed little evidence of an association (figure 5). A reduced risk of attempts<sup>51</sup> but increased risk of ideation<sup>52</sup> were reported from the LA schools cohort (webtable 2).

Of the seven studies that specifically examined anxiety outcomes (figure 6),<sup>35,41,42,44,45,51,52</sup> two reported an association with cannabis use that persisted after adjustment for confounding factors.<sup>42,45</sup> In the ECA study of obsessive-compulsive disorder, an association was observed in a matched sample, but there was little evidence for association in the whole sample when a more valid unconditional analytical approach was used.<sup>41</sup>

Several studies reported putative interactions. In the NY state study,<sup>43</sup> there was a suggestion that risk of

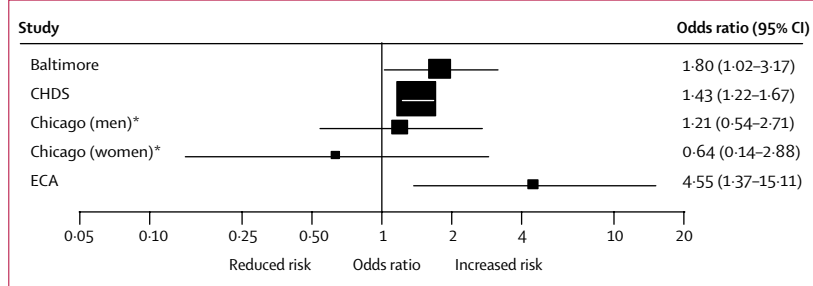
depression increased with earlier age of first use of cannabis. However, in the Dunedin cohort, there was no evidence for a greater risk of depression in people who first used cannabis before, as opposed to after, age 16 years.<sup>31</sup>

See Online for webtable 2



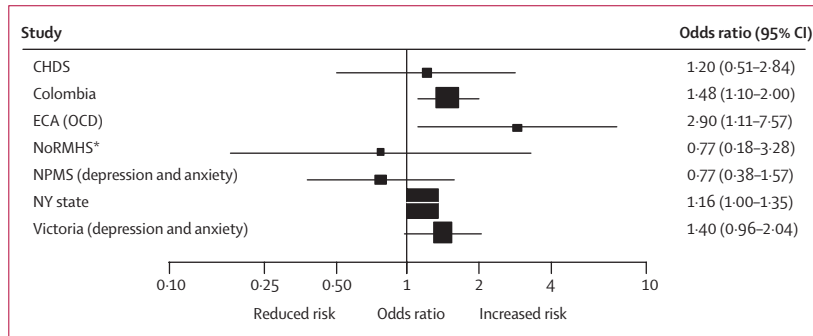
**Figure 4:** Forest plot showing adjusted odds ratios and 95% CI for depression outcomes according to most frequent use of cannabis in individual studies

Depression outcome measures: DSM diagnosis (CHDS, NY state); ICD-10 diagnosis (NoRMHS); DSM symptom lasting  $\geq 2$  weeks (ECA); CIS-R score  $\geq 12$  (NPMS, Victoria); and SCL-90 upper quartile (Colombia). Subgroup data from the Victoria study were incorporated as separate studies. \*Unadjusted results calculated from data in tables in the original study.<sup>44</sup> †Results for the heavy use category were calculated from results for linear trend across four categories of frequency of cannabis use.



**Figure 5:** Forest plot showing adjusted odds ratios and 95% CI for suicidal ideation according to cannabis exposure in individual studies

Cannabis exposure: ever used before age 16 (Baltimore); used  $>40$  occasions (Chicago); frequency of use (linear trend across frequency categories; CHDS); cannabis misuse disorder (ECA). \*Unadjusted results; subgroup data incorporated as separate studies.



**Figure 6:** Forest plot showing adjusted odds ratios and 95% CI for anxiety outcomes according to cannabis exposure in individual studies

Anxiety outcomes: DSM diagnosis (CHDS, ECA, NY state); ICD-10 diagnosis (NoRMHS); CIS-R score  $\geq 12$  (NPMS, Victoria); SCL-90 upper quartile (Colombia). Cannabis exposure: use in past year (ECA, NPMS); use less than once per week for the past 6 months (Victoria); use at least once per month (Colombia); frequency of use (linear trend across frequency categories; CHDS, NY state); cannabis disorder (NoRMHS). OCD=obsessive-compulsive disorder. \*Unadjusted results calculated from data in tables in the original study.<sup>44</sup>

	Attempt to limit reverse causation	Attempt to limit intoxication effects*	Approximate change from crude to adjusted OR (%)†
AddHealth <sup>47</sup>	Not reported. Assessed, but did not exclude or adjust, for baseline suicidal behaviour	Not reported	Only adjusted results presented
AddHealth <sup>48,‡</sup>	Excluded people with depression at baseline (CES-D score above threshold)	Not reported. Used CES-D to measure outcome	45% ↓
Baltimore <sup>49</sup>	Adjusted for childhood depression at age 8 years	Not reported. Used NIMH interview to measure outcome	40% ↓ to 60% ↑
Berkeley <sup>39</sup>	Not reported	Not reported. Used CES-D to measure outcome	Only crude results presented
CHDS <sup>35</sup>	Adjusted for anxiety and depression at baseline	Not reported. Used DIS and DISC to measure outcome	50–60% ↓
CHDS <sup>37</sup>	Adjusted for anxiety and depression at baseline	Not reported. Used DISC and CIDI to measure outcome	25% ↓
Chicago <sup>50</sup>	Not reported	Not reported	Only crude results presented
Columbia <sup>45</sup>	Adjusted for distress (anxiety and depression) at baseline	Not reported. Used SCL-90 to measure outcome	Only adjusted results presented
Dunedin <sup>38</sup>	Adjusted for baseline mental disorder	Not reported. Used DIS and DISC to measure outcome	93% ↓ for all mental disorders
Dunedin <sup>31</sup>	Not reported. Screened, but did not exclude or adjust, for depression at baseline	Not reported. Used DIS to measure outcome	Only adjusted results presented
ECA <sup>41</sup>	Excluded people with history of OCD at baseline	Not reported. Used DIS to measure outcome	215% ↑
ECA <sup>40</sup>	Excluded people with lifetime ever DSM-III-R symptoms of depression >2 weeks	Not reported. Used DIS and symptoms present most days for >2 weeks	10% ↓
LA schools <sup>51</sup>	Adjusted for previous emotional distress, including depression	Not reported. Used CES-D and HSC to measure outcome	Only adjusted results presented
LA schools <sup>52</sup>	Not reported	Not reported. Used CES-D to measure outcome	Only adjusted results presented
LAT <sup>53</sup>	Not reported. Assessed, but did not exclude or adjust, for baseline depressive symptoms	Adjusting for cannabis use at outcome made no difference to results. Used CES-D and CIDI to measure outcome	Only crude results presented
NoRMHS <sup>44</sup>	Not reported. Did not exclude or adjust for baseline measures	Not reported. Used CIDI to measure outcome	Only crude results presented
NPMSS	Excluded people with baseline CIS-R ≥12 Adjusted for CIS-R <12	Not reported. Used CIS-R to measure outcome	80–100% ↓
NY schools <sup>54</sup>	Results calculated by us are with exclusion of people with baseline depressive symptoms	Not reported. Used SCL to measure outcome	Only crude results presented
NY schools <sup>55</sup>	Adjusted for depression score at baseline	Not reported. Used HSC to measure outcome	Only adjusted results presented
NY state <sup>42</sup>	Adjusted for previous depression or anxiety	Not reported. Used DISC to measure outcome	Only adjusted results presented
NY state <sup>43</sup>	Adjusted for previous depression	Not reported. Used CIDI to measure outcome	Only adjusted results presented
Victoria <sup>46</sup>	Adjusted for previous depression and anxiety	Not reported. Used CIS-R to measure outcome	Up to 40% ↓

OR=odds ratio. CES-D=centre for epidemiological studies—depression scale. DIS=diagnostic interview schedule. DISC=diagnostic interview schedule for children. CIDI=composite international diagnostic interview. SCL-90=symptom checklist 90. OCD=obsessive-compulsive disorder. DSM-III-R=diagnostic and statistical manual of mental disorders, third edition, revised. CIS-R=clinical interview schedule—revised. HSC=Hopkins symptom checklist. ↓=decrease. ↑=increase. \*DIS, DISC, and CIDI potentially allow exclusion of intoxication effects, although none of the studies states explicitly that this was done. CES-D, CIS-R, HSC, and SCL do not allow attempts to exclude intoxication effects. †Change between crude OR and that after adjustment for confounding factors was calculated as (crude OR-adjusted OR)/(crude OR-1). ‡Additional data on crude and adjusted estimates were provided by the researchers. §Haynes J, personal communication.

**Table 2: Information on possible alternative causes for associations reported between cannabis use and affective outcomes in 15 cohorts**

There were single reports of interactions between cannabis use and age<sup>37</sup> and sex.<sup>46</sup> As with the results for psychosis, an interaction between cannabis use and COMT genotype was observed in the Dunedin cohort for depression, but not for anxiety.<sup>32</sup>

We assessed the quality of the studies included for affective outcomes by assessing the degree to which the potential effects of reverse causation, intoxication effects, and confounding factors were kept to a minimum within each study (table 2). Only four studies<sup>40,41,48</sup> (Haynes J, personal communication) excluded participants with affective symptoms at baseline. Ten reports<sup>35,37,38,42,43,45,46,49,51,55</sup> adjusted for the baseline measure of the outcome in the analyses but, as discussed earlier, this potentially mixes the effects of cannabis on incidence of affective outcome with those on symptom chronicity or relapse. In seven studies,<sup>31,39,44,47,50,52,53</sup> there was no exclusion of affected individuals or adjustment for baseline measures in the analyses. Three papers<sup>42,43,45</sup> from two cohorts reported that adjustment for baseline measures of the outcome had a negligible effect on results. Attempts to exclude intoxication effects were not explicitly mentioned in any of the 24 studies, although the questionnaires and interviews used for ten of these studies could have enabled raters to exclude symptoms attributed to drug intoxication.

About 50 different confounding factors were reported. Most of these were related to family and peer relationships, adverse life events, criminality, mental health problems, sociodemographic markers, and other substance use. Five studies<sup>39,44,50,53,54</sup> presented only unadjusted results, whereas one<sup>55</sup> made no mention of the confounding factors adjusted for.

For six of the eight studies in which both crude and adjusted results were presented, adjustment led to attenuation of associations with cannabis use, ranging from 10% to 100% reduction. Adjustment for a comprehensive set of confounding factors in the CHDS eliminated reasonably strong associations with depression, anxiety, and suicidal ideation,<sup>35</sup> although associations for depression persisted after adjustment in a longer follow-up of this cohort.<sup>37</sup> In one study of the Dunedin cohort,<sup>38</sup> adjustment for a more comprehensive set of confounding factors than in a more recent report<sup>31</sup> reduced the association between cannabis use and all mental disorders by 90%; however, effects specifically for affective outcomes were not presented. In the Baltimore study, both an increase in effect size for suicidal ideation and an attenuation of association with suicide attempts were observed following adjustment.<sup>49</sup>

Attrition from the studies included for affective outcomes ranged from 4%<sup>31</sup> to 70%,<sup>51</sup> with a median of 20%; loss to follow-up was not reported for two of the studies.<sup>39,45</sup> Cannabis use disorder at baseline was associated with increased attrition in NoRMHS, although weighting of the analyses to account for this made little difference to the results.<sup>44</sup> Attrition was associated with baseline alcohol use and disorganised thinking in the LA schools study,<sup>52</sup>

but was not associated with baseline substance use in the LAT study.<sup>33</sup> However, in the ECA study individuals with baseline depression and cannabis misuse were both more likely to be available for follow-up.<sup>40</sup>

## Discussion

We found a consistent increase in incidence of psychosis outcomes in people who had used cannabis. There was no statistical evidence of publication bias, although this finding was based on only seven studies. The pooled analysis revealed an increase in risk of psychosis of about 40% in participants who had ever used cannabis. However, studies tended to report larger effects for more frequent use, with most studies showing a 50–200% increase in risk for participants who used most heavily. A dose-response effect was observed in all studies that examined the relation to increasing cannabis exposure. Only three studies<sup>26,29,31</sup> examined psychotic disorders as an outcome; the presence of functional impairment makes these studies relevant to clinical practice. The results from these studies were also consistent with an increased risk in people who used cannabis.

Studies included in the pooled analyses used different methods to measure cannabis exposure and to assess outcome. For example, use of the symptom checklist 90 assessment in the CHDS<sup>34</sup> might have led to inclusion of participants without psychotic symptoms as defined in this review. This heterogeneity was reflected in the large *I*<sup>2</sup> values for some of the pooled results. The features of NEMESIS<sup>36</sup> that caused this study to increase between-study heterogeneity to a greater extent than the other studies are not clear, but heterogeneity decreased when this study was omitted from the sensitivity analyses, even though results were largely unchanged.



Arguments for why earlier use of cannabis might have more harmful effects are intuitively compelling, but no robust evidence supports this view. The increased risk of psychosis in people using cannabis from a younger age observed in the Dunedin cohort could indicate a greater cumulative exposure to cannabis rather than a sensitive period of exposure.<sup>31</sup> In the Swedish conscripts study, in which cumulative use of cannabis was examined, no difference in risk according to age at first use was observed.<sup>30</sup> Similarly, evidence for effect modification between cannabis use and *COMT* variation on psychosis risk is very weak; this effect was observed in only a subgroup of people within the Dunedin cohort,<sup>32</sup> and evidence for such an interaction in an experimental setting was also observed in only a subgroup of participants.<sup>56</sup>



Almost all studies reported an increased risk of affective outcomes in people who used cannabis, although CIs were generally consistent with null effects. However, effect sizes were small, and many studies were probably underpowered. For example, odds ratios for depression ranged from 1.3 to 1.6 for the highest exposure categories of weekly or monthly cannabis use, with one exception (the ECA study of cannabis misuse disorder).<sup>40</sup>

An association seen in an observational study does not necessarily reflect a causal relation. Because most of the studies for psychosis excluded people with psychosis at baseline, the observed associations are unlikely to reflect reverse causation. However, the majority of studies for affective outcomes did not adequately address the problem of reverse causation as a possible alternative explanation for any association observed. For cannabis and psychosis, there was evidence of confounding effects, but the associations persisted in almost all studies, even after adjustment for comprehensive lists of variables, including markers of premorbid disturbances that are commonly observed in patients with schizophrenia. All of the studies that reported an association for psychosis adjusted for other drug use, although two of the studies<sup>26,31</sup> made no adjustment for alcohol use. Furthermore, three studies<sup>25,26,31</sup> for psychosis made no adjustment for other mental health disorders at baseline, and measures of disorders adjusted for in the other studies<sup>24,25,29,34</sup> are unlikely to have accurately captured all mental health symptoms at baseline given the scope of the assessment tools generally used.

Residual confounding by these or other factors can never be eliminated from observational studies. Adjustment for confounding factors in studies of affective outcomes seemed to be more important than in studies of psychotic outcomes, and in some studies such adjustment explained all the observed association. There was also more variation for affective outcomes than for psychosis, with increases in crude estimates reported in two studies.<sup>41,49</sup> Furthermore, roughly half the studies made no adjustment for alcohol or other drug use. Confounding factors seem more likely to explain the reported association between cannabis and affective outcomes than that between cannabis and psychosis.

Most studies of psychosis made some attempt to reduce the chance that the outcome examined was due directly to effect of intoxication with cannabis, although this can be a difficult judgment in people who use cannabis frequently. Misdiagnosis as cannabis intoxication was unlikely in the Swedish conscripts study,<sup>29</sup> in which the outcome was admission to hospital with schizophrenia, or in the Dunedin cohort,<sup>31</sup> in which the outcome was presence of schizophreniform symptoms for longer than 1 month. The possibilities of intoxication and withdrawal effects were not considered in any of the studies of affective outcomes, although both of these can result from cannabis consumption.<sup>7,57</sup>

We would expect both confounding factors and intoxication to lead to an increase in the observed association. However, underestimation of effects could also have occurred. Measurement of cannabis use is especially difficult because there is almost certainly large variation in biologically available cannabinoid concentrations, resulting from different sources of cannabis and from different intake practices; self-reported frequency of use is also prone to error. Such misclassification, if ran-

	Review type	Methods	Studies included in review	Meta-analysis
Semple et al <sup>19</sup>	Systematic review of cannabis use and psychosis	Search strategy specified databases, search terms used, and dates of search Stated criteria for inclusion of studies Did not assess study quality Did not provide statement of compliance with MOOSE guidelines	Cross-sectional and longitudinal studies of high-risk groups	Included cross-sectional and longitudinal data Results from this meta-analysis are not consistent with our results; however, use of unadjusted estimates in this meta-analysis, and combining effects for ever-use of cannabis with those for dependence, makes it difficult to compare directly with our findings
Macleod et al <sup>18</sup>	Systematic review of cannabis and other illicit drugs and psychological and social harm	Search strategy specified databases, search terms used, and dates Stated criteria for inclusion of studies Assessed study quality Did not provide statement of compliance with MOOSE guidelines	Longitudinal studies Examined several broad psychosocial outcomes, one of which was psychological problems	None
Arseneault et al <sup>15</sup>	Narrative review of cannabis and psychosis	Search strategy specified databases searched, but not search terms used or dates of search Stated criteria for inclusion of studies Did not describe methods used to assess study quality	Cross-sectional and longitudinal, although results were reported separately	Meta-analysis was of longitudinal studies only. Included duplication of Swedish conscript data and one stratum of subgroup data for the Dunedin study. Combination of effects for ever-use of cannabis with those for dependence makes it difficult to compare with our findings
Henquet et al <sup>17</sup>	Narrative review of cannabis and psychosis	Did not describe search strategy Did not state criteria for inclusion of studies Did not describe methods used to assess study quality	Cross-sectional and longitudinal	Included cross-sectional and longitudinal data Combination of effects for ever-use of cannabis with those for dependence makes it difficult to compare with our findings

Table 3: Summary of previously published systematic reviews or narrative reviews with meta-analyses

dom, would usually make detection of an association more difficult. However, differential misclassification could lead to overestimates of association. For example, stimulant use is more common in people who use cannabis than in those who do not, so under-reporting of stimulant use might differentially affect the results from cannabis users.



Attrition in cohort studies is more likely in people who use drugs and in those who develop mental health problems than in other participants,<sup>38,39</sup> and this would also lead to underestimates of association. Evidence for such a pattern of attrition was present in NoRMHS<sup>44</sup> and the LA schools study.<sup>52</sup> In the ECA study,<sup>40</sup> participants with baseline depression were more likely to remain in the study, although pattern of loss in relation to incident depression is unknown. The extent to which such bias would affect the results is unclear, although modelling for attrition in CHDS,<sup>34</sup> NEMESIS,<sup>26</sup> and NoRMHS<sup>44</sup> suggests that bias caused by attrition had little effect on the overall findings.

Recent estimates of the proportion of adolescents and young adults in the UK who have ever used cannabis are around 40%.<sup>2</sup> If having ever used cannabis increases risk of a psychotic outcome by 1.4 times (as suggested from the pooled analysis), we can estimate that about 14% (95% CI 7–19) of psychotic outcomes in young adults currently in the UK would not occur if cannabis were not consumed. However, such estimates rely heavily on the assumption that the association between cannabis use and psychosis is causal, and that the pooled relative risk is an accurate estimate of this causal effect.



Projected trends for schizophrenia incidence have not paralleled trends in cannabis use over time, and this apparent mismatch has been used as an argument against causal effects.<sup>60</sup> However, other projections suggest that time lags and a lack of reliable incidence

data might mean that changes in schizophrenia incidence are not yet fully apparent.<sup>61</sup>

Even seemingly robust findings from observational studies have sometimes not been confirmed by RCTs.<sup>62</sup> However, in some situations RCTs are not feasible, and reliance must be placed on interpretation of results from the best available evidence from observational studies.<sup>63</sup> The neurobiological sequelae of cannabis use, including modulated activity of dopaminergic, GABAergic, and glutamatergic neurons,<sup>64–66</sup> are consistent with abnormalities described in people with psychotic disorders.<sup>67</sup> Furthermore, evidence that cannabis can produce transient psychotic and mood-altering symptoms in experimental studies<sup>7–10</sup> lends support to a causal explanation for the associations between cannabis use and more chronic psychotic and affective disorders.

We are not aware of any other systematic reviews that focus on the relation between cannabis and affective outcomes. A previous systematic review of cannabis use and psychosis included cross-sectional studies and did not address study quality.<sup>19</sup> Another systematic review examined broader psychosocial outcomes,<sup>18</sup> but the lack of focus specifically on psychotic or affective disorders meant that the explanations for associations could not be examined in detail. Previous meta-analyses from both systematic<sup>19</sup> and narrative<sup>15,17</sup> reviews (table 3) have included cross-sectional data<sup>17,19</sup> or used unadjusted results,<sup>19</sup> and combined effects for ever-use of cannabis with those for dependence.<sup>15,17,19</sup> As might be expected, all report larger effects than observed in this study, although direct comparison of these effects with our findings is difficult.

There are potential problems with meta-analyses of observational data.<sup>68</sup> However, we applied robust methods to identify as many publications as we could, and attempted to interpret the findings as appropriately as possible by including a thorough critique of individual





studies, and by doing a comprehensive assessment of alternative explanations for associations reported.

Even if the methods of future longitudinal studies are more robust, these studies are likely to encounter similar limitations to those discussed here. However, improvement in the measurement of cannabis exposure and elimination of intoxication effects might reduce some of the uncertainty. Animal models of long-term effects of cannabis on neuropsychological domains relevant to psychotic or affective states could also improve knowledge.<sup>69</sup> Further study is needed to establish whether cannabis is more harmful in younger age groups, and whether risk is modified by genetic or other factors. **The question of whether cannabis causes psychotic or affective disorders is perhaps the wrong one to be asking, because it will be difficult to answer with any degree of certainty. What is more pertinent is whether the evidence that is now available can justify policy implications, such as public education campaigns to alert people to the possible risks associated with cannabis.**

In conclusion, we have described a consistent association between cannabis use and psychotic symptoms, including disabling psychotic disorders. The possibility that this association results from confounding factors or bias cannot be ruled out, and these uncertainties are unlikely to be resolved in the near future. Despite the inevitable uncertainty, policymakers need to provide the public with advice about this widely used drug. **We believe that there is now enough evidence to inform people that using cannabis could increase their risk of developing a psychotic illness later in life.** The evidence that cannabis use leads to affective outcomes is less strong than for psychosis but is still of concern. Although individual lifetime risk of chronic psychotic disorders such as schizophrenia, even in people who use cannabis regularly, is likely to be low (less than 3%), cannabis use can be expected to have a substantial effect on psychotic disorders at a population level because exposure to this drug is so common.

#### Contributors

GL secured funding for the study. MB, SZ, GL, and THMM participated in designing of search strategies and undertook searches. THMM, SZ, AL-H, TREB, PBJ, and GL participated in screening of search results and retrieved papers. THMM, SZ, and GL extracted data and appraised quality of papers. THMM and SZ analysed data. THMM, SZ, AL-H, TREB, PBJ, and GL interpreted data. THMM coordinated the review and managed data. THMM and SZ co-wrote the review. AL-H, TREB, PBJ, MB, and GL edited and refined the review. All authors saw and approved the final version of the report.

#### Conflict of interest statement

PBJ and TREB were both invited experts on the Advisory Council on the Misuse of Drugs Cannabis Review in 2005. SZ, PBJ, TJ, GL, and AL-H have received honoraria for lectures and talks or consultancy fees (for work unrelated to cannabis) from pharmaceutical companies. AL-H has received an honorarium from Sanofi-Aventis for attending a meeting about cannabinoid antagonists, and has received consultancy fees from Bristol Myers Squibb and unrestricted research monies from Merck. TREB has received consultancy fees from Servier, Johnson & Johnson, and Bristol-Myers Squibb regarding antipsychotic medication. THMM and MB have no conflicts of interest.

#### Acknowledgments

We thank Helen Davies for assistance with the retrieval of papers, and the authors of the papers we considered for inclusion and the experts we contacted for assistance with the search for suitable papers—Louisa Degenhardt, Wayne Hall, Jonathan Haynes, Robert Ferdinand, John Macleod, Robert Pandina, Robin Murray, Jean Paul Selten, Jim van Os, Helene Verdoux, and Mark Weiser. We also thank Louise Arseneault, David Fergusson, and David Pevalin for providing us with data from additional analyses for our review. This work was funded by the Department of Health, UK. SZ is funded through a Clinician Scientist Award funded by the National Assembly for Wales.

#### References

- 1 NSDUH. Results from the 2004 National Survey on Drug Use and Health: national findings. Rockville: Substance Abuse and Mental Health Services Administration, 2005.
- 2 EMCDDA. The state of the drugs problem in Europe: annual report 2005. European Monitoring Centre for Drugs and Drug Addiction, 2005.
- 3 WHO. Cannabis: a health perspective and research agenda. World Health Organization, 1997.
- 4 Webb E, Ashton CH, Kelly P, Kamali F. Alcohol and drug use in UK university students. *Lancet* 1996; **348**: 922–25.
- 5 Fergusson DM, Horwood LJ. Cannabis use and dependence in a New Zealand birth cohort. *N Z Med J* 2000; **113**: 156–58.
- 6 Schneider M, Koch M. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. *Neuropsychopharmacology* 2003; **28**: 1760–69.
- 7 D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004; **29**: 1558–72.
- 8 Isbell H, Gorodetzky CW, Jasinski D, Claussen U, von Spulak F, Korte F. Effects of (-)-delta-9-trans-tetrahydrocannabinol in man. *Psychopharmacologia* 1967; **11**: 184–88.
- 9 Melges FT, Tinklenberg JR, Deardorff CM, Davies NH, Anderson RE, Owen CA. Temporal disorganization and delusional-like ideation. Processes induced by hashish and alcohol. *Arch Gen Psychiatry* 1974; **30**: 855–61.
- 10 Renault PF, Schuster CR, Freedman DX, Sivic B, de Mello DN. Repeat administration of marijuana smoke to humans. *Arch Gen Psychiatry* 1974; **31**: 95–102.
- 11 Keeler MH. Marijuana induced hallucinations. *Dis Nerv Syst* 1968; **29**: 314–15.
- 12 Tart CT. Marijuana intoxication common experiences. *Nature* 1970; **226**: 701–04.
- 13 Thomas H. A community survey of adverse effects of cannabis use. *Drug Alcohol Depend* 1996; **42**: 201–07.
- 14 RCP. Cannabis and cannabis-based medicines. London: Royal College of Physicians, 2005.
- 15 Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. *Br J Psychiatry* 2004; **184**: 110–17.
- 16 Degenhardt L, Hall W, Lynskey M. Exploring the association between cannabis use and depression. *Addiction* 2003; **98**: 1493–504.
- 17 Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. *Schizophr Bull* 2005; **31**: 608–12.
- 18 Macleod J, Oakes R, Copello A, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet* 2004; **363**: 1579–88.
- 19 Semple DM, McIntosh AM, Lawrie SM. Cannabis as a risk factor for psychosis: systematic review. *J Psychopharmacol* 2005; **19**: 187–94.
- 20 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.
- 21 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–58.
- 22 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.

- 23 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–12.
- 24 Tien AY, Anthony JC. Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. *J Nerv Ment Dis* 1990; **178**: 473–80.
- 25 Henquet C, Krabbendam L, Spauwen J, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ* 2005; **330**: 11.
- 26 van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol* 2002; **156**: 319–27.
- 27 Wiles NJ, Zammit S, Bebbington P, Singleton N, Meltzer H, Lewis G. Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British national psychiatric morbidity survey. *Br J Psychiatry* 2006; **188**: 519–26.
- 28 Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet* 1987; **2**: 1483–86.
- 29 Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ* 2002; **325**: 1199.
- 30 Zammit S. An investigation into the use of cannabis and tobacco as risk factors for schizophrenia. PhD thesis, Cardiff University, 2004.
- 31 Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 2002; **325**: 1212–13.
- 32 Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol Psychiatry* 2005; **57**: 1117–27.
- 33 Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. *Psychol Med* 2003; **33**: 15–21.
- 34 Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. *Addiction* 2005; **100**: 354–66.
- 35 Fergusson DM, Lynskey MT, Horwood LJ. The short-term consequences of early onset cannabis use. *J Abnorm Child Psychol* 1996; **24**: 499–512.
- 36 Fergusson DM, Horwood LJ. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* 1997; **92**: 279–96.
- 37 Fergusson DM, Horwood LJ, Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* 2002; **97**: 1123–35.
- 38 McGee R, Williams S, Poulton R, Moffitt T. A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction* 2000; **95**: 491–503.
- 39 Block JH, Gjerde PF. Personality antecedents of depressive tendencies in 18-year-olds: a prospective study. *J Pers Soc Psychol* 1991; **60**: 726–38.
- 40 Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. *Am J Psychiatry* 2001; **158**: 2033–37.
- 41 Crum RM, Anthony JC. Cocaine use and other suspected risk factors for obsessive-compulsive disorder: a prospective study with data from the epidemiologic catchment area surveys. *Drug Alcohol Depend* 1993; **31**: 281–95.
- 42 Brook JS, Cohen P, Brook DW. Longitudinal study of co-occurring psychiatric disorders and substance use. *J Am Acad Child Adolesc Psychiatry* 1998; **37**: 322–30.
- 43 Brook DW, Brook JS, Zhang C, Cohen P, Whiteman M. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. *Arch Gen Psychiatry* 2002; **59**: 1039–44.
- 44 Beard JR, Dietrich UC, Brooks LO, Brooks RT, Heathcote K, Kelly B. Incidence and outcomes of mental disorders in a regional population: the Northern Rivers Mental Health Study. *Aust N Z J Psychiatry* 2006; **40**: 674–82.
- 45 Brook JS, Rosen Z, Brook DW. The effect of early marijuana use on later anxiety and depressive symptoms. *NYS Psychologist* (New York), January 2001; 35–40.
- 46 Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W. Cannabis use and mental health in young people: cohort study. *BMJ* 2002; **325**: 1195–98.
- 47 Borowsky IW, Ireland M, Resnick MD. Adolescent suicide attempts: risks and protectors. *Pediatrics* 2001; **107**: 485–93.
- 48 Wade TJ, Pevalin DJ. Adolescent delinquency and health. *Can J Criminol Crim Just* 2005; **47**: 619–54.
- 49 Wilcox HC. The development of suicide ideation and attempt: an epidemiologic study of first graders followed into young adulthood. PhD thesis, John Hopkins University, 2003.
- 50 Juon HS, Ensminger ME. Childhood, adolescent, and young adult predictors of suicidal behaviors: a prospective study of African Americans. *J Child Psychol Psychiatry* 1997; **38**: 553–63.
- 51 Newcomb MD, Scheier LM, Bentler PM. Effects of adolescent drug use on adult mental health: a prospective study of a community sample. *Exp Clin Psychopharmacol* 1993; **1**: 215–41.
- 52 Newcomb MD, Vargas-Carmona J, Galaif ER. Drug problems and psychological distress among a community sample of adults: predictors, consequences, or confound? *J Commun Psychol* 1999; **27**: 405–29.
- 53 Windle M, Wiesner M. Trajectories of marijuana use from adolescence to young adulthood: predictors and outcomes. *Dev Psychopathol* 2004; **16**: 1007–27.
- 54 Paton S, Kessler R, Kandel D. Depressive mood and adolescent illicit drug use: a longitudinal analysis. *J Genet Psychol* 1977; **131**: 267–89.
- 55 Kandel DB, Davies M. Adult sequelae of adolescent depressive symptoms. *Arch Gen Psychiatry* 1986; **43**: 255–62.
- 56 Henquet C, Rosa A, Krabbendam L, et al. An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* 2006; **31**: 2748–57.
- 57 Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. *Addiction* 2002; **97**: 621–32.
- 58 Allott K, Chanen A, Yuen HP. Attrition bias in longitudinal research involving adolescent psychiatric outpatients. *J Nerv Ment Dis* 2006; **194**: 958–61.
- 59 Fischer EH, Dornelas EA, Goethe JW. Characteristics of people lost to attrition in psychiatric follow-up studies. *J Nerv Ment Dis* 2001; **189**: 49–55.
- 60 Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend* 2003; **71**: 37–48.
- 61 Hickman M, Vickerman P, Macleod J, Kirkbride J, Jones PB. Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales. *Addiction* 2007; **102**: 597–606.
- 62 Smith GD, Ebrahim S. Data dredging, bias, or confounding. *BMJ* 2002; **325**: 1437–38.
- 63 Wald DS, Wald NJ, Morris JK, Law M. Folic acid, homocysteine, and cardiovascular disease: judging causality in the face of inconclusive trial evidence. *BMJ* 2006; **333**: 1114–17.
- 64 Chen J, Marmor R, Pulles A, Paredes W, Gardner EL. Ventral tegmental microinjection of delta 9-tetrahydrocannabinol enhances ventral tegmental somatodendritic dopamine levels but not forebrain dopamine levels: evidence for local neural action by marijuana's psychoactive ingredient. *Brain Res* 1993; **621**: 65–70.
- 65 Pistis M, Ferraro L, Pira L, et al. Delta(9)-tetrahydrocannabinol decreases extracellular GABA and increases extracellular glutamate and dopamine levels in the rat prefrontal cortex: an in vivo microdialysis study. *Brain Res* 2002; **948**: 155–58.
- 66 Rodriguez de Fonseca F, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M. The endocannabinoid system: physiology and pharmacology. *Alcohol Alcohol* 2005; **40**: 2–14.
- 67 Heresco-Levy U. Chapter XVII-3: Amino acid transmitter systems. In: D'haenen HAH, den Boer JA, Willner P, eds. *Biological psychiatry*. Chichester: Wiley, 2002: 587–600.
- 68 Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998; **316**: 140–44.
- 69 O'Shea M, McGregor IS, Mallet PE. Repeated cannabinoid exposure during perinatal, adolescent or early adult ages produces similar longlasting deficits in object recognition and reduced social interaction in rats. *J Psychopharmacol* 2006; **20**: 611–21.