Testing hypotheses about the relationship between cannabis use and psychosis

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Abstract

Aim: To model the impact of rising rates of cannabis use on the incidence and prevalence of psychosis under four hypotheses about the relationship between cannabis use and psychosis. *Methods:* The study modelled the effects on the prevalence of schizophrenia over the lifespan of cannabis in eight birth cohorts: 1940–1944, 1945–1949, 1950–1954, 1955–1959, 1960–1964, 1965–1969, 1970–1974, 1975–1979. It derived predictions as to the number of cases of schizophrenia that would be observed in these birth cohorts, given the following four hypotheses: (1) that there is a causal relationship between cannabis use and schizophrenia; (2) that cannabis use precipitates schizophrenia in vulnerable persons; (3) that cannabis use exacerbates schizophrenia; and (4) that persons with schizophrenia are more liable to become regular cannabis users. *Results:* There was a steep rise in the prevalence of cannabis use in Australia over the past 30 years and a corresponding decrease in the age of initiation of cannabis use. There was no evidence of a significant increase in the incidence of schizophrenia over the past 30 years. Data on trends the age of onset of schizophrenia did not show a clear pattern. Cannabis use among persons with schizophrenia has consistently been found to be more common than in the general population. *Conclusions:* Cannabis use does not appear to be causally related to the incidence of schizophrenia, but its use may precipitate disorders in persons who are vulnerable to developing psychosis and worsen the course of the disorder among those who have already developed it.

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1. Introduction

Clinical research has shown that high proportions of persons with schizophrenia report regular cannabis use and meet criteria for cannabis use disorders (Fowler et al., 1998; Mueser et al., 1990; Ziedonis and Trudeau, 1997). Epidemiological studies have also found an association between cannabis use and psychosis in the general population (Anthony and Helzer, 1991; Cuffel et al., 1993; Degenhardt and Hall, 2001; Tien and Anthony, 1990).

There has been considerable debate about the reasons for this association (Batel, 2000; Blanchard et al., 2000; Gruber and Pope, 1994; Hall, 1998; Hall and Degenhardt, 2000; McKay and Tennant, 2000; Mueser et al., 1998; Rosenthal, 1998; Thornicroft, 1990). Depending upon the nature of the relationship between cannabis use and psychosis, changes in the prevalence of cannabis use may potentially lead to changes in the incidence, prevalence or age of onset of psychosis.

In Australia, there has been a dramatic increase in the prevalence of cannabis use since the early 1970s (Degenhardt et al., 2000; Donnelly and Hall, 1994; Makkai and McAllister, 1998; McCoy, 1980). The present report assesses the evidence for four hypothesised relationships between cannabis use and psychosis, which would each predict different effects of increased cannabis use on the incidence, prevalence and age of onset of schizophrenia and the prevalence of chronic cannabis use among persons with the disorder.

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1.1. Hypothesis 1: Cannabis use causes psychosis

According to this hypothesis there is a causal link between cannabis use and schizophrenia in the sense that cannabis use causes cases of the disorder that would not otherwise have occurred. This hypothesis has arisen from reports of 'cannabis psychoses' (Basu et al., 1999; Bernardson and Gunne, 1972; Carney et al., 1984; Chopra and Smith, 1974; Eva, 1992; Solomons et al., 1990; Tennant and Groesbeck, 1972; Wylie et al., 1995) and there is some evidence that cannabis users are more likely to report psychotic symptoms (e.g. Andreasson et al., 1987; Degenhardt and Hall, 2001; Tien and Anthony, 1990).

If this hypothesis is correct, then an increase in prevalence of cannabis use among young adults should increase the incidence and ultimately the prevalence of schizophrenia. Since there has been a dramatic rise in the prevalence of cannabis use in Australia, this hypothesis predicts an increase in the greater number of cases of schizophrenia among recent birth cohorts. Since the age of cannabis initiation has also declined, this hypothesis also predicts that the age of onset of schizophrenia would decline in recent birth cohorts. This hypothesis also predicts a rising prevalence of cannabis use among persons with schizophrenia.

1.2. Hypothesis 2: Cannabis use precipitates psychosis among vulnerable individuals

A second hypothesis is that regular cannabis use precipitates schizophrenia *among vulnerable individuals*, that is, among persons who would have developed the disorder regardless of whether they used cannabis or not (Hall, 1998). This is supported by evidence that: (a) persons with first-episode schizophrenia who use cannabis are younger than those who do not (Linszen et al., 1994; Mathers et al., 1991; Rolfe et al., 1993); (b) cannabis use usually precedes the development of psychotic symptoms (Allebeck et al., 1993; Hambrecht and Haefner, 2000; Linszen et al., 1994); and (c) among first-episode cases of psychosis, those who used cannabis were more likely to have a family history of psychosis (McGuire et al., 1995).

According to this hypothesis, an increase in regular cannabis use in the general population would not affect the incidence of schizophrenia but it would reduce the age of onset of psychotic illness among those who used cannabis. That is, the incidence rates of persons using cannabis would be 'brought forward'. If this led to more chronic psychotic disorders (e.g. because earlier onset cases are more likely to relapse) the prevalence of chronic cases of psychosis would increase. This would increase the prevalence of regular cannabis use among persons with schizophrenia.

1.3. Hypothesis 3: Cannabis use worsens the prognosis of persons with schizophrenia

According to this hypothesis, cannabis use would worsen the prognosis of schizophrenic persons by increasing *relapse* to schizophrenia. It is supported by evidence that persons with schizophrenia who use cannabis are more likely to suffer a relapse (Jablensky et al., 1991; Linszen et al., 1994). This hypothesis does not predict an increased incidence of schizophrenia among regular cannabis users. Instead, it predicts that persons with schizophrenia who are regular cannabis users will be more likely to have a relapse after their initial episode. This could increase the number of persons in the population with chronic schizophrenia. It would not affect the age of onset of psychosis. The prevalence of cannabis use among persons with schizophrenia would increase because there would be more cannabis users among chronic cases.

1.4. Hypothesis 4: Regular cannabis use is more likely among persons with psychosis

According to this hypothesis, persons with schizophrenia are more likely to become regular cannabis users, if they use the drug (Mueser et al., 1998). There is no causal relationship between cannabis use and psychosis, so increasing rates of cannabis use will have no effect upon the incidence or prevalence of schizophrenia and there would not be a change in age of onset. There would be an increased prevalence of cannabis use among persons with psychosis.

The predictions generated from each of these four hypotheses are summarised in Table 1; notably, each hypothesis has a unique set of predictions. We used mathematical modelling to assess the plausibility of these four hypotheses. We combined empirically derived information about the epidemiology of cannabis use and psychosis to predict trends in incidence, prevalence and age of onset of schizophrenia according to each of these hypotheses. These *predicted* trends were compared with evidence on *observed* trends in schizophrenia and cannabis use.

2. Method

2.1. Parameters for schizophrenia

2.1.1. Incidence

It was assumed that schizophrenia does not develop before the age of 15 years (Goldstein et al., 1984), and that new cases do not occur after the age of 54 years (Goldstein et al., 1984). Separate specific incidence rates were used for males and females because males have an earlier onset of schizophrenia on average than females

Table 1
Predicted trends in schizophrenia, and in cannabis use among persons with schizophrenia, given an increase in the prevalence of regular cannabis use in the general population

	Trends in schizophrenia			Trends in cannabis use
	Incidence	Prevalence	Age of onset	Prevalence among those with schizophrenia
(1) Causal	↑	↑	↓	↑
(2) Precipitation	→	↑	↓	↑
(3) Worse prognosis	→	↑	→	↑
(4) Increased risk of dependence	→	→	→	↑

Note: → = no change; ↑ = increase; ↓ = decrease.

(Jablensky et al., 1991; Jones and Cannon, 1998). Estimates of the average incidence rate of schizophrenia per 100 000 population per year by age and gender were obtained from a case register in New South Wales, Australia (Goldstein et al., 1984) that covered a period when cannabis was not widely used in Australia (Donnelly and Hall, 1994).

2.1.2. Chronicity of schizophrenia

An earlier expert consensus view on the long-term outcomes of schizophrenia in Australia (Hall et al., 1985) was that: 25% of persons with schizophrenia would have a 'good' outcome (a single episode with 60 days in hospital); 40% would have a 'median' outcome (an average of 0.08 admissions to hospital per year for life); and 35% would have a 'poor' outcome (0.16 admission per year for life).

More recent evidence has supported the estimate that 25% of patients will not relapse after long follow-up periods (Eaton et al., 1992a,b; Mason et al., 1996). A number of other studies have found that relapse tends to be in the first few years after the initial episode, with rates levelling off afterwards (Carone et al., 1991; Eaton et al., 1992a,b; Mason et al., 1996). For the purposes of the present study, we assumed that over a period of 4 years, 75% of incident cases of schizophrenia will relapse and that 25% of cases will have a 'good' outcome (Eaton et al., 1992a,b; Hall et al., 1985; Mason et al., 1996).

Relapse rates are higher for cases with an earlier age of onset (Eaton et al., 1992a,b). Studies using a case register in Victoria, Australia, found that persons with the earliest age of onset (15–19 age group) were most likely to relapse, with the following relative risks (compared to the 15–19 age group) for older age groups: 0.84 (20–29), 0.73 (30–39), 0.68 (40–49), 0.59 (50–59) (Eaton et al., 1992a,b). These data were used to predict the probability of relapse (assuming an overall relapse rate of 75%; Fig. 1).

2.1.3. Mortality in schizophrenia

A meta-analysis by Brown (1997) estimated that the aggregate crude mortality rate of schizophrenia was 189 deaths per 10 000 population per year. The population mortality rate was obtained from Australian Bureau of Statistics and the rate in the general population was assumed equal to the rate among non-schizophrenic persons. For males the average rate of death was nine per 10 000 males per year and for females it was five per 10 000 females per year.

2.2. Parameters for cannabis use

We examined the natural history of cannabis use because it changes during a person's lifetime. We therefore needed estimates of prevalence of cannabis use at each age over the life span of each of the birth cohorts. By combining the estimates of the cumulative lifetime prevalence of cannabis use with the pattern of persistence of cannabis use from the cohort study, we could estimate the number of people at each age in the birth cohort who were still using cannabis.

Data on lifetime patterns of cannabis use were obtained from two sources: a longitudinal study of the natural history of cannabis use (Chen and Kandel, 1995); and an analysis of birth cohorts trends in drug use (Degenhardt et al., 2000) derived from the Australian National Drug Strategy Household Survey (NDSHS).

2.2.1. Natural history of cannabis use

Data on *patterns* of cannabis use in a longitudinal study of cannabis use in the USA (Chen and Kandel, 1995) were used to estimate of the *prevalence* of monthly cannabis use in Australian birth cohorts using data on the lifetime prevalence of cannabis use in the 1998 NDSHS of the Australian population. The proportion using cannabis at least monthly for each birth cohort was estimated by multiplying the above rates by the ratio of the proportion of persons in the birth cohort who had used cannabis to the proportion in Chen and Kandel's cohort.

The modelling also took account of the substantial decline in the age of first cannabis use among successive birth cohorts in Australia (Degenhardt et al., 2000). The mean age of first reported use of cannabis has decreased
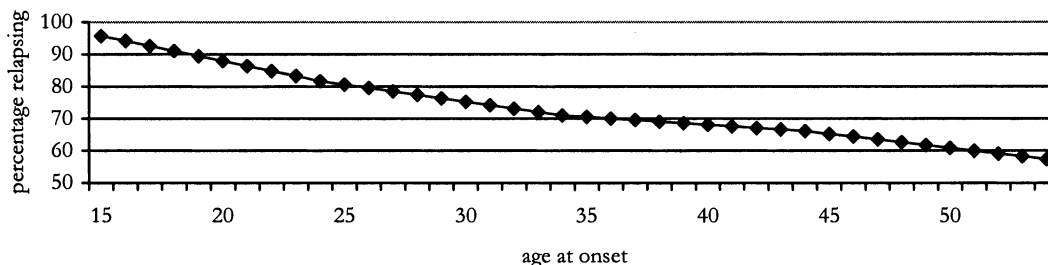
Fig. 1. Estimated percentage of cases of schizophrenia relapsing according to age of onset of first episode.

by approximately 2 years with each successive birth cohort. The following assumptions were made:

- that the curve for each birth cohort was that observed by Chen and Kandel (1995);
- that each of these curves moved to the left by 2 years for each successive birth cohort;
- that the absolute position of these curves could be estimated by anchoring the birth cohort that was the same as the cohort in Chen and Kandel's study (i.e. the 1955–1959 birth cohort). The peak periods of cannabis use for the 1965–1969, 1970–1974, 1975–1979 birth cohorts between were estimated to be between the ages of 15 and 20, compared to 17–22 years for the 1960–1964 birth cohort, 19–24 years for the 1955–1959 birth cohort and so on;
- that there were no differences between birth cohorts in the duration of monthly cannabis use. There were no good data on birth cohort trends in the peak period of use of cannabis, so this simpler assumption was made. It is likely to reduce differences between birth cohorts;
- it was assumed that the prevalence of weekly or more frequent cannabis use was half of the proportion reporting monthly or more frequent use.

2.2.2. Mortality of cannabis users

Our analyses assume that there was no increase in mortality among cannabis users. Research has failed to find increased mortality among cannabis using males aged 34–36 years, after adjusting for alcohol and other drug use (Andreasson and Allebeck, 1990) or among cannabis using males and females aged 15–49 years (Sidney et al., 1997) over 8 years of follow up.

Details of formulae used to generate the models and their predictions are provided in Appendix A.

2.3. Application to Australian population numbers

The size of each birth cohort (by gender) was estimated from data published by the Australian Bureau of Statistics on June 30th of each year. The cohort sizes were estimated from the number in each year of birth who were still alive at 15 years.

3. Results

3.1. Modelling the natural history of cannabis use

Fig. 2 shows the estimated natural history of cannabis use in each of the birth cohorts. The peak prevalence of regular cannabis use occurs earlier in recent birth cohorts while peak prevalence of weekly use was higher for earlier birth cohorts.

3.2. Modelling the prevalence of schizophrenia

Fig. 3 shows the estimated prevalence of schizophrenia among Australian males and females according to age. The prevalence of schizophrenia by age 54 was 1.17% for males, and 1.08% for females. This is at the higher end of the estimated prevalence of schizophrenia (Jablensky et al., 1991; Robins and Regier, 1991) but it corresponds to a point prevalence of schizophrenia in 1998 of 0.7% for the *population* born between 1940 and 1979. This is very similar to previous estimates of the population prevalence of schizophrenia (Jablensky et al., 2000, 1991; Robins and Regier, 1991).

3.3. Modelling the hypothesised relationships

3.3.1. Hypothesis 1: Causal relationship

On this hypothesis, the prevalence of schizophrenia by age 25 years is estimated to be 0.38% among those in the 1940–1944 birth cohort, compared to 0.43% in the 1975–1979 birth cohort. The difference of 0.05% is a 14% increase in prevalence. At age 20 years, the difference between the oldest and youngest birth cohorts in the number of cases of schizophrenia—caused by cannabis use—is 125 cases. The total would increase from 736 males aged 20 years in the 1940–1944 birth cohort, to 861 in the 1975–1979 birth cohort. This is an increase of 17% (between the calendar years 1960–1964 and 1995–2000) in the number of cases aged 20 years with schizophrenia coming to the attention of treatment services.

Table 2 shows these results in terms of the number of additional incident cases that would have occurred by age 35 years on this hypothesis. Among the more recent birth cohorts—those born from the 1960s and later—by
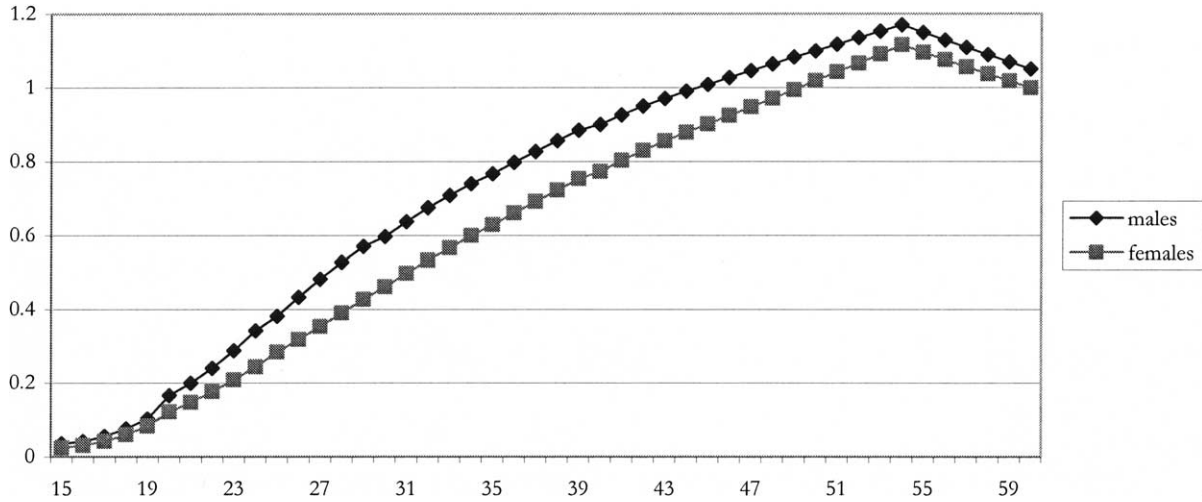
Fig. 2. Modelled prevalence of schizophrenia over the lifespan according to gender.

the time they were 35 years old, there would be an additional 1225–1438 cases of schizophrenia per birth cohort. This would be an increase in the number of incident cases of schizophrenia of around 10% for each birth cohort. The number of new cases in the later cohorts (1225 cases) is almost 10 times larger than those in the oldest birth cohort (180 additional cases).

3.3.2. Hypothesis 2: Cannabis precipitates schizophrenia among vulnerable individuals

Table 3 shows the number of cases in each birth cohort whose onset would occur a year earlier if cannabis use precipitated schizophrenia. The age at which this would have the most marked effect would be age 14, when the only incident cases would be among
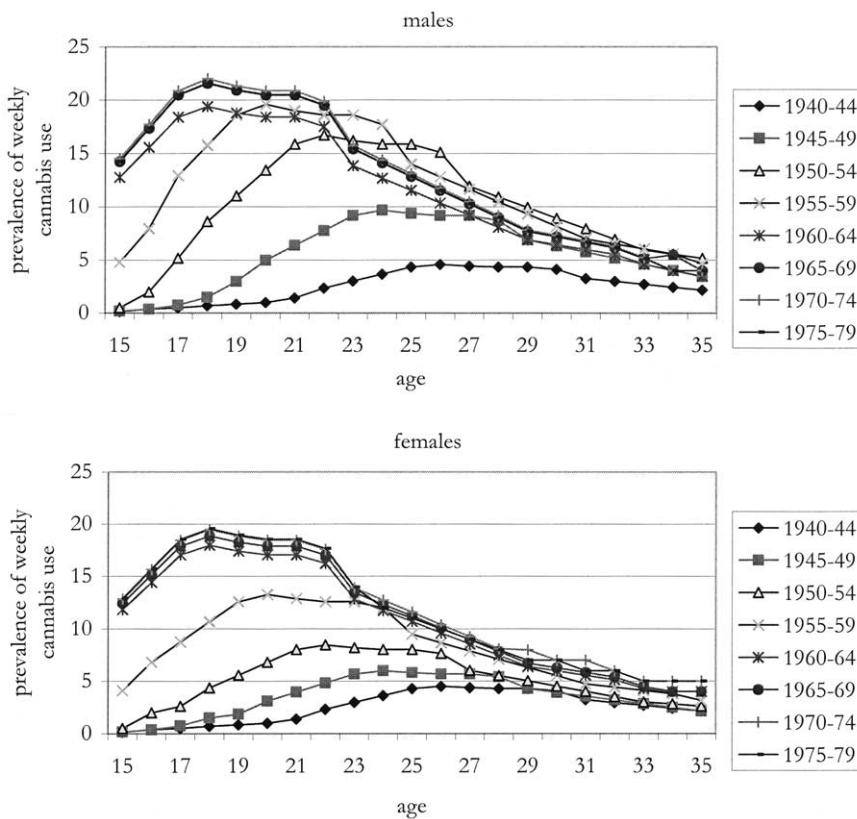

Fig. 3. Model of the natural history of cannabis use among Australian males and females by birth cohort.

Table 2
Hypothesis 1—Modelled number of incident cases of psychosis by 35 years caused by cannabis use by the age of 35 years, by gender and birth cohort

	Total incident cases by 35 years assuming no link		Total incident cases by 35 years if cannabis use caused psychosis		Number of incident cases by 35 years caused by cannabis	
	Males	Females	Males	Females	Males	Females
1940–44	3891	2898	3990	2979	99	81
1945–49	5444	3903	5759	4051	315	147
1950–54	5870	4380	6482	4613	612	233
1955–59	6572	4896	7373	5289	801	387
1960–64	7181	5301	7984	5831	803	511
1965–69	6995	5197	7768	5748	773	532
1970–74	7625	5664	8480	6268	856	582
1975–79	6948	5128	7689	5631	742	483

Table 3
Hypothesis 2—Modelled number of additional cases that would be precipitated 1 year earlier by cannabis use by gender and birth cohort

	Cases precipitated at 14 years		Cases precipitated at 19 years	
	Males	Females	Males	Females
1940–1944	0.2	0.01	2	0.5
1945–1949	0.4	0.05	13	2
1950–1954	1	0.07	32	5
1955–1959	10	1	46	13
1960–1964	31	16	44	19
1965–1969	49	16	44	20
1970–1974	54	18	49	22
1975–1979	48	17	44	20

Table 4
Hypothesis 3—Modelled number of additional chronic cases of psychosis due to cannabis use observed by the age of 35 years, by gender and birth cohort

	Additional chronic cases by age 35 years	
	Males	Females
1940–44	12	10
1945–49	38	17
1950–54	68	25
1955–59	82	39
1960–64	77	49
1965–69	70	50
1970–74	76	54
1975–79	63	43

cannabis users, and at age 19, when persons using cannabis regularly have higher incidence rates. In the 1940–1944 cohort, less than one case would have been precipitated at age 14 years whereas this would rise to 50 cases by age 14 among the younger male cohorts.

3.3.3. Hypothesis 3: Cannabis worsens prognosis

According to the hypothesis that cannabis use worsens prognosis, there would be an additional 106–130 chronic cases of schizophrenia caused by cannabis use by age of 35 years in the more recent birth cohorts (Table 4). However, these would comprise only 1% of all chronic cases by this age. This is because relapse rates among young adults were already very high so most cases would relapse regardless of whether they used cannabis use or not.

3.3.4. Hypothesis 4: Regular cannabis use is more likely among persons with psychosis

Fig. 4 shows the predicted prevalence of weekly cannabis use among persons with schizophrenia if such persons are twice as likely as those in the general population to become weekly users if they use cannabis in the past year. The prevalence of weekly cannabis use

increases markedly among successive birth cohorts: among males 5% of those aged 20 years, among the 1940–1944 birth cohort would report weekly cannabis use, compared to over 40% of those born after 1965. A similar pattern is observed among females with schizophrenia.

3.4. Evaluation of the four hypotheses

The sections below discuss the available data on trends in the incidence and prevalence of psychosis, in the age of onset of psychosis, and in the prevalence of cannabis use among persons with psychosis; and compare these data with the predictions of the four hypotheses. Table 5 summarises the results of these comparisons.

3.4.1. Trends in the incidence of psychosis

Numerous studies conducted in many countries, including Australia (Parker et al., 1985), have reported *declines* in the incidence of schizophrenia over the past 30 years (Eagles and Whalley, 1985; Geddes et al., 1993; Joyce, 1987; Kendell et al., 1993; Munk-Jorgensen, 1995; Munk-Jorgensen and Mortensen, 1992; Suvisaari
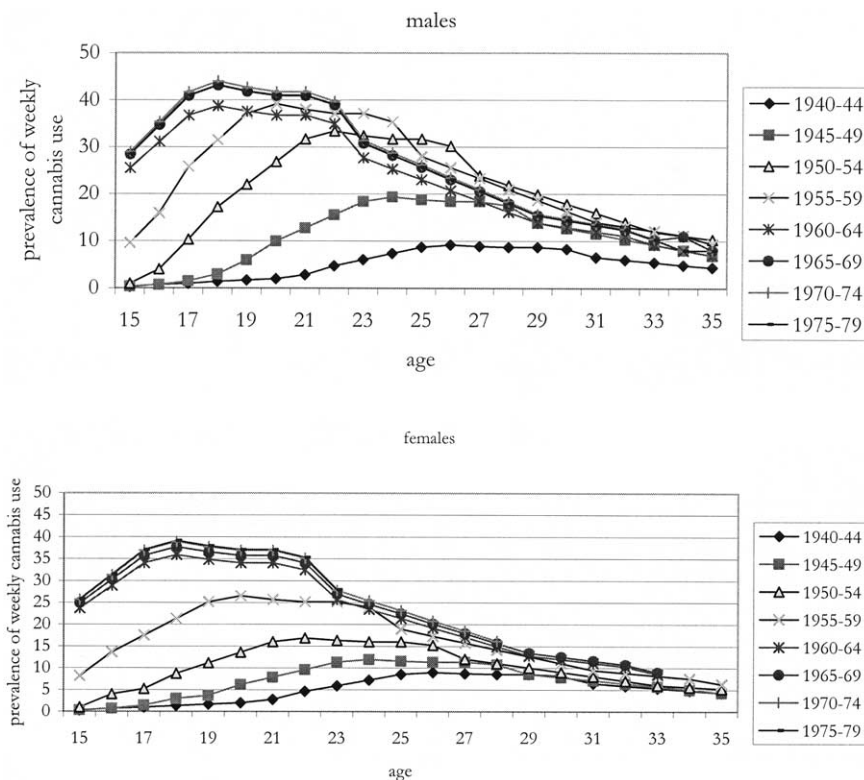
males

females

Fig. 4. Hypothesis 4—Modelled prevalence of weekly cannabis use among persons with schizophrenia by age and birth cohort.

et al., 1999). This has not been universal, however, with some reporting stable or increased rates (Bamrah et al., 1992; Castle et al., 1991; Haefner and an der Heiden, 1986; Harrison et al., 1991). One study concluded that incidence rates of psychosis in Australia had *not* changed in the period 1848–1978 (Haefner, 1987). It appears unlikely that there has been an increase in the incidence of schizophrenia in Australia. Given uncertainty about whether there has been a decrease in incidence, the most conservative conclusion is that *the incidence rates of schizophrenia have remained stable and possibly decreased* over the past several decades. It is unlikely that they have increased.

As hypothesis 1 predicted an increase in the incidence of psychosis, the available evidence does not support hypothesis 1. The other three hypotheses were consistent with this evidence: all predicted that increases in the prevalence of cannabis use would have little or no effect upon the incidence of psychosis.

The evidence that the incidence of psychosis has remained stable *is* consistent with hypothesis 2. So too is: recent evidence that more cases of schizophrenia are diagnosed as 'drug-induced' (although this could reflect clinicians' assumptions that substance use is precipitating the disorder, Brewin et al., 1997); and the fact that cases in more recent birth cohorts have a younger average age of onset (DiMaggio et al., 2001).

3.4.2. Trends in the prevalence of psychosis

The data presented above also suggested that the prevalence of psychosis has not increased. This was *not* consistent with the increased prevalence of hypothesis 1,

Table 5
Consistency of predicted and actual trends in schizophrenia, and in cannabis use among persons with schizophrenia

	Trends in schizophrenia			Trends in cannabis use
	Incidence	Prevalence	Age of onset	Prevalence among those with schizophrenia
(1) Causal	X	X	?	?
(2) Precipitation	✓	?	?	?
(3) Worse prognosis	✓	✓	?	?
(4) Increased risk of dependence	✓	✓	?	?

Note: ✓ = evidence appeared to support the prediction of this hypothesis; X = evidence did not appear to support the prediction of this hypothesis; ? = there was insufficient evidence to determine the nature of the trends.

something that would certainly have been noted by case registers.

It is more difficult to assess the validity of hypothesis 3, which predicted a very small (at most 1%) increase in the number of chronic cases of schizophrenia by age 35 years. An increase of this size would be difficult, if not impossible, to detect using existing epidemiological and clinical data. This means that even if cannabis use increases the rate of relapse, it will make a very small difference to the number of persons with chronic schizophrenia.

Hypotheses 3 and 4 did not predict any change in the prevalence of psychosis. These predictions are also consistent with the limited data on the prevalence of schizophrenia.

3.4.3. Trends in the age of onset of schizophrenia

A recent study of first episode psychosis found a lower age of onset in more recent birth cohorts (DiMaggio et al., 2001). The evidence on the age of onset among first-episode cases of schizophrenia who use cannabis use is less certain. Some studies have found that such cases had a significantly younger age of onset than non-users of cannabis (Rolfe et al., 1993) but a number of studies have *not* done so (Gut-Fayand et al., 2001; McGuire et al., 1995).

The limited evidence on the average age of onset of schizophrenia makes it difficult to draw any conclusions about this indicator. Some evidence that the age of onset of schizophrenia has decreased in more recent birth cohorts is consistent with hypotheses 1 and 2 but clinical samples of first-episode psychosis have not consistently found that cannabis use is associated with an earlier onset of psychosis. Better controlled studies may clarify this issue.

3.5. Trends in the prevalence of cannabis use among persons with schizophrenia

It is difficult to interpret evidence on changes in the prevalence of regular cannabis use among schizophrenic persons over the past three decades. First, many studies report rates of cannabis use disorders in the lifetime rather than the past year. Second, selection biases in clinical samples (Berkson, 1946; Caron and Rutter, 1991; Galbaud Du Fort et al., 1993) make it difficult to know whether variations in prevalence across different samples reflect changes in referral processes or changes in prevalence of use. Third, there are few data on the prevalence of cannabis use among persons with schizophrenia in the *Australian* population. These have shown higher rates of lifetime (Fowler et al., 1998) and past year prevalence of dependence (Fowler et al., 1998) than in the Australian population (Hall et al., 1999). Because these studies are all recent, there is not much that can be concluded about trends in the prevalence of

cannabis use among persons with psychosis in Australia. A conservative assumption is that the prevalence of cannabis use has increased among persons with schizophrenia at a similar rate to that in the general population of Australia over this period (Degenhardt et al., 2000).

The data on trends in the prevalence of cannabis use among persons with psychosis in Australia or anywhere else are so limited that it is impossible to draw any conclusions. The high rates predicted by hypothesis 4 are consistent with the findings in recent studies (Degenhardt et al., 2000; Fowler et al., 1998; Jablensky et al., 2000) but we do not know what rates of cannabis use were in previous years. If we make the reasonable assumption that rates of lifetime cannabis use have gone up among persons with schizophrenia at the same rate as in the Australian community (Donnelly and Hall, 1994), then these recent data are consistent with the hypothesis that persons with schizophrenia are more likely to become regular cannabis users than peers without the disorder.

4. Discussion

4.1. Does cannabis use cause psychosis?

The hypothesis that cannabis causes schizophrenia was not supported by the data on trends in the incidence of this psychosis in Australia. There was no evidence that there has been an *increase* in incidence over the past 30 years of the magnitude predicted by the hypothesis. This suggests that cannabis use has *not* caused cases of psychosis that *would not otherwise have occurred*. Even if regular cannabis use *did* double the risk of users developing schizophrenia (the 'doubling' of risk being the best estimate), the prevalence of schizophrenia in the population would increase from 1 to 2%. An increase of 1000 cases per birth cohort—as was predicted by our modelling—would have been noticed in clinical settings. The widespread discussion of apparent *declines* in the incidence of schizophrenia suggests that this hasn't occurred. Even if some of the environmental risk factors for schizophrenia have been reduced, such as poor maternal nutrition, infectious disease, and poor antenatal and perinatal care (Eagles, 1991; Takei et al., 1996), it seems unlikely that the decline in incidence from these causes would have *exactly* offset an increase of 1000 incident cases per birth cohort predicted by the hypothesis that cannabis causes schizophrenia.

4.2. Does cannabis use precipitate psychosis?

This hypothesis is consistent with the evidence of a reduction in the age of onset of psychosis among persons born in more recent cohorts (DiMaggio et al.,

2001) and with some findings that first episode psychosis cases who used cannabis were younger than non-users. It would also explain the recent increase in the diagnosis of 'drug-induced' psychoses (Brewin et al., 1997).

4.3. Does cannabis use worsen prognosis?

The third hypothesis made surprisingly little difference to the number of chronic cases that would be seen by age 35 years. It is consistent with the elevated rates of cannabis use among persons with psychotic illnesses, and with the results of prospective studies that have been carried out evaluating this issue.

4.4. Is regular cannabis use more likely among persons with psychosis?

This hypothesis is consistent with the high prevalence of cannabis use in Australian samples of persons with psychosis. If we assume that rates of cannabis use among persons with schizophrenia have gone up in parallel with those in the Australian community (Donnelly and Hall, 1994), then these recent data are consistent with this hypothesis.

4.5. Study limitations

Modelling of any trends such as those examined here has limitations, since it is based upon assumptions that may not be completely accurate. In the case of the present paper, two issues in particular must be noted.

The first is potential changes in the potency of cannabis use over time. This is an issue that has been a matter of some debate in recent years in Australia, as in other countries, with some claims that the THC content of cannabis has increased 30-fold over the past three decades. The data on this issue have been examined by Hall and Swift, who concluded that the limited evidence available suggested that the THC content of cannabis may have increased by 3–4% over this period (Hall and Swift, 2000). In any rate, if cannabis use were a cause of psychosis de novo, an increase in the potency of cannabis would be expected to result in an increase in the prevalence of psychosis, given the rise in cannabis use over the same period.

The second concerns changes in the classification of schizophrenia over the period examined here. Over time, the criteria used to define schizophrenia have become increasingly based upon empirically validated and rigorous definitions of the disorder. In particular, there has been increasing precision with which subtypes of psychotic illness have been defined. Unfortunately, given the limitations of the data available, it is not possible to examine trends in the clinical subtypes of psychosis with any degree of confidence.

5. Conclusions

This study has used modelling (incorporating data-based parameters) to predict what changes we would expect to see in the incidence and prevalence of schizophrenia if each of four hypotheses about the relationships between cannabis use and psychosis were true. The claim about cannabis and psychosis is widely understood in the popular media and public debate in Australia to imply that cannabis use *has* increased the number of cases of psychosis in the population (in the sense of causing cases of psychosis that would not otherwise have occurred). It is therefore interesting that using plausible assumptions, the present modelling exercise suggests that (a) cannabis use *as a cause of cases* of psychosis does not fit the data; and (b) it would be difficult to detect any increases even if cannabis use *was a cause of incidence* among those vulnerable to the disorder.

Notably, if there were a common causal mechanism for the association between cannabis use and psychosis, whereby common factors increased the likelihood of both cannabis use and psychosis, we would expect to see increases in psychosis along with increases in cannabis use. Since this was not the case, there does not appear to be strong support for common causes completely explaining the association that has been observed.

The other three hypotheses provided a better fit to the available data but because of data limitations it was difficult to decide between them. If cannabis use acts as a precipitant of psychosis, we would have seen *small* increases in the number of early onset cases. If cannabis use made relapse to psychotic symptoms, we would have seen *small* increases in the number of chronic cases. Finally, if persons with psychosis were more likely to become regular cannabis users, we would expect to see only a higher prevalence of regular cannabis use in this population. Future research needs to test these hypotheses in prospective studies. The results of this study suggest that persons at risk of psychosis may be advised of this possible relationship and counselled against using cannabis.

A similar approach to modelling may be useful in empirically assessing the plausibility of hypotheses about relationships between risk factors and the incidence and prevalence of other mental disorders in the population.

Appendix A: Equations

C   prevalence of regular cannabis use
I   age-specific incidence rate of schizophrenia
R   age-specific relapse rate of schizophrenia

Hypothesis 1: causal relationship

It was hypothesised that weekly cannabis use doubled the risk of developing schizophrenia—in other words, that regular cannabis users had an *incidence* rate of schizophrenia that was double that among persons who did not use cannabis. This risk ratio is based on previous work by Tien and Anthony (1990), Andreasson et al. (1987), and the NSMHWB (Degenhardt and Hall, 2001).

N(incident cases atyear n)

$= (I_n^**C_n^**2$

$+ I_n^**(1 - C_n))^**$N(without schizophrenia atyear n)

N(chronic cases atyear 2)

$=$ N(incident cases year 1)*R*0.25

N(chronic cases atyear 3)

$=$ N(incident cases year 2)*R*0.25

$+$ N(incident cases year 1)*R*0.5

N(chronic cases atyear 4)

$=$ N(incident cases year 3)*R*0.25

$+$ N(incident cases year 2)*R*0.5

$+$ N(incident cases year 1)*R*0.75

N(chronic cases atyear 5)

$=$ N(incident cases year 4)*R*0.25

$+$ N(incident cases year 3)*R*0.5

$+$ N(incident cases year 2)*R*0.75

$+$ N(incident cases year 1)*R

Hypothesis 2: Cannabis use precipitates psychosis among vulnerable individuals

This hypothesis assumes that there is no effect of regular cannabis use upon overall incidence or chronicity of psychosis, but that among persons who use cannabis there is a reduced age of onset of psychosis.

It was assumed that persons using cannabis develop the illness 1 year earlier than those who do not use cannabis regularly. This estimate was taken from the study of Linszen and others in which those who used cannabis were on average 1 year younger than those who did not use cannabis (Linszen et al., 1994).

N(incident cases atyear n)

$= I_n^**$N(without schizophrenia atyear n)

N(chronic cases atyear 2)

$=$ N(incident cases year 1)*R*0.25

N(chronic cases atyear 3)

$=$ N(incident cases year 2)*R*0.25

$+$ N(incident cases year 1)*R*0.5

N(chronic cases atyear 4)

$=$ N(incident cases year 3)*R*0.25

$+$ N(incident cases year 2)*R*0.5

$+$ N(incident cases year 1)*R*0.75

N(chronic cases atyear 5)

$=$ N(incident cases year 4)*R*0.25

$+$ N(incident cases year 3)*R*0.5

$+$ N(incident cases year 2)*R*0.75

$+$ N(incident cases year 1)*R

Hypothesis 3: Cannabis use worsens prognosis

It was assumed that the chance of relapse (i.e. the occurrence of further psychotic episodes) was increased by 2.5 times among weekly cannabis users. This was based upon the findings of the Linszen and colleagues study, which found that those using cannabis at least weekly were 2.5 times more likely to relapse to psychotic symptoms (Linszen et al., 1994).

The model also assumed that (a) there is no association between cannabis use and *precipitation* of psychosis; and (b) that the percentage of persons using cannabis is initially the same among schizophrenic and non-schizophrenic persons.

N(incident cases atyear n)

$= I_n^**$N(without schizophrenia)

N(chronic cases atyear 2)

$=$ N(incident cases year 1)*(2*R*C + R*(1 - C))/4

N(chronic cases atyear 3)

$=$ N(incident cases year 2)*(2*R*C + R*(1 - C))/4

$+$ N(incident cases year 1)*(2*R*C

$+ R*(1 - C))/2$

N(chronic cases atyear 4)

$=$ N(incident cases year 3)*(2*R*C + R*(1 - C))/4

$+$ N(incident cases year 2)*(2*R*C

$+ R*(1 - C))/2$

$+$ N(incident cases year 1)*(2*R*C

$+ R*(1 - C))*0.75$

N(chronic cases atyear 5)

$$= \text{N(incident cases year 2)}*(2*R*C + R*(1-C))/4$$
$$+ \text{N(incident cases year 2)}*(2*R*C$$
$$+ R*(1-C))/2 + I_2^**(2*R*C + R*(1-C))*0.75$$
$$+ \text{N(incident cases year 2)}*(2*R*C + R*(1-C))$$

Hypothesis 4: Regular cannabis use is more likely among persons with psychosis

This hypothesis assumes that there is no effect of cannabis use upon either incidence or outcome (chronicity) of psychosis. The prevalence of regular (weekly) cannabis use among persons with psychosis was assumed to be double that in the general population. This is taken from research suggesting that regular or dependent cannabis use is twice as likely among persons who meet criteria for psychosis (Andreasson et al., 1987; Tien and Anthony, 1990). This hypothesis assumes that there is no effect of cannabis use upon either incidence or outcome (chronicity) of psychosis. The prevalence of regular (weekly) cannabis use among persons with psychosis will be assumed to be double that in the general population. This is taken from research suggesting that regular or dependent cannabis use is twice as likely among persons who are likely to meet criteria for psychosis (Andreasson et al., 1987; Tien and Anthony, 1990).

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