What has research over the past two decades revealed about the adverse health effects of recreational cannabis use?

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ABSTRACT

Aims To examine changes in the evidence on the adverse health effects of cannabis since 1993. Methods A comparison of the evidence in 1993 with the evidence and interpretation of the same health outcomes in 2013. Results Research in the past 20 years has shown that driving while cannabis-impaired approximately doubles car crash risk and that around one in 10 regular cannabis users develop dependence. Regular cannabis use in adolescence approximately doubles the risks of early school-leaving and of cognitive impairment and psychoses in adulthood. Regular cannabis use in adolescence is also associated strongly with the use of other illicit drugs. These associations persist after controlling for plausible confounding variables in longitudinal studies. This suggests that cannabis use is a contributory cause of these outcomes but some researchers still argue that these relationships are explained by shared causes or risk factors. Cannabis smoking probably increases cardiovascular disease risk in middle-aged adults

In epidemiological studies, ÔheavyÕ or ÔregularÕ cannabis use is usually deÞned as daily or near-daily use [6]. This pattern, when continued over years and decades, predicts increased risk of many of the adverse health effects attributed to cannabis that are reviewed below [6]. Unless stated otherwise, the remainder of this paper deals with the adverse effects of cannabis smoking, especially the adverse health effects of regular, typically daily, cannabis smoking.

OUR APPROACH TO THE LITERATURE IN 1993

In 1993 there were very few epidemiological studies of the health effects of cannabis. The literature was dominated by (i) animal studies from the 1970s on the toxicity, teratogenicity and carcinogenicity of cannabis and THC; and (ii) human laboratory studies from the late 1970s and early 1980s on the effects of sustained cannabis use over 7Ð35 days on the health of college students. There was a small number of clinical studies of adverse health effects in heavy cannabis users from the same period [7,8].

In the early 1990s in Australia (as elsewhere) there were strongly polarized views on the health effects of cannabis. The published appraisals of the limited evidence were refracted through the prism of the appraisersÕ preferred policies towards cannabis (decriminalization or legalization of personal use versus intensiÞed public education and law enforcement campaigns to discourage use). We adopted the following approaches to maximize the chances that our review would be seen as credible by advocates of these very different competing public policies towards cannabis use.

First, Nadia Solowij, Jim Lemon and I applied the standard rules for making causal inferences about the health effects of any drug to cannabis. That is, we looked for: (i) epidemiological evidence of an association between cannabis use and the health outcome in case–control and prospective studies; (ii) evidence that reverse causation was an implausible explanation (e.g. evidence from prospective studies that cannabis use preceded the outcome); (iii) evidence from prospective studies that had controlled for potential confounding variables (such as other drug use and characteristics on which cannabis users differed from non-users); and (iv) clinical and experimental evidence which supported the biological plausibility of a causal relationship [9].

Secondly, we speciÞed the standard of proof that we would use in inferring that cannabis was a probable cause of an adverse health effect; namely, evidence that made it more likely than not that cannabis was a cause of the adverse health effect. As we pointed out, very few conclusions could be drawn if we demanded proof beyond reasonable doubt. We also identiÞed possible adverse health effects that required further investigation, e.g. if animal and/or human evidence indicated an association between cannabis use and an adverse health effect which was biologically plausible.

Thirdly, we were prepared to infer that cannabis could have adverse health effects when it: shared a route of administration with cigarette smoking, e.g. respiratory disease, or produced similar acute effects to those of alcohol, e.g. on driving and crash risk; and had similar pharmacological effects to other long-acting central nervous system (CNS) depressant drugs, e.g. benzodiazepines.

Fourthly, we compared the probable adverse health effects of cannabis with the known adverse health effects of alcohol and tobacco. We aimed to do so in a way that used the same evidential standards in drawing causal inferences about the probable adverse health effects of all three drugs.

In the following analysis I apply these criteria to the more substantial research evidence that has accumulated over the past 20 years on the adverse health effects of cannabis. For each type of adverse health effect, I (i) briefly summarize the conclusions drawn in 1993; (ii) explain the reasons given for these conclusions; and (iii) compare the conclusions reached in 1993 with the inferences that may reasonably be drawn in 2013. The review begins with acute adverse health effects, those that may arise from a single episode of intoxication. It then considers the adverse health and psychological effects of regular cannabis use over periods of years and decades.

ADVERSE ACUTE HEALTH EFFECTS

In 1993 the evidence indicated that the risk of a fatal overdose from using cannabis was extremely small. This remains an uncontroversial conclusion, because the dose of THC that kills rodents is extremely high. The estimated fatal dose in humans derived from animal studies is between 15 [10] and 70 g [3]. This is a far greater amount of cannabis that even a very heavy cannabis user could use in a day [10]. There are also no reports of fatal overdoses in the epidemiological literature [11]. There have been case reports of cardiovascular fatalities in seemingly otherwise healthy young men after smoking cannabis [12] that are discussed below under ÔCardiovascular effectsÕ of cannabis smoking.

In 1993 we identiÞed the following adverse acute effects of cannabis use: (i) unpleasant experiences such as anxiety, dysphoria and paranoia, especially among naive

in high doses, especially among those with a personal or family history of psychosis; and (v) an increased risk of low birth weight babies, if cannabis was used during pregnancy.

The acute adverse effects of anxiety, panic reactions and psychotic symptoms continue to be reported, espe-

These studies have a number of limitations. First, self-reported rates of cannabis use during pregnancy are typically low (2Ð6%). Studies that have measured cannabis use using urinalyses suggest that there is considerable under-reporting of use, which probably attenuates associations between cannabis use and poor birth outcomes. Secondly, it has often been difÞcult to fully adjust for the effects of major confounders such as cigarette smoking in analyses of the effects of cannabis use on birth weight. None the less, there is a good case on the grounds of prudence for recommending that women should avoid using cannabis while pregnant, or while attempting to become pregnant.

Postnatal effects of maternal cannabis use

In 1993 a small number of studies reported increased rates of developmental abnormalities in children born to women who used cannabis during pregnancy, such as developmental delays in the visual system and increased tremor and startle shortly after birth [30]. These effects were not reported consistently in later assessments; e.g. some were not detected at the age of 1 month or on ability tests at 6 and 12 months. Others were reported at 36 and 48 months, but not at 60 and 72 months [30]. As these children entered adolescence, maternal cannabis was associated with poorer cognitive performance. In the Ontario study, at age 12 years, there were no differences in full-scale IQ scores between children who were and were not exposed to cannabis, but there were differences in perceptual organization and higher cognitive processes [30]. Tennes et al [24], by contrast, found no IQ differences at 1 year between the children of users and nonusers in 756 women, a third of whom used cannabis during pregnancy.

In the past 20 years another cohort of low-income women with higher rates of regular cannabis use [31] has reported lower scores on memory and verbal scales of the StanfordÐBinet Intelligence Scale at age 3 in children born to 655 low-income women (half African American and half Caucasian) in Pittsburgh between 1990 and 1995. By age 10, maternal cannabis use at all stages of

users deÞned by DSM-III had a problem that warranted professional help.

During the past 20 years, cannabis abuse and dependence have remained the most common form of drug dependence after alcohol and tobacco in epidemiological surveys in Australia, Canada and the United States. These disorders have affected an estimated 1Ð2% of adults in the past year, and 4Ð8% of adults during their life-time [6,39]. The life-time risk of developing dependence among those who have ever used cannabis was estimated at 9% in the United States in the early 1990s [39] as against 32% for nicotine, 23% for heroin, 17% for cocaine, 15% for alcohol and 11% for stimulants [40,41]. In longitudinal studies, the risk of developing cannabis dependence has been estimated as one in six among those users who initiated in adolescence [39] and half of daily cannabis users [42].

The evidence for a cannabis withdrawal syndrome has strengthened since 1993. In laboratory studies, humans develop tolerance to THC [43] and cannabis users who seek help often report withdrawal symptoms that make it more difÞcult to achieve abstinence. The most common withdrawal symptoms include anxiety, insomnia, appetite disturbance and depression [44], often of sufÞcient severity to impair everyday functioning [45]. A recent double-blind controlled clinical trial showed that these withdrawal symptoms were markedly attenuated by an oral cannabis extract (Sativex) [46].

It is now difÞcult to argue that cannabis dependence does not require professional attention. The number of cannabis users seeking help to quit or control their cannabis use has increased during the past two decades in the United States, Europe [47] and Australia [6,48,49]. The increase has usually occurred a decade or so after increased cannabis use among young adults [49]. This increase is not explained by increased court diversion of users into treatment in countries that retain criminal penalties for cannabis use: the same increase has occurred in the Netherlands, where cannabis use was decriminalized more than 40 years ago [50]. In 2011 cannabis was the primary drug problem for 48% of individuals entering drug treatment, and for 58% of new treatment entrants in the Netherlands.

The adverse health and social consequences of cannabis use reported by cannabis users who seek treatment for dependence appear to be less severe than those reported by alcohol and opioid-dependent people [6,51], but rates of recovery from cannabis dependence among those seeking treatment are similar to those for alcohol [52]. Clinical trials of cognitive behaviour therapy for cannabis dependence show that only a minority remain abstinent 6 and 12 months after treatment, but treatment substantially reduces the severity of problems and the frequency of their cannabis use in most who receive treatment [53,54].

Chronic cannabis use and cognitive and brain function

Cognitive impairment

In 1993 caseÐcontrol studies reported that regular cannabis users had poorer cognitive performance than non-cannabis-using controls, but it was unclear whether this was because cannabis use impaired cognitive performance, people with poorer cognitive functioning were more likely to become regular cannabis users, or some combination of the two [9]. Very few studies had matched users and non-users on estimated intellectual function before using cannabis [55], and only one study had measured cognitive performance before cannabis use [56]. Both these studies found greater cognitive impairments in frequent and/or long-term cannabis users after controlling for differences in baseline cognitive ability.

The increased number of better-controlled studies that have been reported since 1993 (see [57,58] for reviews) have consistently found deÞcits in verbal learning, memory and attention in regular cannabis users, and these deÞcits have usually but not always been related to the duration and frequency of cannabis use, the age of initiation and the estimated cumulative dose of THC received [59,60]. It still remains unclear whether cognitive function recovers fully after cessation of long-term cannabis use. Solowij [55,60] found partial recovery after 2 yearsÕ abstinence, but brain event-related potentials still showed impaired information processing that was correlated with years of cannabis use. Bolla *et al.* [61] found persistent dose-related impairment in neurocognitive performance after 28 days of abstinence in young heavy users (who had used on average for 5 years). Pope *et al.* [62], by contrast, reported full recovery after 28 daysÕ abstinence. It also remains unclear whether any cognitive impairment reßects the residual effects of chronic cannabis use, or more enduring changes in brain function produced by the cumulative effects of THC exposure [59].

A longitudinal study from the Dunedin birth cohort has suggested recently that sustained heavy cannabis use over several decades can produce substantial differences in cognitive performance that may not be wholly reversible. This study assessed changes in IQ between age 13 (before cannabis was used) and at age 38 in 1037 New Zealanders born in 1972 or 1973 [63]. It found that early and persistent cannabis users showed an average decline in IQ of 8 points compared with those who had not used cannabis at all, and cannabis users who had not used cannabis in this sustained way.

Detailed analyses pointed to persistent cannabis use as the most plausible explanation for the cognitive decline. First, the decline in IQ was largest in those who began using cannabis in adolescence and continued near-daily use throughout adulthood. Secondly, it persisted after

statistical adjustment for recent cannabis use, for alcohol, tobacco and other drug use, and for symptoms of schizophrenia. Thirdly, the same effects were observed in cannabis users who Þnished high school, in whom the decline also persisted after statistically controlling for educational level attained. Fourthly, there was some recovery if users quit using for a year or more. There was no IQ decline in cannabis users who started in young adulthood and had not used for a year or more before follow-up.

It is worth stressing two things about this study. First, these effects on IQ were found only in the small proportion of cannabis users who initiated in adolescence and persisted in daily use throughout their 20s and into their 30s. No effects were found in those who initiated later or in daily users who ceased use earlier in adulthood. Secondly, the 8-point decline in IQ in the heavy sustained users was not trivial: it was half a standard deviation

factors. These Þndings are supported by two earlier analyses of US twin-study data [74,75].

Other drug use

In 1993 in the United States, Australia and New Zealand epidemiological studies reported consistently that: (i) regular cannabis users were more likely to use heroin and cocaine; and (ii) the younger a person was when they

of the Swedish cohort found a doseÐresponse relationship between frequency of cannabis use at age 18 and risk of schizophrenia during the whole follow-up period. This effect persisted after controlling statistically for confounding factors. They estimated that 13% of cases of schizophrenia could be averted if all cannabis use had been prevented in the cohort. The Swedish cohort Þndings have been supported by the results of smaller longitudinal studies in the Netherlands [93], Germany [94] and New Zealand [95,96]. All these studies have found a relationship between cannabis use and psychotic disorders or psychotic symptoms, and these relationships persisted after adjustment for confounders.

A meta-analysis of these longitudinal studies reported that psychotic symptoms or psychotic disorders were more common among those who had ever used cannabis (a pooled OR of 1.4, 95% CI = 1.20, 1.65) [97]. The risk of psychotic symptoms or psychotic disorders was higher in regular users (OR of 2.09, 95% CI = 1.54, 2.84). Reverse causation was addressed in some of these studies by excluding cases who reported psychotic symptoms at baseline, or by statistically adjusting for pre-existing psychotic symptoms. The common cause hypothesis was harder to exclude, because the association between cannabis use and psychosis was attenuated after statistical adjustment for potential confounders, and no study assessed all confounders.

Researchers who remain sceptical about a casual explanation often argue that a causal hypothesis is inconsistent with the absence of any increase in the incidence of schizophrenia, as cannabis use has increased among young adults. There is mixed evidence on trends in schizophrenia incidence. An Australian modelling study did not Þnd any increased psychosis incidence after steep increases in cannabis use during the 1980s and 1990s [98], but a similar British modelling study [99] argued that it was too early to detect any increase in psychosis incidence in Britain. Two case register studies in Britain [100] and Switzerland [101] reported an increased incidence of psychoses in recent birth cohorts, but a British study of people treated for schizophrenia in general practice failed to do so [90].

It is difÞcult to decide whether cannabis use has had any effects on psychosis incidence, because even if the relationship were causal, cannabis use would produce a very modest increase in incidence. The detection of any such increases is complicated by changes in diagnostic criteria and psychiatric services for psychosis, the poor quality of administrative data on the treated cases of psychosis, and possibly by social improvements (e.g. in antenatal care) that may have reduced incidence of psychosis during the period in which cannabis use increased.

Our best estimate is that the risk of developing a psychosis doubles from approximately 7 in 1000 in non-users [102] to 14 in 1000 among regular cannabis users. If we assume that cannabis use plays a causal role in psychosis, it will be difÞcult to reduce psychosis incidence by preventing cannabis uptake in the whole population: an estimated 4700 young men in the United Kingdom aged 20Ð24 years would have to be dissuaded from smoking cannabis to prevent one case of schizophrenia [99]. If the risks of cannabis use are independent and multiplicative with genetic risk, then a doubling of risk would be an important piece of information for people who have an affected Þrst-degree relative: it would mean that their risk would increase from 10 to 20% if they used cannabis regularly [103].

There are also important risk messages about cannabis use for young people who experience psychotic symptoms. Young people with psychoses or psychotic symptoms who use cannabis have an earlier average age of Þrst-episode psychosis [104]. More positively, young people with a Þrst episode of psychosis who stop using cannabis use have better clinical outcomes than those who persist in using, as measured by fewer psychotic symptoms and better social functioning [105,106].

Cannabis use and other mental disorders

In 1993, epidemiological studies such as the Epidemiologic Catchment Area Study and National Comorbidity Study found high rates of comorbidity between cannabis use disorders and anxiety and depressive disorders, other substance use disorders and antisocial personality disorders [9]. There were, however, few longitudinal studies available in 1993 to decide on the best explanations of these relationships.

In longitudinal studies conducted since our earlier review, the relationship between regular cannabis use and depression has been weaker than that for cannabis and psychosis [107]. A follow-up of the Swedish cohort by Manrique-Garcia and colleagues found that depression was 1.5 times more common in those who reported the heaviest cannabis use at age 18 than in non-users, but the association was no longer signiÞcant after adjustment for confounders [108]. Fergusson & Horwood [109] found a doseÐresponse relationship between frequency of cannabis use by age 16 and depressive disorder, but the relationship was no longer statistically signiÞcant after adjusting for confounders. A meta-analysis of these studies [97] reported a modest association between cannabis use and depressive disorders (OR = 1.49, 95% CI = 1.15, 1.94) and concluded that support for a causal hypothesis was weak, because most of these studies had not controlled adequately for confounders or excluded the possibility that depressed young people were more likely to use cannabis. Similar conclusions were drawn from a combined analysis of data from four Australasian birth cohorts [110].

dose-related way (see reviews [128,129]), but that tolerance to these effects developed rapidly in healthy young adults. There was clinical evidence that cannabis smoking could produce symptoms of angina in older adults with cardiovascular disease who used cannabis [130].

The evidence has not increased a great deal since 1993, but it is consistent with cannabis smoking having adverse cardiovascular effects in middle-aged and older adults. A caseÐcross-over study [131] of 3882 patients who had had a myocardial infarction found that cannabis use acutely increased the risk of a myocardial infarction: it quadrupled the risk in the hour after smoking cannabis. A prospective study of 1913 of these patients found a doseÐresponse relationship between frequency of cannabis use and mortality over 3.8 years [132]. These Þndings support the older laboratory studies showing that cannabis smoking can produce angina in patients with heart disease [130].

The cardiovascular risks of cannabis smoking are probably highest in older adults, but younger adults with undiagnosed cardiovascular disease may also be at risk. A French study, for example, of 200 cannabis-related hospitalizations in the Toulouse area between January 2004 and December 2007 included several cases of myocardial infarction and a fatal stroke in young adults who had recently used cannabis and had no other known risk factors for these disorders [133]. These case reports suggest that cannabis smoking can provoke fatal cardiovascular events in young individuals with undiagnosed cardiovascular disease.

Cannabis and cancer

THC and other cannabinoids are not potential carcinogens in microbial assays, such as the Ames test [134,135] or tests using rats and mice [136]. Cannabis smoke is carcinogenic in standard laboratory assays [134,135,137]. The fact that it is cannabis smoke that is carcinogenic [21] suggests that cannabis smoking may be a cause of cancers of the lung and the upper aerodigestive

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Þndings and the incidence of these cancers did not increase over the period 1979Ð95 in the United States [151Ð153].

Male cancers

An elevated risk of prostate cancer was reported among cannabis smokers in Sidney et alÕs study [140] of cancer incidence during an 8.6-year follow-up of 64 855 members of the Kaiser Permanente Medical Care Program. There was no overall excess of cancer when those who had ever used cannabis or who were current users were compared to those who were non-users at study entry (RR = 0.9, 95% CI = 0.7, 1.2). However, males who smoked cannabis had an increased risk of prostate cancer, as did males who were current cannabis smokers [140]. Confounding by other life-style factors was a possible explanation of the Þnding, because AIDS-related deaths were higher among cannabis users in this study.

There is more cause for concern about recent reports of an increased risk of testicular cancer among cannabis users. Daling et al [154] reported a caseÐcontrol study of cannabis use among 369 men diagnosed with a testicular germ cell tumour and 979 age-matched controls. They found a higher rate of cannabis use among cases (OR = 1.7, 95% CI = 1.1, 2.5). The risk was higher for a non-seminoma (OR = 2.3, 95% CI = 1.4, 4.0) and increased for those who began to use cannabis before the age of 18 and those who used cannabis more than weekly. These Þndings have since been replicated in two further US caseÐcontrol studies [155,156]. These studies found a doubling of risk of non-seminoma testicular tumours among cannabis users and suggestive evidence that risk increased with earlier initiation and more frequent use of cannabis. The replication of these Þndings in three caseÐcontrol studies indicates an effect requiring further investigation. It is also a biologically plausible effect, given that cannabinoid receptors are found in the male reproductive system.

THE HEALTH EFFECTS OF INCREASED THC IN CANNABIS PRODUCTS

In 1993 there were claims that the THC content of cannabis had increased sharply. Analyses of US cannabis seizures reported a 30% increase in THC content, but there were no good time trend data on THC levels in cannabis outside the United States as late as 1999 [157]. Since 2000 it has become clearer that the THC content of cannabis products increased during the 1990s and early 2000s in the United States and in many other developed countries [5,158,159]. It is less clear whether the increased THC content has been accompanied by substantial reductions in CBD content, a cannabinoid that some researchers argue may moderate the adverse effects of THC [160].

How may the use of cannabis products with increased THC content affect the likelihood of adverse health effects? Some argue that the effects will be minimal, because users titrate their doses of THC to achieve the desired level of intoxication, but recent evidence suggests that regular cannabis users titrate their THC doses incompletely when given more potent cannabis products [161].

The impacts of increased potency on cannabis use should be a research priority. The following are some plausible hypotheses which assume that the effects of increased cannabis potency will depend upon the extent of usersÕ experience with cannabis. A higher THC content may increase anxiety, depression and psychotic symptoms in naive users. This may explain the increased emergency room attendances for cannabis in the United States. It may also deter continued use in those who experience these effects. More potent cannabis products may also increase the risks of dependence and psychotic symptoms in regular users. Adverse effects on the respiratory and cardiovascular systems may be reduced to the extent that regular users titrate their THC dose by smoking less.

WHAT HAVE WE LEARNED IN 20 YEARS?

We know much more in 2013 about the adverse psychosocial effects of cannabis than we did in 1993. This is largely because many more epidemiological studies have been conducted on the effects of cannabis use in adolescence and young adulthood on psychosocial outcomes in the late 20s and early 30s (e.g. [63,162,163]). The best-designed and most informative of these studies have been two New Zealand birth cohort studies whose members lived through a historical period during which a large proportion used cannabis during adolescence and young adulthood; sufÞcient numbers of these had used cannabis often enough, and for long enough, to provide information about the adverse effects of regular and sustained cannabis use. ConÞdence in the results of the New Zealand studies has been increased by the replication of their results in cohort studies in Australia (e.g. [164]), Germany [165] and the Netherlands [93]. The fact that cannabis dependence and some of these adverse effects have also been reported in the Netherlands (where cannabis has been decriminalized for nearly 40 years) makes it unlikely that these adverse psychosocial effects can be attributed to legal policies towards cannabis.

The epidemiological evidence has strengthened for many of the probable adverse health effects that we identiÞed in 1993. There have been consistent associations found between regular (especially daily) cannabis use and adverse health and psychosocial outcomes, relationships

Table 1 Summary of major adverse health outcomes of recreational cannabis use.

that have often shown dose–response relationships, and that have persisted after statistical adjustment for plausible confounding factors. In the summary that follows, I list the conclusions that I believe can now be reasonably drawn in the light of evidence that has accrued over the past 20 years. See Table 1 for a summary of the type of evidence on which each conclusion is based.

Adverse effects of acute use

- Cannabis does not produce fatal overdoses as do opioids.
- There is a doubling of the risk of car crashes if cannabis users drive while intoxicated.
- This risk increases substantially if users also consume intoxicating doses of alcohol.
- Maternal cannabis use during pregnancy modestly reduces birth weight.

Adverse effects of chronic use

Psychosocial outcomes

- Regular cannabis users can develop a dependence syndrome, the risks of which are around 1 in 10 of all cannabis users and 1 in 6 among those who start in adolescence.
- Regular cannabis users double their risks of experiencing psychotic symptoms and disorders, especially if they have a personal or family history of psychotic disorders, and if they initiate cannabis use in their mid-teens.
- Regular adolescent cannabis users have lower educational attainment than non-using peers.
- Regular adolescent cannabis users are more likely to use other illicit drugs.
- Regular cannabis use that begins in adolescence and continues throughout young adulthood appears to produce cognitive impairment but the mechanism and reversibility of the impairment is unclear.
- Regular cannabis use in adolescence approximately doubles the risk of being diagnosed with schizophrenia or reporting psychotic symptoms in adulthood.
- All these relationships have persisted after controlling for plausible confounders in well-designed studies, but some researchers still question whether adverse effects are related causally to regular cannabis use or explained by shared risk factors.

Physical health outcomes

- Regular cannabis smokers have higher risks of developing chronic bronchitis, but it is unclear if it impairs respiratory function.
- Cannabis smoking by middle-aged adults probably increases the risks of myocardial infarction.

Declaration of interests

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