

Author postprint of Hall, W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction* 110, 19-35. 10.1111/add.12703

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

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Abstract

Background and Aims: To examine changes in the evidence on the adverse health effects of cannabis since publishing an influential review of the literature in 1993.

Method: A comparison of the epidemiological evidence and conclusions reached in a 1993 literature review with the evidence and interpretation of the same health outcomes in 2013.

Results: Epidemiological research in the past 20 years has clearly shown that driving while cannabis-impaired approximately doubles car crash risk and that around 10 regular cannabis users develop a dependence syndrome. Regular cannabis use in adolescence and young adulthood predicts approximately double the risks of: early school leaving and welfare dependence in adulthood, and of cognitive impairment, psychoses, depression and anxiety disorders in adulthood. Regular cannabis use in adolescence is strongly associated with the use of other illicit drugs (50 fold in better controlled studies). These associations between regular use and poor outcomes have persisted after controlling for plausible confounding variables in longitudinal studies. This suggests that cannabis use plays a contributory cause in producing these outcomes but some researchers still argue that these relationships are explained by the effects of shared causes or risk factors. Cannabis smoking probably increases cardiovascular disease risk in middle aged adults but its effects on respiratory function and respiratory cancer remain unclear because most cannabis smokers have smoked or still smoke tobacco. More research is needed to understand the effects that increases in the THC content of cannabis products may have had on their adverse health effects.

Conclusions: The epidemiological literature in the past 20 years has confirmed that cannabis use increases the risk of accidents, can produce dependence and that there are consistent associations between regular cannabis use and poor psychosocial outcomes and mental health in adulthood that warrant efforts to discourage adolescent cannabis use.

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Why are we concerned about recreational cannabis use?

Over the past half century recreational cannabis use has become almost as common as tobacco use among adolescents and young adults. Since its use was first reported over 40 years ago in the US, recreational cannabis use has spread globally to other developed countries, and more recently, low and middle income countries [1,2].

The effects sought by cannabis users – euphoria and increased sociability - seem to be primarily produced by delta-9-tetrahydrocannabinol (THC) [3]. These effects may be modulated by cannabidiol (CBD), a nonpsychoactive cannabinoid found in many cannabis products [3]. The THC content is highest in the flowering tops of the female cannabis plant. The THC content of cannabis has increased over the past 30 years, in the USA from < 2% in 1980 to 8.5% in 2006 [4]. THC content has also increased in the Netherlands and probably in other developed countries [5]

Cannabis is usually smoked in a “joint” or with a water pipe (sometimes with tobacco added) because smoking is the most efficient way to achieve the desired psychoactive effects [3]. A dose of 2 to 3 mg of THC will produce a “high” in occasional users who typically share a single joint with others. Regular users may smoke up to three to five joints of potent cannabis a day [6].

In epidemiological studies “heavy” or “regular” cannabis use is usually defined as daily or near daily use [6]. This pattern, when continued over years and decades, predicts increased risks of many of the adverse health effects attributed to cannabis that are reviewed below [6]. Unless otherwise stated, the remainder of this article 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 (1) animal studies from the 1970s on the toxicity, teratogenicity and carcinogenicity of cannabis and THC; and (2) human laboratory studies from the late 1970s and early 1980s on the effects of sustained cannabis use over 7 to 35 days on the health

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of college students. There were 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 polarised views on the health effects of cannabis. The published appraisals of the limited evidence were refracted through the prism of the appraisers' preferred policies towards cannabis (decriminalisation or legalisation of personal use vs. intensified public education and law enforcement campaigns to discourage use). We adopted the following approaches to maximise 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: (1) epidemiological evidence of an association between cannabis use and the health outcome in case-control and prospective studies; (2) evidence that reverse causation was an implausible explanation (e.g. evidence from prospective studies that cannabis use preceded the outcome); (3) 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 (4) clinical and experimental evidence which supported the biological plausibility of a causal relationship [9].

Second, we specified 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 identified 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.

Third, 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 CNS depressant drugs e.g. benzodiazepines.

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Fourth, 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 (1) briefly summarise the conclusions drawn in 1993; (2) explain the reasons given for these conclusions; and (3) 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.

1. 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 g [10] and 70 g [3]. This is far greater amount of cannabis than 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 cardiovascular effects of cannabis smoking.

In 1993 we identified the following adverse acute effects of cannabis use: (i) unpleasant experiences such as anxiety, dysphoria, and paranoia, especially among naive users; (ii) cognitive impairment, especially of attention and memory; (iii) psychomotor impairment that could impair a person's ability to drive a motor vehicle while intoxicated; (iv) an increased risk of psychotic symptoms 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.

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The acute adverse effects of anxiety, panic reactions and psychotic symptoms continue to be reported, especially by naïve users [6]. Over the past decade there has been an increase in the number of attendances at hospital emergency rooms in the USA in which cannabis is “mentioned” [13]. This could reflect an increase in acute adverse effects in naïve users as the average THC content of cannabis products has risen, an issue that is discussed further below.

A. Car crash injuries and deaths

In 1993 it was clear from laboratory studies that cannabis and THC produced dose-related impairments in reaction time, information processing, perceptual-motor coordination, motor performance, attention, and tracking behaviour. This suggested that cannabis could potentially cause car crashes if users drove while intoxicated but it was unclear whether cannabis use in fact did so. Studies in driving simulators suggested that cannabis-impaired drivers were aware of their impairment and compensated for these effects by slowing down and taking fewer risks. There were similar findings in the few studies on the effects of cannabis use on driving on the road (see [14] for a review).

In 1993 there were major problems in interpreting the few epidemiological studies of cannabis use in fatal car crashes. Most reported on cannabis metabolites which only indicated that cannabis had been used in the days before the accident; they did not show that the drivers were cannabis-impaired at the time of the accident. Moreover, in many of these studies a substantial proportion of drivers with cannabis in their blood also had high blood alcohol levels, making it difficult to distinguish between the effects of cannabis and alcohol on accident risk [9].

In the past decade, better-designed epidemiological studies have found that cannabis users who drive while intoxicated approximately double their risk of a car crash. Gerberich et al. [15], for example, found that cannabis users had higher rates of hospitalisation for injury from all causes than former cannabis users or non-users in 64,657 patients from a Health Maintenance Organization. The risk of motor vehicle accidents (RR = 1.96) persisted after statistical adjustment for confounding in men. Mura et al [16] found a similar relationship in a case control study of THC in the serum of 900 persons hospitalised in France with motor vehicle injuries and 900 age and sex matched controls admitted to the same hospitals for reasons other than trauma.

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A meta-analysis of 9 case-control and culpability studies [17] found that recent cannabis use (indicated by THC in blood or self-reported cannabis use) doubled the risk of a car crash (OR = 1.92 95% CI: 1.35, 2.73). The risk was marginally higher in: better designed studies (2.21 vs. 1.78), in case-control rather than driver culpability studies (2.79 vs. 1.65) and in studies of fatalities rather than injuries (2.10 vs. 1.74). Very similar results were reported in another meta-analysis [18] (pooled risk of 2.66) and in a systematic review of laboratory and epidemiological studies [19].

In summary, the epidemiological and laboratory evidence on the acute effects of cannabis strongly suggests that cannabis users who drive while intoxicated increase their risk of motor vehicle crashes 2-3 times [20] as against 6-15 times for comparable intoxicating doses of alcohol. Cannabis use was estimated to account for 2.5% of traffic deaths in France as against 29% for alcohol. The risk of an accident increases substantially if cannabis users also have elevated blood alcohol levels [19].

B. Reproductive effects of cannabis use

1. Foetal development and birth defects

In 1993 animal studies suggested that high doses of cannabis extract caused growth retardation and birth malformations [21] but epidemiological studies did not consistently find an increased risk of birth defects among women who reported using cannabis during pregnancy. It was also difficult to interpret the few studies that did report increased rates of birth defects (e.g [22]) because cannabis users were more likely to smoke tobacco, and use alcohol and other illicit drugs during pregnancy [23]. They were also less likely to seek antenatal care, and had poorer nutrition than women who did not use cannabis [24]. Zuckerman et al [25] reported the most convincing failure to find an increased risk of birth defects in a study of a large sample of women among whom there was a substantial rate of cannabis use that was measured by urinalysis rather than self-report.

A meta-analysis [26] of studies in the 1980s and 1990s suggested that regular cannabis use during pregnancy reduced birth weight, although the effect was smaller than that for tobacco smoking. Several large epidemiological studies have since reported that cannabis use in pregnancy is associated with reduced birth weight (e.g [27,28]). This effect has generally persisted after statistically controlling for other drug use (e.g [25,28,29]). Several of these

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studies also reported that women who used cannabis had a shorter duration of labour and an increased risk of babies small for gestational age [27].

These studies have a number of limitations. First, self-reported rates of cannabis use during pregnancy are typically low (2%-6%). Studies that have measured cannabis use used urinalyses suggest that there is considerable under-reporting of use, which probably attenuates associations between cannabis use and poor birth outcomes. Second, it has often been difficult to fully adjust for the effects of major confounders such as cigarette smoking in analyses of the effects of cannabis use on birth weight. There is nonetheless a good case on the grounds of prudence for recommending that women should avoid using cannabis while pregnant, or while attempting to become pregnant.

2. Post-natal 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 consistently reported in later assessments; e.g. some were not detected at the age of one 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 organisation 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 Stanford-Binet 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 pregnancy was associated with delinquency and problem behaviour [32]. Cannabis-exposed children also performed more poorly on reading and spelling tests and were rated lower on academic achievement by their teachers [33]. These findings were confirmed at age 14 when the association between prenatal cannabis use and poorer school performance was shown to be

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mediated by the child's lower cognitive ability, higher rates of attentional and mood disorders, and by these children initiating cannabis use before the age of 14 [34].

The behavioural effects of prenatal cannabis exposure have only been reported in two cohort studies and the effects have been most consistent in the cohort of lower income women with higher rates of use [35]. The dose-response relationship in one of these studies is suggestive of a causal role for cannabis. Uncertainty remains because of the small number of studies, the small samples of women in each, and the researchers' limited ability to control for the confounding effects of other drug use during pregnancy, maternal drug use post-birth and poor parenting. These studies have also been unable to control for a plausible explanation of some of the effects of maternal cannabis use, namely, genetic differences in IQ and in the risks of conduct and substance use disorders between cannabis-using mothers and their non-using peers [35]. Nonetheless, as with the evidence on birth weight, it is prudent to counsel women against using cannabis during pregnancy.

2. Adverse health effects of *chronic* cannabis use

Epidemiological studies of cannabis use are usually unable to measure the doses of delta-9-tetrahydrocannabinol (THC) and other cannabinoids (e.g. cannabidiol) that regular cannabis users receive [36]. In the absence of these data, epidemiological studies have defined "heavy" or "regular" cannabis use as daily or near-daily use [6]. This is the pattern of use that has been most consistently associated with adverse health and psychological outcomes.

A major challenge in interpreting associations between regular cannabis use and adverse health outcomes in epidemiological studies is that regular cannabis users differ from non-users in a variety of ways that may reflect baseline differences in their risks of adverse outcomes. Regular cannabis users, for example, are more likely to use alcohol, tobacco and other illicit drugs and they differ from non-users in their risk-taking and other behaviour [6]. Statistical methods of control have been used to test the plausibility of confounding as an explanation of these relationships and fixed effects regression have been used to test for unknown fixed differences between users and nonusers (e.g [37]). Some researchers have expressed doubts about whether the first strategy can be wholly successful [38].

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A. Cannabis dependence

The conclusions of our 1993 review on cannabis dependence provoked some scepticism. We used the DSM-III definition of cannabis dependence that included impaired control over cannabis use and difficulty ceasing use despite harms caused by it. DSM-III cannabis abuse and/or dependence had been the most common type of illicit substance use disorder identified in US mental health surveys of the 1980s and 1990s [9]. Critics of this epidemiological evidence argued that very few of cannabis users defined by DSM-III had a problem that warranted professional help.

Over 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 USA. These disorders affect an estimated 1%-2% of adults in the past year, and 4%-8% of adults during their lifetime [6,39]. The lifetime risk of developing dependence among those who have ever used cannabis was estimated at 9% in the USA 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 users those 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 difficult to achieve abstinence. The most common withdrawal symptoms include anxiety, insomnia, appetite disturbance and depression [44], often of sufficient 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 difficult 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 over the past two decades in the USA, Europe [47], and Australia [6,48,49]. The increase has usually occurred a decade or so after increased cannabis use among young adults [49]. The 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 decriminalised over 40 years ago [50]. In 2011 cannabis was the

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primary drug problem for 48% of persons 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 persons [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].

B. Chronic cannabis use and cognitive and brain function

1. Cognitive impairment

In 1993 case-control 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, persons 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 of these studies found greater cognitive impairments in frequent and/or long term cannabis users after controlling for differences in baseline cognitive ability.

The many more better-controlled studies that have been reported since 1993 (see [57,58] for reviews) have consistently found deficits in verbal learning, memory and attention in regular cannabis users and these deficits 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 fully recovers after cessation of long term cannabis use. Solowij [55,60] found partial recovery after 2 years' 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 days' abstinence. It also remains unclear whether any cognitive impairment reflects

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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 recently suggested 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 1,037 New Zealanders born in 1972 or 1973 [63]. It found that early and persistent cannabis users showed an average decline in IQ of eight 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. Second, it persisted after statistical adjustment for recent cannabis use, for alcohol, tobacco and other drug use, and for symptoms of schizophrenia. Third, the same effects were observed in cannabis users who finished high school, in whom the decline also persisted after statistically controlling for educational level attained. Fourth, 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 only found 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. Second, the 8 point decline in IQ in the heavy sustained users was not trivial: it was a half standard deviation lower than their peers. This means that the average IQ of these heavy users was below 70% of their peer group. These cognitive effects were evident to close acquaintances of the study participants. Heavy cannabis users were rated as having more problems with memory and attention in everyday life than peers who did not use cannabis in this way.

2. Brain structure and function

In our 1993 review, we found a 22 year old study using air encephalography which suggested that heavy cannabis use produced structural brain damage [64]. This study was heavily

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criticised because it involved a small number of users, the effects of other drug use were not well controlled and there were major doubts about validity of air encephalography. Since then better methods of brain imaging studies have reported changes in brain function and structure in heavy cannabis users.

Positron emission tomography (PET) studies have shown a down-regulation of cannabinoid receptors in regular cannabis users which persisted for up to a month after abstinence [65]. Functional imaging studies of chronic cannabis users (e.g [66]) have shown reduced activity in brain regions that are involved in memory and attention after 28 days of abstinence [56]. Magnetic Resonance Imaging studies have reported structural changes in the hippocampus, prefrontal cortex and cerebellum in chronic cannabis users. Yücel et al [67], for example, reported reduced hippocampal and amygdala volumes in 15 long term users who had smoked 5 or more joints a day for 10 or more years. These reductions were largest in users with the longest duration of use.

Reviews of functional and structural neuroimaging studies of chronic cannabis users [68,69] indicate that there is a need for larger, better controlled neuroimaging studies that use standardised tasks and measures. The potential cognitive effects of chronic cannabis use are of special concern because it is the least cognitively able young people who are most likely to begin early cannabis use and to use regularly throughout young adulthood.

C. The psychosocial consequences of adolescent cannabis use

1. Educational outcomes

In 1993 cross-sectional studies found that regular cannabis users had poorer educational attainments than non-using peers [70] but it was uncertain which was cause and which effect. That is, we could not tell whether this association arose because: (1) cannabis use was a contributory cause of poor school performance; (2) cannabis use was more likely in young people with poor educational attainment; or (3) that cannabis use and poor educational attainment were caused by common factors [70]. Explanations (1) and (2) could both be true, if poor school performance made young people more likely to become regular cannabis users, and regular cannabis use, in turn, further impaired school performance.

Longitudinal studies have found that a relationship between cannabis use before the age of 15 and early school leaving persisted after adjustment for confounders (e.g [71]). A recent meta-

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analysis of three Australian and New Zealand longitudinal studies [72] showed that the earlier the age of first cannabis use, the lower the chances of completing school and undertaking post-secondary training. These effects persisted after adjustment for parental social class and other measures of disadvantage. The authors estimated that early use of cannabis contributed to 17% of the risk of failing to complete high school or post-secondary training. The adverse effects of cannabis use on educational outcomes may be amplified by school policies that exclude students who are caught using cannabis from secondary school.

It is plausible that educational outcomes in regular cannabis users are impaired as a result of a combination of: a higher pre-existing risk of educational problems in those who become regular cannabis users, the adverse effects of regular cannabis use on learning in school, increased affiliation of regular cannabis users with other cannabis using peers who reject school, and a strong desire among younger cannabis users to make a premature transition to adulthood by leaving school [70].

A recent analysis of Australian twin study data has raised some doubts about whether the association between adolescent cannabis use and early school leaving is causal [73]. Verweij et al found that the association between the two was better explained by shared genetic and environmental risk factors for early cannabis use and early school leaving. An analysis of twins who were discordant for early cannabis use found no difference in risk of early school leaving between the twins who did and did not use cannabis, suggesting that the association was explained by shared genetic and environmental risk factors. These findings are supported by two earlier analyses of US twin study data [74,75].

2. Other drug use

In 1993 in the United States, Australia and New Zealand epidemiological studies consistently reported that: (1) regular cannabis users were more likely to use heroin and cocaine; and (2) the younger a person was when they first used cannabis, the more likely they were to do so [76]. Three explanations were offered for these patterns: (1) that cannabis users have more opportunities to use other illicit drugs because these are supplied by the same black market as cannabis; (2) that early cannabis users were more likely to use other illicit drugs for reasons that are unrelated to their cannabis use (e.g. risk taking or sensation seeking); and (3) that the

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pharmacological effects of cannabis increased a young person's propensity to use other illicit drugs [6].

Epidemiological research since 1993 has reported similar patterns of drug involvement in a number of countries (e.g [77]) although the order in which drugs are used can vary with the prevalence of different types of illicit drug use in the adult population [78]. Research has also supported the first two hypotheses in that young people in the USA who have used cannabis report more opportunities to use cocaine at an earlier age [79] and socially deviant young people (who are also more likely to use cocaine and heroin) start using cannabis at an earlier age than their peers [80]. A simulation study [81] indicated that shared risk factors could explain the observed relationships between cannabis and other illicit drug use in the USA.

The shared risk factor hypothesis has been tested in longitudinal studies by assessing whether cannabis users are more likely to report heroin and cocaine use after statistically controlling for plausible confounding factors (e.g [82]). Adjustment for confounders (including unmeasured fixed ones using fixed effects regression) [83] has not eliminated the relationship between regular cannabis use and the use of other illicit drugs [84].

Studies of twins who are discordant for cannabis use (i.e. one used cannabis and the other did not) have tested whether the relationship between cannabis use and the use of other illicit drugs is explained by a shared genetic vulnerability to use drugs. Lynskey et al [85] found that the twin who had used cannabis was more likely to have used other illicit drugs than the co-twin who had not. This relationship persisted after controlling for non-shared environmental factors. Similar results have been reported in discordant twin studies in the USA [86] and the Netherlands [86].

The order of involvement with cannabis and other illicit drugs, and the increased likelihood of using other illicit drugs, are the most consistent findings in epidemiological studies of drug use in young adults. The interpretation of these relationships remains contested but the relationships between regular cannabis use and other illicit drug use have persisted after statistical adjustment for the effects of confounding variables in both longitudinal studies and discordant twin studies.

Research over the past 20 years has revealed a changing relationship between cannabis and other drug use. In 1993, cigarette smoking was generally initiated well before cannabis use

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and regular tobacco smoking was a predictor of regular cannabis use. As a result of the success in the 2000s of public health campaigns to prevent tobacco smoking among young people, cannabis smoking is increasingly initiated by young people who have not smoked tobacco. A number of recent studies have reported that these cannabis smokers are now more likely to become tobacco smokers after using cannabis, a pattern described as a “reverse gateway” [87]. This finding probably reflects a combination of: a shared route of administration (smoking) [88], cannabis users mixing with tobacco smokers, and possibly the effects of mixing tobacco and cannabis in joints. There is suggestive evidence for the latter in the fact that the effect was much stronger in an Australian study of adolescents [87] where it is common to combine tobacco and cannabis than in a US study where this practice seems to be less common [89].

D. Cannabis use and mental health

1. Psychosis and schizophrenia

In 1993 there were reports that regular cannabis use was associated with psychotic symptoms (disordered thinking, hallucinations and delusions) and that regular cannabis use occurred at higher rates among persons with schizophrenia, a disorder in which persons report severe psychotic symptoms over months, and often experience substantial social disability, a loss of motivation, disturbed behaviour and cognitive deficits [90].

In 1993 our review found one large prospective study that supported a causal role for cannabis, a 15 year follow up study of rates of schizophrenia among 50,465 Swedish male conscripts. Conscripts who had tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia over the next 15 years than those who had not [91]. After statistical adjustment for a personal history of psychiatric disorder by age 18 and parental divorce, those who had used cannabis 10 or more times by age 18 were 2.3 times more likely to receive a diagnosis of schizophrenia than those who had not used cannabis.

Critics argued that this study had not addressed confounding and reverse causation. Studies since then have attempted to do so. Zammit et al.’s [92] 27-year follow up of the Swedish cohort found a dose-response relationship between frequency of cannabis use at age 18 and risk of schizophrenia during the whole follow up period. This effect persisted after statistically controlling 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

Author postprint of Hall, W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction* 110, 19-35. 10.1111/add.12703

Swedish cohort findings have been supported by the results of smaller longitudinal studies in the Netherlands [93], Germany [94] and New Zealand [95,96]. All of 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 odds ratio of 1.4 [95% confidence interval: 1.20, 1.65]) [97]. The risk of psychotic symptoms or psychotic disorders was higher in regular users (odds ratio 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 find 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 persons treated for schizophrenia in general practice failed to do so [90].

It is difficult 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 over the period in which cannabis use increased.

Our best estimate is that the risk of developing a psychosis doubles from around 7 in 1000 in nonusers [102] to 14 in 1000 among regular cannabis users. If we assume that cannabis use

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plays a causal role in psychosis, it will be difficult to reduce psychosis incidence by preventing cannabis uptake in the whole population: an estimated 4700 young men in the UK aged 20 to 24 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 important piece of information for persons who have an affected first 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 persons with psychoses or psychotic symptoms who use cannabis have an earlier average age of first episode psychosis [104]. More positively, young persons with a first 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].

2. 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 significant after adjustment for confounders [108]. Fergusson and Horwood [109] found a dose-response relationship between frequency of cannabis use by age 16 and depressive disorder, but the relationship was no longer statistically significant 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 adequately controlled for confounders, or excluded the

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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].

In clinical samples there are much higher rates of cannabis use disorders among persons diagnosed with bipolar disorders than in the general population (e.g [111-114]). In one longitudinal study, cannabis use at baseline predicted an increased risk of manic symptoms in a 3 year follow up [115]. In some clinical studies, persons with bipolar disorders who continue to use cannabis have more manic episodes and are less satisfied with their lives than bipolar peers who do not use cannabis [113]. These findings suggest that regular cannabis use may play a contributory causal role in bipolar disorders but the case is not yet proven because these studies have not adequately controlled for confounding variables or ruled out reverse causation [113].

Several case-control and cohort studies have reported associations between cannabis use and suicide in adolescents and young adults. For example, a New Zealand case-control study [116] of suicide attempts that resulted in hospitalisation found that 16% of the 302 suicide attempters had a cannabis disorder compared with 2% of 1028 community controls. Controlling for social disadvantage, depression and alcohol dependence substantially reduced but did not eliminate the association (adjusted odds ratio of 2).

The evidence from prospective studies is mixed. Fergusson and Horwood [109], for example, found a dose-response relationship between frequency of cannabis use by age 16 and self-reported suicide attempts but the association did not persist after controlling for confounders. A recent analysis of the data from this cohort [117] using econometric methods found that more than weekly cannabis use increased the likelihood of reporting suicidal ideation but only *in males*. Patton et al [118], by contrast, found that cannabis was only associated with self-harm in *females*. Rasic et al [119] reported that heavy cannabis use increased the risk of depression but did not affect suicide risk. An attempted meta-analysis of similar studies [97] concluded that the designs of these studies and measures used were too varied to meaningfully quantify risk and most of the studies had not excluded reverse causation or adequately controlled for confounding.

A recent study of mortality among 6445 persons treated for a cannabis use disorder in Norway found an elevated risk of suicide (OR=5.3 (CI: 3.3, 7.79) [120]). This sample included much heavier problematic cannabis users than have been studied in the cohort studies. Moreover, a

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substantial proportion of these problem cannabis users had also injected illicit drugs, a behaviour that substantially increases suicide mortality [51]. Exclusion of cannabis users who were known to be injectors at the time of treatment marginally reduced the suicide risk (OR=4.8, 95% CI: 2.4, 8.9). The study relied upon case registers so there was a limited ability to control for other possible confounders but it suggests that pre-existing suicide risk may be elevated among heavy cannabis users who seek treatment.

E. Adverse health effects of long term cannabis smoking

1. Respiratory system

In 1993 there were studies reporting that regular cannabis smokers reported more symptoms of chronic bronchitis (wheeze, sputum production and chronic coughs) than non-smokers (see [121] for a review). Follow up studies of regular cannabis-only smokers also found impaired respiratory function and pathological changes in lung tissue like those preceding the development of chronic obstructive pulmonary disease [121].

Since 1993 epidemiological studies have raised concerns about the respiratory risks of cannabis smoking without producing a clear picture because most cannabis smokers also smoke tobacco or are former smokers (see [122] for a review). A cohort study of members of an HMO reported that cannabis-only smokers had more health service use for respiratory infections than non-users of cannabis [123]. In other cohort studies, the effects of long term cannabis smoking on respiratory function were less clear [121]. A longitudinal study of 1037 New Zealand youths followed until the age of 26 [124] reported impaired respiratory function in dependent cannabis users but a longer term follow up of a larger sample of US cannabis users did not replicate this finding [123]. Chronic cannabis smoking did not increase the risk of emphysema in follow up studies of cannabis smokers in the USA [125,126] and New Zealand [127].

The large US cohort study that followed over 5000 young adults for 20 years [125] found a dose response relationship between cigarette smoking and poor respiratory function but the relationship with cannabis smoking was more complicated: low levels of cannabis smoking (a median of 3-5 joints each month) appeared to increase respiratory function but respiratory function declined in daily cannabis smokers. The authors hypothesised that the effects of cannabis smoking may depend upon the frequency of use: at lower frequency of use, it

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increases respiratory volume, either because of frequent deep inhalation and breath-holding or possibly because THC has bronchodilatory effects; at higher frequencies of use, these effects were over-ridden by the cumulative adverse effects of cannabis smoke on lung function.

2. Cardiovascular effects

In 1993, we found laboratory studies had reported that cannabis smoking increased heart rate in a 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 case-crossover 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 dose-response relationship between frequency of cannabis use and mortality over 3.8 years [132]. These findings 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 hospitalisations 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.

3. 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]

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suggests that cannabis smoking may be a cause of cancers of the lung and the upper aerodigestive tract (mouth, tongue, oesophagus) and bladder [134].

a) Respiratory cancers

In 1993 the main reasons for suspecting that cannabis use could cause lung and upper respiratory tract cancers was that cannabis smoke contained many of the same carcinogens as tobacco smoke [138]. In a few case-control studies, regular cannabis smokers had shown pathological changes in lung cells of the type that precede lung cancer in tobacco smokers [139]. There were also case reports of lung cancer in young adults who did not smoke tobacco but there were no case control or prospective studies showing higher rates of any of these cancers among cannabis smokers [9].

The epidemiological studies since 1993 have produced inconsistent results. Sidney et al [140] did not find an increased risk of respiratory cancer in an 8.6 year follow up of 64,855 members of the Kaiser Permanente Medical Care Program but rates of regular cannabis use were low and follow up stopped at age 42. Zhang et al [141] reported an increased risk (odds ratio (OR) of 2) of squamous cell carcinoma of the head and neck among cannabis users in 173 cases and 176 controls. The effect persisted after adjusting for cigarette smoking, alcohol use, and other risk factors. But three other case-control studies failed to find any association between cannabis use and these cancers [142].

Case-control studies of lung cancer have produced more consistent associations but in all these studies cannabis smoking has been confounded by cigarette smoking [143]. A Tunisian case-control study of 110 cases of hospital diagnosed lung cancer and 110 community controls found an association with cannabis use (OR= 8.2) that persisted after adjustment for cigarette smoking. A pooled analysis of three Moroccan case-control studies also found an elevated risk of lung cancer among cannabis smokers, but their cannabis users all also smoked tobacco [144]. A New Zealand case-control study of lung cancer in 79 adults under the age of 55 years and 324 community controls [145] found a dose-response relationship between frequency of cannabis use and lung cancer risk. A US case-control study found an association between cannabis smoking and head and neck and lung cancers but the associations were no longer significant after controlling for tobacco use [146].

A recent 40 year follow up of lung cancer cases in the Swedish conscript cohort [147] found a doubling of the risk of lung cancer among conscripts who had smoked cannabis 50 or more

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times by age 18. This survived adjustment for cigarette smoking (which showed the expected dose response relationship to lung cancer) but the ability to fully adjust for tobacco smoking was limited because 91% of heavy cannabis smokers at age 18 also smoked tobacco. Larger cohort and better designed case-control studies that control for cigarette smoking are needed to clarify lung cancer risk among long term regular cannabis smokers [142].

b) Maternal cannabis use and childhood cancers

Cannabis smoking during pregnancy has been associated with cancers among children. Three case control studies examined cannabis use as one of many risk factors for these cancers and found an association [148-150]. Unlike respiratory cancers, there was no a priori reason to expect a relationship between cannabis use and the risk of developing any of these cancers. We concluded in 1993 that these associations were unlikely to be causal. Since then there have been no further studies replicating these findings and the incidence of these cancers did not increase over the period 1979-1995 in the USA [151-153].

c) Male cancers

An elevated risk of prostate cancer was reported among cannabis smokers in Sidney et al.'s 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% confidence interval: 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 lifestyle factors was a possible explanation of the finding 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 case control study of cannabis use among 369 men diagnosed with a testicular germ cell tumor 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 nonseminoma (OR= 2.3 (95% CI: 1.4, 4.0) and it increased for those who began to use cannabis before the age of 18 and those who used cannabis more than weekly. These findings have since been replicated in two further US case-control studies [155,156]. These studies found a doubling of risk of a nonseminoma testicular tumors among cannabis users and

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suggestive evidence that risk increased with earlier initiation and more frequent use of cannabis. The replication of these findings in three case-control 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.

3. The health effects of increased THC in cannabis products

In 1993 there were claims that the THC content of cannabis had sharply increased. 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 USA 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 USA 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 incompletely titrate their THC doses 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 users' 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 USA. 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.

4. What have we learned in 20 years?

We know much more in 2013 about the adverse psychosocial effects of cannabis than we did in

Author postprint of Hall, W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction* 110, 19-35. 10.1111/add.12703

1993. This is largely because many more epidemiological studies have been done 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 in which a large proportion used cannabis during adolescence and young adulthood; and sufficient numbers of these used cannabis often enough, and for long enough, to provide information about the adverse effects of regular and sustained cannabis use. Confidence 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 decriminalised 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 identified in 1993. There have been consistent associations found between regular (especially daily) cannabis use and adverse health and psychosocial outcomes, relationships 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.

Adverse effects of acute use

- Cannabis does not produce fatal overdoses like 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.

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- 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 impaired 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 causally related to regular cannabis use or explained by shared risk factors.

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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.

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[temporary list- renumbering will occur following reformatting]

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Table 1: summary of major adverse health outcomes of recreational cannabis use

	Evidence	Level of evidence	Strength of effect
<i>Acute effects</i>			
Fatal overdose	+++	No case reports	0
RT crashes	++	Cohort & case control	2 fold
Low birth weight	++	Cohort	
<i>Chronic effects</i>			
Dependence	+++	Cohort studies	1 in 10 among ever users
Educational outcomes	++	Cohort & case control	2 fold in regular users
Cognitive impairment	++	Cohort & case control	Difficult to quantify
Psychosis	++	Cohort studies	2 fold in regular users
Depression	+?	Cohort studies	Probable confounding
Suicide	+?	Cohort studies	2 fold in regular users
<i>Chronic bronchitis</i>			
Chronic bronchitis	++	Cohort studies	2 fold in regular users
Respiratory impairment	+?	Cohort studies	Mixed
Cardiovascular disease	++	Cohort & case control	3-4 fold for MI
<i>Cancers</i>			
testicular cancers	++	Case-control	2-3 fold
Respiratory cancers	+?	Case-control	Confounded by smoking

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