Adverse health effects of non-medical cannabis use

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For over two decades, cannabis, commonly known as marijuana, has been the most widely used illicit drug by young people in high-income countries, and has recently become popular on a global scale. Epidemiological research during the past 10 years suggests that regular use of cannabis during adolescence and into adulthood can have adverse effects. Epidemiological, clinical, and laboratory studies have established an association between cannabis use and adverse outcomes. We focus on adverse health effects of greatest potential public health interest—that is, those that are most likely to occur and to affect a large number of cannabis users. The most probable adverse effects include a dependence syndrome, increased risk of motor vehicle crashes, impaired respiratory function, cardiovascular disease, and adverse effects of regular use on adolescent psychosocial development and mental health.

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Introduction

Psychoactive preparations of *Cannabis sativa* have been used for over 4000 years for medical and religious purposes.[1] Over the past 50 years, they have been increasingly adopted by adolescents and young adults for recreational use—in social settings to increase sociability and produce euphoric and intoxicating effects. Since cannabis use was first reported over 40 years ago by US college students, its recreational or non-medical use has spread globally, first to high-income countries, and recently to low-income and middle-income countries[2,3] (figures 1 and 2).

Uncertainties exist about the number of people who use cannabis because of lack of timely, good-quality data in most countries. The UN Office on Drugs and Crime has estimated that in 2006 cannabis was used by 166 million adults (3·9% of the global population aged 15–64 years).[4] Use was the highest in the USA, Australia, and New Zealand, followed by Europe. These countries reported higher rates of cannabis use than did the Middle East and Asia.[4] Some African countries are also thought to have high rates of cannabis use.[4] Because of their large populations, 31%, 25%, and 24% of the world's cannabis users are estimated to be from Asia, Africa, and the Americas, respectively, compared with 18% in Europe and 2% in Oceania[4] (figure 1).

Pattern of cannabis use

In the USA, rates of cannabis use in young adults peaked in 1979, which was followed by a long decline until the early 1990s, when use increased again, before levelling off towards the end of the decade.[5] A similar rise in its use in the early 1990s, followed by decline or stabilisation in recent years, has been reported in Australia and western Europe.[5]

Research in the USA has indicated that about 10% of those who ever use cannabis become daily users, and 20% to 30% become weekly users.[5] Cannabis use in the USA typically begins in the middle to late teenage years and peaks in the early and middle 20s. Use declines steeply after young people enter full-time employment, marry, and have children.[6]

No reliable information exists about the concentration of Δ-9-tetrahydrocannabinol and other cannabinoids (eg, cannabidiol) in commonly used cannabis products. In epidemiological studies, heavy or regular cannabis use is usually defined as every day or almost every day use.[5] This pattern, when continued over years, predicts an increased risk of some adverse health effects.[5] This review summarises the most probable adverse health effects of cannabis use during the years since the last review in 1997 by WHO.[7]

Cannabis

The effects of cannabis depend on the dose received, the mode of administration, the user's previous experience with this drug, and the set and setting—ie, the user's expectations, attitudes towards the effects of cannabis, the mood state, and the social setting in which it is used.[5] The main reason why most young people use cannabis is to experience a so-called high: mild euphoria, relaxation, and perceptual alterations, including time distortion and intensification of ordinary experiences such as eating, watching films, listening to music, and engaging in sex.[8] When used in a social context, the so-called high could be accompanied by infectious laughter, talkativeness, and increased sociability. These effects typically occur 30 min after smoking and last for 1–2 h.[9]

The primary psychoactive constituent of cannabis preparations is Δ-9-tetrahydrocannabinol (THC).[9] THC produces psychological and physical effects that are similar to those that users report after smoking cannabis,[10] and drugs that block the effects of THC on brain receptors also block the effects of cannabis in animals and human

Search strategy and selection criteria

We searched PubMed and Thompson Reuters Web of Science citation indexes for articles published in the past 10 years on adverse health effects of cannabis, with the search terms "cannabis", "marijuana abuse", "marijuana smoking", "epidemiologic studies", "adverse effects", "substance related disorders", "lung diseases", "respiration disorders", "cardiovascular diseases", "coronary disease", "traffic accidents", "automobile driving", "mental disorders", and "adolescent". Most selected studies were published in English since 1997. Additional publications were identified from the ones selected and from books, edited works, and reports in the field.

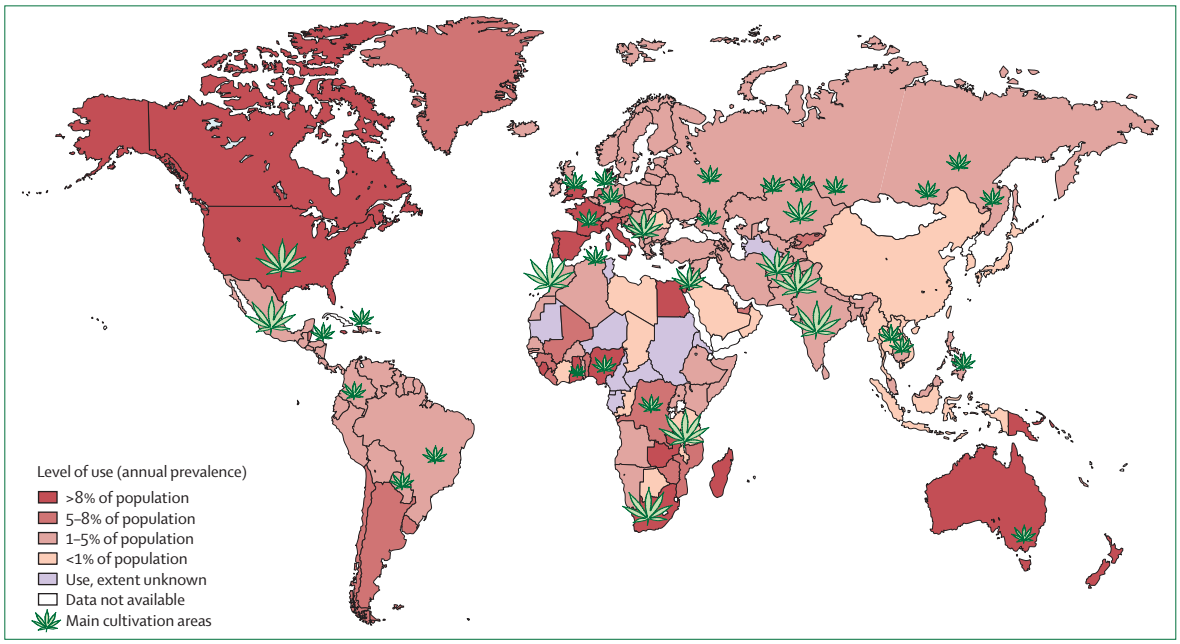

Figure 1: **Use of cannabis in 2006–07 (or latest year available)**
The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the UN. Sources: UN Office on Drugs and Crime (UNODC) annual report questionnaires data, US Department of State reports, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Drug Abuse Information Network for Asia and the Pacific (DAINAP), UNODC Global Assessment Programme on Drug Abuse (GAP), and Inter-American Drug Abuse Control Commission (CICAD). Reproduced, with permission, from UNODC.[4]

beings.[9] The effects of THC can be modulated by cannabidiol (CBD), a non-psychoactive cannabinoid present in many cannabis products.[9]

THC acts on at least two types of cannabinoid receptors (CB_1 and CB_2) in the brain.[9] The CB_1 receptor is widely distributed in brain regions involved in cognition, memory, reward, pain perception, and motor coordination.[11] It also responds to a naturally occurring (or endogenous) ligand—anandamide—which produces effects similar to THC but is less potent and shorter acting.[9] Neuroimaging studies indicate that THC increases activity in the frontal and paralimbic regions and in the cerebellum of the human brain.[12]

The THC content is highest in the flowering tops of the female cannabis plant. Marijuana (THC content 0·5% to 5%) comprises the dried flowering tops and leaves of the plant. Hashish (THC content 2% to 20%) consists of dried cannabis resin, and hash oil is an oil-based extract of hashish (THC content 15% to 50%).[3] In the USA, THC content of cannabis increased from less than 2% in 1980 to 4·5% in 1997 and 8·5% in 2006.[13] THC content also increased in the Netherlands and probably in other countries.[14] No data are available on changes in CBD content.

Cannabis is usually smoked in a joint or a water pipe (sometimes with tobacco added) because this is the most efficient way to achieve the desired psychoactive effects.[9] The amount of THC delivered to the lungs varies between 20% and 70%, and 5% to 24% reaches the brain.[9] A dose of 2–3 mg of THC will produce a high in occasional users who typically share a single joint with others. Regular users might smoke up to 3–5 joints of potent cannabis a day for several reasons, including development of tolerance and to experience stronger effects.[5]

Health effects of cannabis

We looked for evidence: that an association exists between cannabis use and outcomes in case–control and prospective studies; that reverse causation was an implausible explanation of the association (evidence from prospective studies that cannabis use preceded the outcome); from prospective studies that controlled for potential confounding variables (such as other drug use and characteristics on which cannabis users differed from non-users); and that a causal association was biologically plausible.[5] Our focus was on adverse health effects that are of greatest potential public health interest—that is, those with the greatest probability of affecting a substantial proportion of cannabis users.

Acute effects

The dose of THC that kills rodents is very high and the estimated fatal human dose is between 15 g and 70 g,[9,15] which is much higher than that smoked by a heavy user.[15] The most common acute adverse effects are anxiety, panic reactions, and psychotic symptoms, all of which are most often reported by naive users.[5]

In the laboratory, cannabis and THC produce dose-related impairment[16] in reaction time, information processing, perceptual–motor coordination, motor

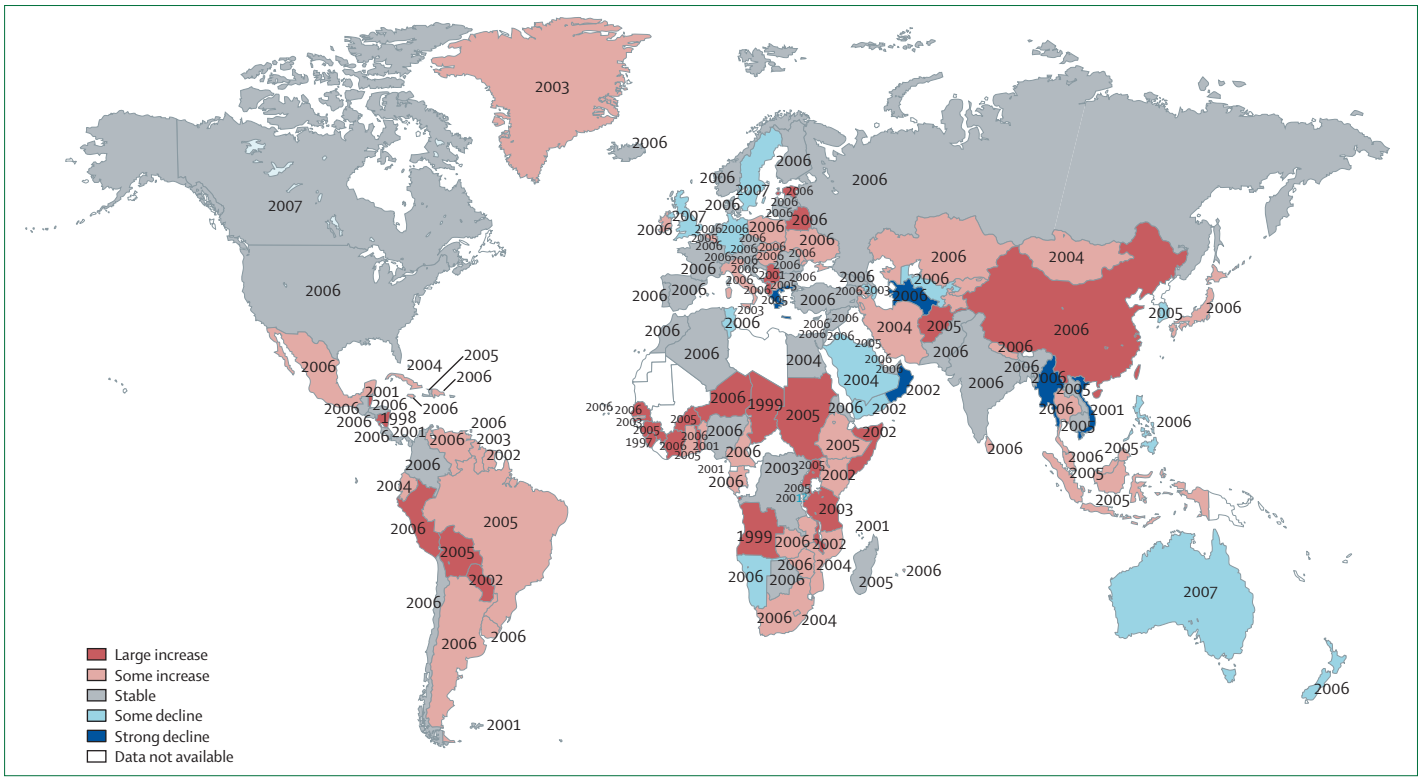

Figure 2: **Changes in the use of cannabis in 2006 (or latest year available)**
The boundaries and names shown and the designations used on this map do not imply official endorsement or acceptance by the UN. Sources: UN Office on Drugs and Crime (UNODC) annual report questionnaires data, national household surveys submitted to UNODC, US Department of State (Bureau for International Narcotics and Law Enforcement Affairs), International Narcotics Control Strategy Report, law enforcement reports, UNODC, meetings of Heads of Law Enforcement Agencies (HONLEA), UNODC illicit drug trends publications for various countries, Drug Abuse Information Network for Asia and the Pacific (DAINAP), UNODC Global Assessment Programme on Drug Abuse (GAP), and UNODC Data for Africa project. Reproduced, with permission, from UNODC.[4]

performance, attention, and tracking behaviour.[16,17] These effects can increase the risk of accidents if users drive while intoxicated. Studies of the effects of cannabis upon on-road driving found more modest impairments than those caused by intoxicating doses of alcohol because cannabis-affected people drive more slowly and take fewer risks.[18] Nonetheless, some experimental studies have shown diminished driving performance in response to emergency situations.[19] Epidemiological studies also suggest that cannabis users who drive while intoxicated are at increased risk of crashes. Gerberich and colleagues[20] found that cannabis users had higher rates of hospital admission for injury from all causes than had former cannabis users or non-users in a group of 64 657 patients from a health maintenance organisation. The risk of motor vehicle accidents (relative risk 1·96) persisted after statistical adjustment in men. Mura and colleagues[21] showed a similar relation in a study of THC in the serum of 900 individuals admitted to a French hospital for motor vehicle injuries and 900 age-matched and sex-matched controls. Drummer and colleagues,[22] who assessed THC in the blood in 1420 Australian drivers killed in accidents, showed that cannabis users were more likely to be culpable than were non-users (odds ratio [OR] 2·5). Individuals with blood THC concentrations greater than 5 μg/mL had a higher accident risk (OR 6·6) than those without THC. Laumon and colleagues[23] compared blood THC concentrations in 6766 culpable and 3006 non-culpable drivers in France between October, 2001, and September, 2003. The investigators showed increased culpability in drivers with THC concentrations of more than 1 μg/mL (OR 2·87). A dose–response relation between THC and culpability persisted after controlling for blood alcohol concentration, age, and time of accident. They estimated that 2·5% of fatal accidents in France can be attributed to cannabis and 29% to alcohol. Driving after having taken cannabis might increase the risk of motor vehicle crashes 2–3 times[16] compared with 6–15 times with alcohol. The policy challenge is to specify a concentration of THC in the blood that legally defines impaired driving.[24]

Reproductive effects

High doses of cannabis cause growth retardation and malformations in animals,[25] but epidemiological studies have given scarce evidence for an increased risk of birth defects in women who use cannabis during pregnancy. Interpretation of the few associations that have been reported[26] is difficult because cannabis users are also more likely to use tobacco, alcohol, and other illicit drugs during pregnancy,[27] and less likely to seek antenatal care

and have poorer nutrition than women who do not use cannabis.[28] Zuckerman and colleagues[29] reported that no increased risk of birth defects could be seen in a large group of women who use cannabis. Cannabis use in pregnancy has been most consistently associated with reduced birthweight in large epidemiological studies.[30] A meta-analysis[31] showed that regular cannabis smoking during pregnancy decreased birthweight, although less so than tobacco smoking, probably through the effects of carbon monoxide on the developing fetus.

Mild developmental abnormalities have been reported in children born to women who used cannabis during pregnancy.[32] These include developmental delay in the visual system shortly after birth, and increased tremor and startle;[32] however, no effects were seen at 1 month, or on ability tests at 6 and 12 months. Behavioural effects were subsequently reported at 36 and 48 months but not at 60 and 72 months.[32] At 12 years of age, children who were exposed to cannabis did not differ on full-scale intelligence quotient (IQ) scores from those not exposed, but there were small differences in higher cognitive processes (eg, perceptual organisation and planning).[32]

Other studies have given mixed results. Tennes and colleagues[28] found no differences at 1 year between children of users and those of non-users. Day and colleagues[33] followed up children born to 655 women in Pittsburgh between 1990 and 1995, and found poorer performances on memory and verbal skills of the Stanford-Binet intelligence scale in 3-year-old children of cannabis users. By 10 years of age, children born to cannabis users showed increased delinquency and behavioural problems.[34]

Postnatal behavioural effects of prenatal cannabis exposure seem modest.[35] The causal interpretation of any such effects is weakened by the inability of these studies to control for the confounding effects of other drug use during pregnancy, poor parenting, and genetic factors.[35]

Chronic effects

With no data for THC and other cannabinoids, chronic cannabis use has usually been defined as almost daily use over a period of years. Epidemiological studies cited below have reported associations between this pattern of cannabis use during adolescence and various adverse health outcomes. The major challenge in the interpretation of these studies is to rule out alternative explanations of the associations. Cannabis use is highly correlated with use of alcohol, tobacco, and other illicit drugs, all of which adversely affect health.[5] Regular cannabis users also differ from non-users before they use cannabis in ways that could affect their risk of some outcomes, especially behavioural ones.[5] Statistical control of confounding has been used to assess these relations but some epidemiologists doubt the success of this strategy.[36]

Cannabis dependence is characterised by impaired control over cannabis use and difficulty in ceasing use despite its harms. In Australia, Canada, and the USA, cannabis dependence is the most common type of drug dependence after that on alcohol and tobacco.[5] It has affected 1–2% of adults in the past year, and 4–8% of adults during their lifetime.[5,37] The lifetime risk of dependence in cannabis users has been estimated at about 9%,[37] rising to one in six in those who initiate use in adolescence.[37] The equivalent lifetime risks are 32% for nicotine, 23% for heroin, 17% for cocaine, 15% for alcohol, and 11% for stimulant users.[38] Those at highest risk of cannabis dependence have a history of poor academic achievement, deviant behaviour in childhood and adolescence, rebelliousness, poor parental relationships, or a parental history of drug and alcohol problems.[37]

Animals and human beings develop tolerance to many of the effects of THC.[39] The cannabinoid antagonist SR141716A causes a withdrawal syndrome in rats, mice, and dogs that is reversed by THC.[39] Cannabis users seeking help to stop report withdrawal symptoms that include anxiety, insomnia, appetite disturbance, and depression.[40] Over the past 20 years, increasing numbers of people have sought help in the USA, Europe, and Australia to stop using cannabis.[5] Some of this escalation might be explained by increased treatment of users as a legal requirement; however, a rise has also occurred in the Netherlands where cannabis use has been decriminalised.[41] Cognitive–behavioural therapy reduces cannabis use and cannabis-related issues, but only 15% of people remain abstinent 6–12 months after treatment.[5]

Effects of long-term cannabis smoking on respiratory function are less clear.[42] Regular cannabis smokers report more symptoms of chronic bronchitis (wheeze, sputum production, and chronic coughs) than do non-smokers.[42] The immunological competence of the respiratory system in cannabis-only smokers is also impaired, increasing their health service use for respiratory infections.[43] A longitudinal study of 1037 young people in New Zealand followed until the age of 26 years[44] found impaired respiratory function in cannabis-dependent users, but this finding was not replicated in longer-term follow-up of US users.[43] Chronic cannabis smoking did not increase the risk of emphysema in follow-up studies over 8 years in cannabis-only smokers in the USA[45] and New Zealand.[46] Cannabis smoke contains many of the same carcinogens as does tobacco smoke, with some in higher concentrations.[47] It is also mutagenic and carcinogenic in the mouse skin test, and chronic cannabis smokers show pathological changes in lung cells that precede the development of lung cancer in tobacco smokers.[48]

Epidemiological studies have not consistently reported increased risks of upper respiratory tract cancers. Sidney and colleagues[49] studied cancer incidence in an 8·6-year follow-up of 64855 members of the Kaiser Permanente Medical Care Program. They showed no increased risk of respiratory cancer in current or former cannabis users. Zhang and colleagues[50] reported an increased risk (OR 2) of squamous cell carcinoma of the head and neck in cannabis users in 173 cases and 176 controls that persisted

after adjusting for cigarette smoking, alcohol use, and other risk factors. Three other case–control studies of these cancers, however, have failed to find any such association.[51]

Case–control studies of lung cancer have produced more consistent associations with cannabis use but their interpretation is uncertain because of confounding by cigarette smoking.[52] A Tunisian case–control study of 110 cases of hospital-diagnosed lung cancer and 110 community controls indicated an association of lung cancer with cannabis use (OR 8·2) that persisted after adjustment for cigarette smoking.[53] A pooled analysis of three Moroccan case–control studies also showed an increased risk of lung cancer in cannabis smokers, all of whom also smoked tobacco.[53] A New Zealand case–control study[54] of lung cancer in 79 adults under the age of 55 years and 324 community controls found a dose–response relation between frequency of cannabis use and lung cancer risk. A US case–control study showed a simple association between cannabis smoking and head and neck and lung cancers, but these associations were not significant after controlling for tobacco use.[55] Larger cohort and better designed case–control studies are needed to clarify whether any such risks from chronic cannabis smoking exist.[51]

Evidence exists to support the adverse cardiovascular effects of cannabis use. Cannabis and THC increase heart rate in a dose-dependent way. These drugs marginally affect healthy young adults who quickly develop tolerance,[56,57] but concern exists about adults with cardiovascular disease.[56,57] A case-crossover study by Mittleman and colleagues[58] of 3882 patients who had had a myocardial infarction showed that cannabis use can increase the risk of myocardial infarction 4·8 times in the hour after use. A prospective study of 1913 of these individuals reported a dose–response relation between cannabis use and mortality over 3·8 years.[59] Risk increased 2·5 times for those who used cannabis less than once a week to 4·2 times in those who used cannabis more than once a week. These findings are supported by laboratory studies that indicate that smoking cannabis provokes angina in patients with heart disease.[60]

CNS effects

Poor cognitive functioning is a risk factor for regular cannabis use; however, whether chronic cannabis use impairs cognitive performance is not clear.[17] Studies that matched users and non-users on estimated intellectual function before cannabis use[17] or on cognitive performance assessed before cannabis use[61] have found subtle cognitive impairments in frequent and long-term cannabis users.[61]

Deficits in verbal learning, memory, and attention are most consistently reported in heavy cannabis users, but these have been variously related to duration and frequency of use, and cumulative dose of THC.[62] Debate continues about whether these deficits are caused by acute drug effects, residual drug effects, or the effects of cumulative THC exposure.[62] Whether cognitive function recovers after cessation of cannabis use is also unclear. Solowij[17] showed partial recovery after 2 years of abstinence but brain event-related potential measures still showed impaired information processing that was correlated with years of use. Bolla and colleagues[63] found indications of persistent dose-related impairment in neurocognitive performance after 28 days of abstinence in heavy young users (5 years of use) but Pope and colleagues[64] reported recovery after 28 days' abstinence.

Acute and chronic cannabis use is associated with changes in brain function that can be detected by cerebral blood flow, positron emission tomography (PET), and electroencephalography (EEG). Block and colleagues,[65] for example, showed that, after 26 h of abstinence, regular users had lower resting brain blood flow than had controls in the posterior cerebellum and prefrontal cortex. Functional imaging studies[66] have shown less activity in brain regions involved in memory and attention in chronic cannabis users than in non-users, even after 28 days of abstinence.[61] Changes in cannabinoid receptor activity in the hippocampus, prefrontal cortex, and cerebellum have been seen in chronic cannabis users. Yücel and colleagues[67] reported reduced volumes of the hippocampus and the amygdala in 15 long-term users who had smoked five or more joints a day for 10 or more years. These reductions increased with the duration of use. More functional brain imaging studies on larger samples of long-term users are needed to see if cognitive impairments in long-term users are correlated with structural changes in brain areas implicated in memory and emotion.

Psychosocial effects

Cannabis use is associated with poor educational attainment.[68] However, whether cannabis use is a contributory cause of poor school performance, is a consequence of poor educational attainment, or poor educational attainment is the result of common factors is unclear.[68] The first two possibilities could both be true if poor school performance increased cannabis use, which further impaired school performance.

Longitudinal studies have shown a relation between cannabis use in young individuals before the age of 15 years and early school leaving that has persisted after adjustment for confounders.[69] The most plausible hypothesis is that impaired educational outcomes are attributable to a combination of higher pre-existing risk, effects of regular cannabis use on cognitive performance, increased affiliation with peers who reject school, and a strong desire to make an early transition into adulthood.[68] Adolescent cannabis users who leave school early are more likely to be unemployed and depend on social welfare, and are less satisfied with their lives and their relationships than are peers in their late 20s.[70]

Other illicit drug use

In the USA, Australia, and New Zealand, regular cannabis users were most likely to later use heroin and cocaine, and

Panel 1: **Acute and chronic adverse effects of cannabis use**

Acute adverse effects

- Anxiety and panic, especially in naive users
- Psychotic symptoms (at high doses)
- Road crashes if a person drives while intoxicated

Chronic adverse effects

- Cannabis dependence syndrome (in around one in ten users)
- Chronic bronchitis and impaired respiratory function in regular smokers
- Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders
- Impaired educational attainment in adolescents who are regular users
- Subtle cognitive impairment in those who are daily users for 10 years or more

Panel 2: **Possible adverse effects of regular cannabis use with unknown causal relation**

- Respiratory cancers
- Behavioural disorders in children whose mothers used cannabis while pregnant
- Depressive disorders, mania, and suicide
- Use of other illicit drugs by adolescents

the earlier the age at which a young person uses cannabis, the more likely they are to use heroin and cocaine.[71] Three explanations have been given for these patterns of drug involvement: cannabis users have more opportunities to use other illicit drugs because cannabis is supplied by the same black market; those who are early cannabis users are more likely to use other illicit drugs for reasons that are unrelated to their cannabis use; and pharmacological effects of cannabis increase the propensity to use other illicit drugs.[5] Young people in the USA who have used cannabis report more opportunities to use cocaine at an early age.[72] Socially deviant young people (who are more likely to use cocaine and heroin) start using cannabis at an earlier age than do their peers.[73] A simulation study[74] has shown that the second (common cause) hypothesis, if true, would reproduce all the associations between cannabis and other illicit drug use.

The common causal hypothesis has been assessed in longitudinal studies to see whether cannabis users are more likely to report heroin and cocaine use after statistically controlling for confounders.[75] Adjustment for confounders (including unmeasured ones with fixed-effects regression)[76] has weakened but not eliminated the associations between regular cannabis use and the use of other illicit drugs.[77] Studies of discordant twins have tested the hypothesis that the association is explained by a shared genetic vulnerability to use cannabis and other illicit drugs. Lynskey and colleagues[78] assessed the association between cannabis and other illicit drug use in 136 monozygotic and 175 dizygotic twin pairs in which one twin had used cannabis before the age of 17 years, and the other had not. The twin who had used cannabis was more likely to have used other illicit drugs than was their co-twin who had not, and the association persisted after controlling for non-shared environmental factors.

Animal studies suggest some ways in which the effects of cannabis could predispose cannabis users to use other illicit drugs.[11] First, cannabis, cocaine, and heroin all act on the brain reward centre in the nucleus accumbens.[79] Second, the cannabinoid and opioid systems in the brain interact with each other.[80]

Cannabis and mental health

Cannabis use has been associated with increased risk of psychiatric disorders. A 15-year follow-up of 50 465 Swedish male conscripts reported that those who had tried cannabis by age 18 years were 2·4 times more likely to be diagnosed with schizophrenia than those who had not.[81] Risk increased with the frequency of cannabis use and remained significant after statistical adjustment for a few confounding variables. Those who had used cannabis ten or more times by 18 years of age were 2·3 times more likely to be diagnosed with schizophrenia than those who had not. Zammit and colleagues[82] reported a 27-year follow-up of the same cohort. These investigators also showed a dose–response relation between frequency of cannabis use in individuals aged 18 years and risk of schizophrenia during the follow-up, and this association persisted after controlling for the effects of other confounding factors. They estimated that 13% of schizophrenia cases could be averted if cannabis use was prevented. These findings have been supported by longitudinal studies in the Netherlands,[83] Germany,[84] and New Zealand,[85,86] all of which indicated that the association persisted after adjustment for confounders.

A meta-analysis of these longitudinal studies reported a pooled OR of 1·4 (95% CI 1·20–1·65) of psychotic symptoms or psychotic disorders in those who had ever used cannabis.[87] Risk of psychotic symptoms or disorders was higher in regular users than in non-users (OR 2·09, 95% CI 1·54–2·84). Reverse causation was addressed in most of these studies by exclusion of cases reporting psychotic symptoms at baseline or by statistically adjusting for pre-existing psychotic symptoms. The common causal hypothesis was difficult to exclude because the association between cannabis use and psychosis was attenuated after statistical adjustment for potential confounders, and no study assessed all major confounders.

Evidence is conflicting on whether incidence of schizophrenia increases as cannabis use increases in young adults, as would be expected if the association was causal. An Australian study[88] did not show clear evidence of increased psychosis incidence despite steep increases in cannabis use during the 1980s and 1990s. A similar study[89] suggested that it was too early to see any increased incidence in England and Wales in the 1990s. A British[90] and a Swiss study[91] reported increases in the incidence of psychoses in recent birth cohorts but another British study failed to do so.[92]

Non-consistent and weak associations have been reported between cannabis use and depression. Fergusson and Horwood,[93] for example, found a dose–response relation between frequency of cannabis use in individuals aged 16 years and depressive disorder, but the association was not significant after adjusting for confounders. A meta-analysis of these studies[87] reported an association between cannabis use and depressive disorders (OR 1·49, 95% CI 1·15–1·94). The investigators argued, however, that these studies had not controlled for confounders and had not convincingly excluded the possibility that depressed young people are more likely to use cannabis.

Several case–control studies have shown a relation between cannabis use and suicide in adolescents, but whether this is causal is unclear. For example, a New Zealand case–control study[94] of serious suicide attempts resulting in hospitalisation found that 16% of the 302 people attempting suicide met criteria for cannabis dependence or abuse compared with 2% of the 1028 community controls. Controlling for social disadvantage, depression, and alcohol dependence substantially reduced, but did not eliminate, the association (OR 2).

The evidence from prospective studies is mixed. Fergusson and Horwood,[93] for example, found a dose–response relation between frequency of cannabis use in individuals aged 16 years and a self-reported suicide attempt, but the association did not persist after controlling for confounders. Patton and colleagues[95] reported that cannabis was associated with self-harmful behaviour in women but not in men, after controlling for depression and alcohol use. A meta-analysis[87] reported that these studies were too heterogeneous to estimate risk, and few had excluded reverse causation or properly controlled for confounding.

Increased THC content in cannabis products

Concerns have been expressed over the past 20 years about putative increases in the potency of cannabis products,[5] which recent studies suggest may have occurred during the late 1990s.[14] It is unclear whether increased THC content has been accompanied by any changes in CBD content. Any health effects of increased potency depend on whether users are able and willing to titrate their dose of THC, and might also vary with the experience of users. A high THC content can increase anxiety, depression, and psychotic symptoms in naive users, while increasing the risk of dependence and psychotic symptoms if regular users do not titrate their dose. Adverse effects on respiratory and cardiovascular systems could be reduced if regular users titrate the dose of THC and reduce the amount they smoke. Increased potency could also increase the risk of road traffic crashes if users drive while heavily intoxicated.[5]

Conclusions

Acute adverse effects of cannabis use include anxiety and panic in naive users, and a probable increased risk of accidents if users drive while intoxicated (panel 1). Use during pregnancy could reduce birthweight, but does not seem to cause birth defects. Whether cannabis contributes to behavioural disorders in the offspring of women who smoked cannabis during pregnancy is uncertain.

Chronic cannabis use can produce a dependence syndrome in as many as one in ten users. Regular users have a higher risk of chronic bronchitis and impaired respiratory function, and psychotic symptoms and disorders, most probably if they have a history of psychotic symptoms or a family history of these disorders. The most probable adverse psychosocial effect in adolescents who become regular users is impaired educational attainment. Adolescent regular cannabis users are more likely to use other illicit drugs, although the explanation of this association remains contested. Regular cannabis use in adolescence might also adversely affect mental health in young adults, with the strongest evidence for an increased risk of psychotic symptoms and disorders.

Some other adverse effects are associated with regular cannabis use (panel 2), but whether they are causal is not known because of the possible confounding effects of other drugs (tobacco for respiratory cancers; tobacco, alcohol, and other drugs for behavioural disorders in children whose mothers smoked cannabis during pregnancy). In the case of depressive disorders and suicide, the association with cannabis is uncertain. For cognitive performance, the size and reversibility of the impairment remain unclear. The focus of epidemiological and clinical research should be on clarifying the causative role of cannabis for these adverse health effects.

The public health burden of cannabis use is probably modest compared with that of alcohol, tobacco, and other illicit drugs. A recent Australian study[96] estimated that cannabis use caused 0·2% of total disease burden in Australia—a country with one of the highest reported rates of cannabis use. Cannabis accounted for 10% of the burden attributable to all illicit drugs (including heroin, cocaine, and amphetamines). It also accounted for around 10% of the proportion of disease burden attributed to alcohol (2·3%), but only 2·5% of that attributable to tobacco (7·8%).

Contributors

Wayne Hall and Louisa Degenhardt identified key publications, and jointly wrote and revised the review.

Conflicts of interest

We declare that we have no conflicts of interest.

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