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Cannabis Controversies: How genetics can inform the study of comorbidity

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Abstract

Aims—To review three key and controversial comorbidities of cannabis use – other illicit drug use, psychosis and depression as well as suicide, from a genetically informed perspective.

Design—Selective review.

Results—Genetic factors play a critical role in the association between cannabis use, particularly early-onset use and use of other illicit drugs, psychosis and depression as well as suicide, albeit via differing mechanisms. For other illicit drugs, while there is strong evidence for shared genetic influences, residual association that is attributable to causal or person-specific environmental factors cannot be ruled out. For depression, common genetic influences are solely responsible for the association with cannabis use but for suicidal attempt, evidence for person-specific factors persists. Finally, even though rates of cannabis use are inordinately high in those with psychotic disorders, there is no evidence of shared genetic etiologies underlying this comorbidity. Instead, there is limited evidence that adolescent cannabis use might moderate the extent to which diathesis influences psychosis.

Conclusions—Overlapping genetic influences underlie the association between early-onset cannabis use and other illicit drug use as well as depression and suicide. For psychosis, mechanisms other than shared genetic influences might be at play.

Keywords

cannabis; comorbidity; twin; genetics; psychosis; gateway

Well recognized as the most ubiquitously used illicit drug in developed nations and, currently, the center of considerably attention in the United States for its evanescing illicit status, cannabis has long been the eye of a great deal of controversy. Worldwide, rates of cannabis use remain high, particularly in youth (1–3). For instance, the 2012 Monitoring the Future Survey noted that 45.2% of U.S. 12th graders reported a lifetime history of cannabis use (2). Likewise, according to the European Monitoring Center for Drugs and Drug Addiction's 2013 report, 0.8–40% of those aged 15–24 years report lifetime cannabis use (1). Cumulative incidence is equally high in Oceania (42%) (4). Further, while not amongst the most addictive of psychoactive substances (5), a modest but significant proportion (10–20%) of chronic cannabis users develop cannabis use disorders (6).

The acute effects of cannabis intoxication increase risk for unintentional injury and motor vehicle accidents (7) in particular when the drug is used in conjunction with alcohol (8).

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However, what has, perhaps, elicited a greater degree of scientific and public scrutiny is the alleged relationships between cannabis use and comorbid mental health conditions across the lifespan. Three key outcomes have dominated this debate:

a. Is cannabis use a gateway to the use of harder illicit drugs?

b. Is cannabis use a risk factor for psychotic illness?

c. Does cannabis use increase the risk of affective disorders and suicide?

In this review, we examine these three outcomes from a genetically informed perspective. This approach has considerable potential to expand our understanding of the relationship between cannabis use, misuse and each of these outcomes for three principal reasons. First, there is substantial evidence that cannabis use and use disorders are heritable with genetic influences explaining approximately 40–48% and 51–59% for use and problem use respectively (9). Second, there is also substantial evidence for the role of heritable variation in the outcomes under review (other illicit drug use: h^2=50–70% (1011); psychosis: h^2=80% (12); depression: h^2=30% (13); suicide: h^2=40–50% (14)). Third, and importantly, increasing acceptance of gene-environment interplay in shaping the etiology and developmental course of behavior and psychopathology implicates genetically informed processes as key contributors to comorbidity (15–17).

Regardless of the biological slant of this review, the mechanisms proposed in explanation of these (see Figure 1), and as such all, comorbidities can be broadly categorized as:

Causal

A prominent, albeit controversial explanation of the comorbidity between cannabis use and psychiatric morbidity and other behavioral outcomes is that cannabis use directly increase risks of these conditions through causal mechanisms (Figure 1A) that may include the pharmacological properties of the drug itself (Figure 1A1.). For instance, as some of the acute effects of tetrahydrocannabinol (THC), the psychoactive component in cannabis, include psychotic symptoms, some have argued that cannabis use may cause psychosis via enduring alterations in brain regions that are activated during acute cannabis-intoxication (18; 19). However, investigators have argued that a more plausible causal pathway may involve socio-environmental factors (20)(Figure 1A2).

Reverse causation

Alternatively, it is possible that psychiatric conditions cause cannabis (or other drug use, Figure 1B) as has been proposed, for example, in the self-medication hypothesis (21) which posits that drug use develops in an attempt to ameliorate the negative states associated with common mental health problems such as depression (22).

Correlated Liabilities

That cannabis use shares risk and protective influences with the outcomes listed in (a)-(c) is evident (Figure 1C). For example, adolescent exposure to cannabis use often co-aggregates with other putatively deviant or precocious behaviors, such as conduct problems and early consensual sex, which in turn, are also associated with use of other illicit drugs (23–25). There are environmental factors, such as neighborhood characteristics (e.g. easy access to cannabis in a neighborhood that also promotes early delinquent activity), that bind these behaviors together (26; 27) and, importantly, also genetic influences. For example, numerous studies have shown that underlying early drug use and other problem behaviors is a general, highly heritable predisposition to externalizing behaviors (28; 29).

Activation of Diathesis

In this instance (Figure 1D), cannabis might be viewed as an environmental trigger of genetic vulnerability to an outcome, say psychotic illness (30; 31). Also referred to as a gene-environment interaction, a few studies have found that a variant in the gene encoding catechol-o-methyltransferase (*COMT*) is associated with a higher likelihood of psychotic features during adulthood but only if individuals had used cannabis during adolescence (32). As the variant itself did not correlate with the use of cannabis during adolescence, this effect was not due to correlated liabilities nor was the variant alone associated with psychotic illness.

Disentangling causal mechanisms and correlated liabilities in human studies

The etiological explanations supporting the role of adolescent exposure to cannabis use on later occurrence of (a) – (c) are amongst the most controversial and elusive. There are other outcomes (e.g. educational achievement, cognition and working memory) that have been addressed to a limited degree with genetic methodologies and hence, are not included (some of that research and a significantly extended description of the research presented here is reviewed elsewhere (33)). Several prospective methodologies have been brought to bear on these hypotheses, however, the unequivocal demonstration of causality is a challenge even in well-crafted longitudinal studies that allow for the statistical control of multiple confounding factors (34). In particular, genetic influences that might contribute to, for instance, both early cannabis use and subsequent illicit hard drug use need to be accounted for.

While causation cannot be proved with any degree of certainty in human subject research, pairs of twins discordant for cannabis exposure afford one elegant framework for disproving causation (35; 36) as illustrated in Figure 2. We use the example of the association between cannabis use and use of hard drugs. The classical twin design capitalizes on differences between identical or monozygotic (MZ) twins, who share all their segregating genes and fraternal or dizygotic (DZ) twins who only share 50% of them. It is also assumed that both MZ and DZ twins reared together are equally matched for familial environment (the equal environments assumption) (37). As all MZ twin pairs, including those discordant for cannabis use, are perfectly correlated for their segregating genes and for familial environment, any residual association between cannabis exposure and, say, subsequent hard drug use, within the pairs of discordant twins, can be attributed to non-familial sources, such as individual-specific environments and causal processes (Figure 2). Only those pairs of twins where one twin uses cannabis but the other does not are selected. Within these discordant pairs, if the MZ twin who uses cannabis is also more likely to report use of hard drugs, relative to their identical co-twin who does not use cannabis (i.e. a significant odds-ratio when comparing the risk within the pair of twins), then even after accounting for shared genetic and familial influences, cannabis use is associated with use of hard drugs. The mechanisms that contribute to this residual association are person-specific (i.e. experienced by the cannabis-using twin but not their co-twin) and might include socio-environmental factors (affiliations with drug-using peers or exposure to adverse neighborhoods) or pharmacological (e.g. receptor cross-sensitization) and epigenetic modifications, which may act via putatively causal or non-causal pathways. Therefore, such a residual association in pairs of MZ twins is necessary but not sufficient evidence in favor of causation. On the other hand, absence of such a residual association provides strong support for the lack of causal inference. In addition, the pattern of association in discordant twins, when compared with association in pairs of unrelated individuals provides considerable insight into contributors to the association – these are illustrated in Figure 3.

Cannabis & the Gateway Theory

In 1975, Kandel posited that cannabis use, particularly with adolescent onset, was a "gateway" to the use of other illicit or hard drugs (38). The gateway process involves sequence (onset of gateway drug prior to use of hard drugs), association (increased likelihood of hard drug use in those who use cannabis) and, controversially, causation (39). Accordingly, researchers have demonstrated that cannabis use does occur prior to use of harder drugs, such as cocaine and heroin (40) and that, relative to non-users, cannabis users are considerably more likely to subsequently report use of hard drugs (41). However, the evidence for causation, or that cannabis use exerts a causal influence on the likelihood of using other illicit drugs, has been less unequivocal. Evidence for causation draws primarily from prevention and intervention studies that have noted that delaying or ceasing the onset of cannabis use has notable effects on use of harder drugs (42; 43). However, these studies also note that these prevention strategies are not drug-specific and hence, generally reduce exposure to risk influences that correlate with early use of cannabis and later experimentation with harder drugs. While prevention studies rely on social mechanisms of causation (i.e. early cannabis use causes use of hard drugs via exposure to deviance-prone environments), a rodent study has noted that adolescent exposure to cannabis, even when controlling for environmental similarity, leads to increased preference for other drugs (e.g. opiates)(44), implicating biological mechanisms, such as cross-sensitization. Although widely cited in support of the gateway hypothesis, such preclinical studies focus on the process of drug sensitization, which occurs after onset of use, rather than initiation of use and therefore are not applicable to the gateway hypothesis.

Using the discordant twin method, Lynskey and colleagues (36) selected pairs of MZ and DZ twins where one twin had used cannabis prior to age 17 and the other had used it later or not at all. They found that regardless of zygosity, individuals who used cannabis prior to age 17, when compared to their MZ or DZ cotwin (who was a never or late-onset user) were more likely to report use and misuse of harder drugs as well as cannabis use disorders. Even after adjustment for covariates such as tobacco and early alcohol use, conduct disorder, major depression and social anxiety, early onset cannabis users were at 2.4 to 3.9 increased odds of use of drugs like cocaine, hallucinogens, sedatives and opioids and twice as likely as their co-twins to meet criteria for dependence on hard drugs and alcohol. This excess risk in MZ twins indicated that causal explanations could not be excluded.

Since that initial publication, 4 studies (45–48) have systematically replicated this association. In particular, in a Dutch sample, Lynskey and colleagues (47) found that rates of party and hard drug use were considerably elevated (18 *vs*. 4%) in the cannabis-using twin relative to their co-twin and even after adjustment for confounders, the residual association between cannabis use and use of hard/party drugs persisted. The authors suggested that, as this association remained in a sample for whom cannabis was legal, the previously observed associations between cannabis and other drug use could not be explained by the legal status of cannabis. Similarly, utilizing all twins (not just those from discordant pairs), Agrawal and colleagues (48) found that this correlation could be partially ascribed to person-specific factors that influenced both early-onset of cannabis use and the subsequent use of hard drugs. In particular, Cleveland & Wiebe attribute this effect to the natural developmental course of substance use, which is genetically influenced (49).

Cannabis and Psychosis

Rates of cannabis use and misuse are particularly high in those with psychotic disorders, especially those with early onset of these illnesses. For instance, Koskinen and colleagues (50) report a mean lifetime rate of 27.1% for cannabis use disorders in a meta-analysis of

schizophrenia patients while another systematic meta-analysis (51) revealed that cannabis users, on average, had an onset of psychotic illness 2.7 years prior to non-users. Prospective studies have been remarkably informative as well, showing that the pooled (meta-analysis) odds of developing psychosis in cannabis users is 2.1 (52). The association is particularly strong in those who start to use cannabis at an early age – for example, Arseneault and colleagues (53) found that rates of schizophreniform disorder in those who had used cannabis by age 15 was more than threefold greater than in others.

In positing mechanisms that link cannabis use to psychosis, the role of reverse causation has been largely eliminated (31; 54–56). In contrast, the causal hypothesis has received significant attention. Causation has been strongly asserted on account of longitudinal studies showing a persisting association between cannabis use and psychosis even after accounting for confounders as well as preexisting psychotic symptoms (57–60). Unfortunately, these studies have had limited ability to control for genetic factors as twin studies adequately powered to study psychotic illness are rare. Additionally, the causal mechanisms that underpin this relationship are likely to be complex. Persuasive support for this arises from the observation that during periods of increasing cannabis use, rates of psychosis have remained fairly constant (61; 62). If cannabis use caused psychosis, a significantly higher rate of the latter would be expected.

An appealing alternative to direct causation is that cannabis use precipitates psychosis in individuals with pre-existing vulnerabilities. In support of this hypothesis, Caspi and colleagues (63) examined whether individuals that carried the Valine (Val) allele of a missense polymorphism (rs4680) in the catechol-O-methyltransferase (*COMT*) gene are at heightened risk for developing psychotic disorders. *COMT* codes for an enzyme that is instrumental in the degradation of endogenous amines, including dopamine, which is well known to mediate the psychoactive effects of THC. Preliminary evidence supports the role of reduced enzymatic activity and slower dopamine metabolism in Val carriers (64). Furthermore, genetic (e.g. knock-out) and pharmacological attenuation of *COMT* activity has been noted to modify cannabis-induced effects on endophenotypes related to schizoprenia (e.g. sensorimotor gating (65)). In the Caspi et al study of 803 individuals, cannabis use prior to age 17 was examined as the activator of diathesis, as indexed by the Val158Met polymorphism in *COMT* to predict psychosis outcomes at age 26. For schizophreniform disorder, the odds-ratios reflecting the association with adolescent cannabis use were 10.9, 2.5 and 1.1 in the Val/Val, Val/Met and Met/Met (Met for Methionine) individuals respectively. Similar effects were seen for hallucinations and delusions, however when adult-onset cannabis use was examined, no significant associations were noted for any of the psychotic outcomes. Furthermore, presence of the Val allele was not associated with increased or decreased likelihood of adolescent cannabis exposure.

While intuitively appealing, the above genotype x environment interaction model has witnessed only limited replication. For instance, Zammit and colleagues (66), examined whether cannabis use at age 14 was associated with psychotic symptoms at age 16 in the Avon Longitudinal Study of Parents and Children (N=2630). There was no support for an interaction between cannabis exposure and *COMT* genotype and sensitivity analyses indicated a high degree of variability in the interaction findings based on the outcomes and exposure definition under study. However, in a smaller sample of patients with psychotic disorder (N=31) and healthy controls (N=25), carriers of the Val allele showed hallucinations after cannabis exposure (recorded via experience sampling) but only if they had reported a prior history of psychosis proneness (67). Similarly, in another psychiatric patient population (N=157), decreasing copies of the Val allele were associated with decreasing age at onset of psychotic disorder in lifetime cannabis users whereas the reverse was noted (decreasing age at onset with decreasing copies of Val allele) for lifetime

nonusers (68). In addition, a recent study (N=533) posits that the predictive effect of the interaction between cannabis use and *COMT* genotype on psychosis is only exerted in those with a history of childhood abuse (69). Finally, contradictory evidence from a recent study (N=748 patients) of *COMT* haplotypes in two Spanish samples indicates a higher degree of association between lifetime cannabis use and schizophrenia in Met (not Val) carriers (70).

It appears likely that if cannabis exposure activates diathesis to psychosis (via *COMT*) then this effect is limited to individuals with additional vulnerabilities (e.g. psychosis proneness) or adverse exposures (e.g. childhood abuse). Alternatively, it is also possible that overlapping genetic (and environmental) factors link cannabis use and psychosis. However, gene association studies with *COMT*, as well as other dopaminergic (e.g. *DRD2*), cannabinoid (e.g. *CNR1*) and cholinergic (e.g. *CHRNA7*) polymorphisms have failed to show consistent associations with cannabis use and psychosis (71). Overall, the small sample size of a number of these studies limits their generalizability and meta-analysis across studies is needed. Adequately powered samples of psychotic disorders (e.g. Schizophrenia and Bipolar Disorder in the Psychiatric Genomics Consortium) with genomewide association data (72) might provide the most promising search for all variants whose influence on psychosis is moderated by early cannabis exposure.

Cannabis, depression and suicide

The links between cannabis and depression as well as suicide have been noted in both cross-sectional and longitudinal studies (22; 73; 74) – for instance, a recent meta-analysis notes an odds-ratio of 1.62 for the likelihood of depression in heavy cannabis users (73). Another meta-analysis of four Australasian datasets found that, even upon adjustment for confounders, weekly cannabis use was modestly associated with depression, particularly during adolescence (75). Similarly, for suicide, van Ours et al (76) found that frequent cannabis use (several times per week) was associated with suicidal ideation, particularly in males. In contrast, Price and colleagues, using a cohort of 50,087 Swedish male conscripts reported no association between repeated cannabis use (> 50 times) and completed suicide (odds-ratio 1.04) after adjustment for confounders (77).

As with psychosis, there is limited evidence that depression and suicidal ideation cause an increase in cannabis use, putatively via mechanisms of self-medication (78). While some researchers have found support for cannabis use exerting a causal influence on depression and suicide (79), others posit that confounding factors, which lead to a network of correlated risk influences is responsible (80). We are aware of three studies that have explored the genetic overlap between cannabis involvement and depression or suicide. Using a sample of adopted and non-adopted offspring, Marmorstein and colleagues (81) found that parental history of cannabis use disorder was associated, at a trend level, with major depressive disorder in non-adopted offspring even after accounting for offspring cannabis use disorder, indicating evidence for familial co-aggregation. Specifically examining their genetic overlap, Fu et al (82) noted that antisocial personality disorder was a complete mediator of the genetic overlap between cannabis use disorder and major depressive disorder in male twins. Finally, one study (83) has utilized the discordant twin design to explore whether the links between cannabis involvement, including early use and dependence, and depression as well as suicidal ideation and attempt are explained by individual-specific/causal factors. Even after accounting for covariates, such as childhood trauma exposure, use of cannabis prior to age 17 was associated with suicidal attempt (odds-ratio=3.49; but not with ideation or major depression). This association could not be equated to 1.0 even in genetically-identical/MZ twin pairs indicating that while shared genetic influences may be solely responsible for the association between early cannabis use and depression, potential causal

or individual-specific non-causal factors played a role in the relationship between early cannabis use and suicidal attempt, over and above their shared genetic underpinnings.

An attractive candidate gene system for the links between cannabis use, depression and suicide is the endogenous cannabinoid system. In particular, the gene encoding the cannabinoid receptor 1 (*CNR1*) to which endocannabinoids and THC bind, is an excellent target. There is well-documented evidence for the role of the endocannabinoid system in the regulation of mood, particularly in the context of stress adaptation for which it interfaces with the Hypothalamic-Pituatary-Adrenal axis (84; 85). For instance, rodents administered a cannabinoid receptor 1 (CB1) antagonist engage in more depressive and anhedonic behaviors upon administration of chronic mild and unpredictable stress (86). In humans as well, clinical trials for the anti-obesity medication Rimonabant, also a CB1 antagonist, found a high rate of serious adverse events related to suicidality that consequently led to its discontinuation (87; 88). In addition, studies have documented that variants in *CNR1* in conjunction with stress exposure are related to low mood (89; 90). While THC binds to CB1 to exert its psychotropic effects, and this is well documented in rodent models, human association studies with variants in *CNR1* have yielded equivocal findings (10).

Considerations and caveats

Genetically informed methods provide a powerful tool to unpack comorbidity and co-occurrence. However, even elegant methods such as the discordant twin design have their caveats. Recently, O'Brien and colleagues (91) concluded that the origins of twin discordance (for early onset cannabis use) are as pertinent as the sequelae of this discordance (e.g. other illicit drug use or low academic achievement). They advocate for a case-crossover (person-as-own-control) as an attractive alternative, however note the limitation of unmeasured covariates (92).

Another caveat of the twin design is that genetic relatedness is indexed by matching for segregating genes which should not be confused with all biological mechanisms that could be in play. Of note, epigenetic mechanisms are not controlled for in the twin design and indeed, it is not uncommon to find epigenetic differences within pairs of MZ twins (93). Epigenetics, broadly defined, refers to heritable variation that cannot be solely attributed to modifications in the sequence of DNA (94). Epigenetic change is a key contributor to psychiatric illnesses (95) and that such mechanisms underlie substance use is becoming more widely accepted (96–99). The extent to which such epigenetic modification can be implicated in discordant MZ correlations (those that reflect causal or shared individual-specific factors) remains to be investigated. For instance, Mill and colleagues have found evidence for discordance in methylation (increased methylation typically indexes gene silencing) signatures for the *COMT* gene in MZ twin pairs (100). Furthermore, there is evidence for stress-related methylation of the Val158 (rs4680) allele, which in turn, predicts aspects of human cognition, such as working memory (101).

In instances where causation has been implied (e.g. the gateway hypothesis), Mendelian randomization is an intriguing alternative possibility. Relying on the Mendelian law of random and independent assortment of alleles, this conceptualization of epidemiological causation suggests that the functional alleles that modify the likelihood of early cannabis use (i.e. *exposure*) should predict later outcomes to which early cannabis use is causally related (e.g. illicit drug use) (102). The allele-outcome association is considered a sound test of causation as it is unencumbered by confounding social factors. For instance, Irons et al (103) reported that the non-protective allele of the functional variant (rs671) in *ALDH2*, which reduces alcohol use due to reduced acetaldehyde clearance and consequently, flushing, was not associated with increased likelihood of other substance use in Asian Americans (i.e. a

test of the alcohol-drug gateway). While intuitively appealing, tests of this nature are challenging in studies of cannabis exposure. First, no genomic variants have been robustly and causally implicated in the etiology of early cannabis use (or any cannabis-related measure for that matter)(104; 105). Secondly, those that have been studied are likely to relate to cannabis as much as they do to putative confounders (e.g. *CNR1* variation is associated with cannabis exposure but also with alcohol involvement, a putative confounder (106)).

Finally, that cannabinoids might exert a causal influence at a cellular level cannot be ruled out. For instance, a recent study shows that, in rodents, administration of THC was associated with reduced spatial working memory via activation of astroglial cannabinoid 1 receptors, which, in turn, activated glutamate receptors that led to long-term depression in synaptic strength in the hippocampus (107). While there are questions regarding how the levels of THC administered to the rodents compare with typical patterns of human cannabis use, this study (and others) hints at possible causal mechanisms that operate with such a degree of biological intricacy so as to remain entirely undetected in genetic epidemiological experiments.

Cannabis controversies – a redux

In the United States, the legal standing of cannabis is at a watershed with two states passing legislation permitting large scale commercialization (108) while in many other countries there is ongoing controversy surrounding the appropriate legal approach to recreational cannabis use (109). That cannabis use can be implicated in the (co)-occurrence of major psychiatric disorders (e.g. depression, psychosis), reduced life opportunities (e.g. low academic achievement) and death (e.g. suicide) are often cited as barriers to its legalization. A review of the literature quickly notes that while the evidence for a straightforward causal link between cannabis and these outcomes is tenuous at best (34), any rational public health policy regarding the regulation of cannabis cannot ignore these potential harms (110–112). What genetic studies do is shed light on these mechanisms. There is overwhelming support for a cluster of risk and protective influences, including familial, genetic and environmental factors that contribute to their co-occurrence. Thus, while genetic research may never put to bed the controversy surrounding the legality of cannabis use, nor should it, we believe that such studies have made and continue to substantially impact our understanding of the manner in which cannabis use and misuse produces societal and personal harm.

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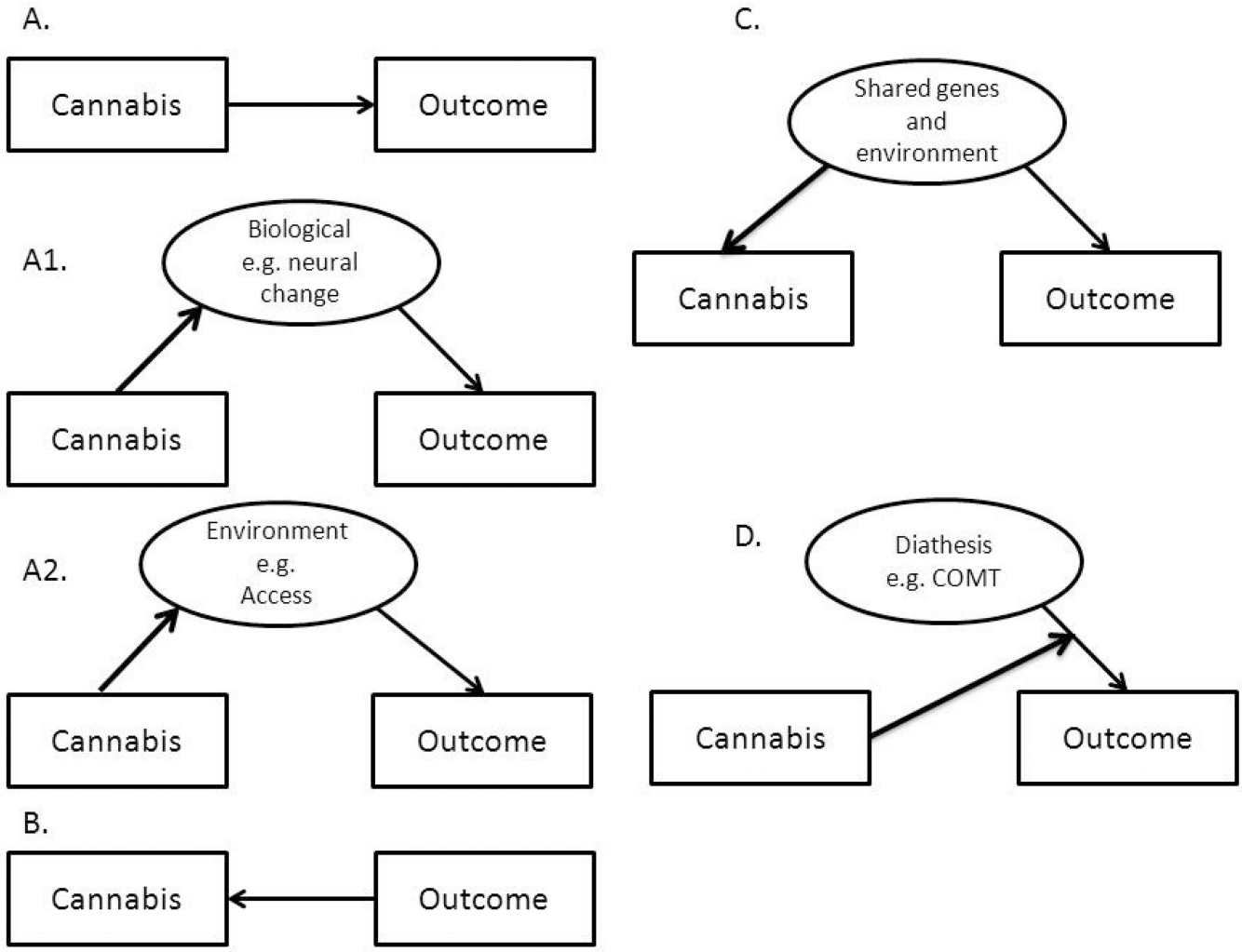

FIGURE 1.

Multiple possible mechanisms that may link cannabis use and misuse to mental health outcomes, including other illicit drug use, depression and suicide as well as psychosis. Panel A: Cannabis use directly causes outcome; A1 depicts how this causal effect may be exerted via alterations in biological pathways (such as receptor cross-tolerance) while A2 demonstrates a similar causal effect mediated by environmental exposures (such as access to drug supplier). Panel B demonstrates reverse causation, such as self-medication. Panel C shows how cannabis use and outcomes might be related via common genetic and environmental underpinnings. Panel D illustrates stress-diathesis (or gene-environment interaction) – cannabis use modifies the extent to which diathesis (such as select genotypes in the catechol-o-methyltransferase gene) influences the outcomes.

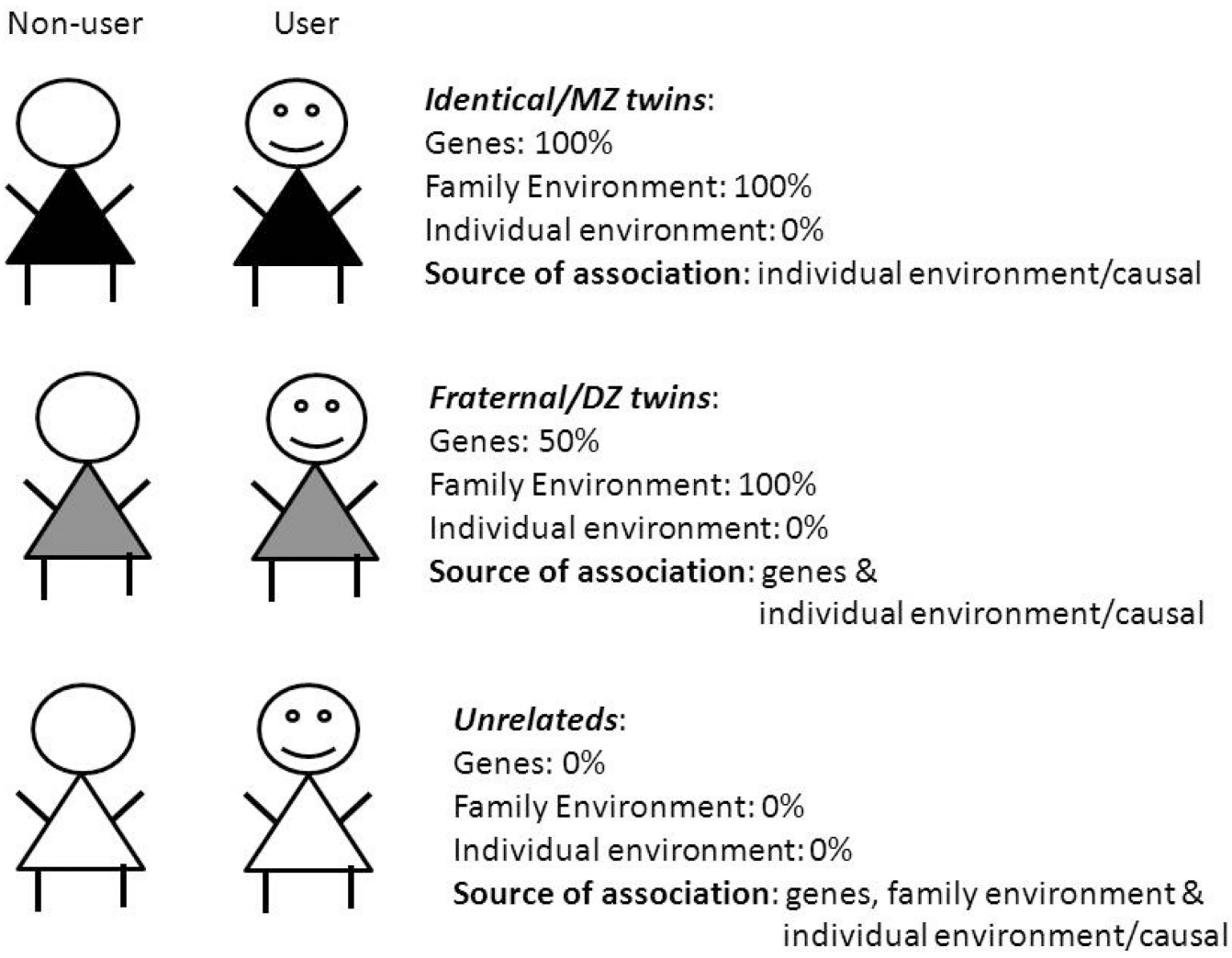

FIGURE 2.

The discordant twin design is illustrated. Pairs of twins (MZ=monozygotic/identical; DZ=dizygotic/fraternal) discordant for cannabis use are matched to varying degrees for genetic and environmental factors allowing for residual associations to be explained by unshared factors. Pairs of unrelated individuals are shown for comparison.

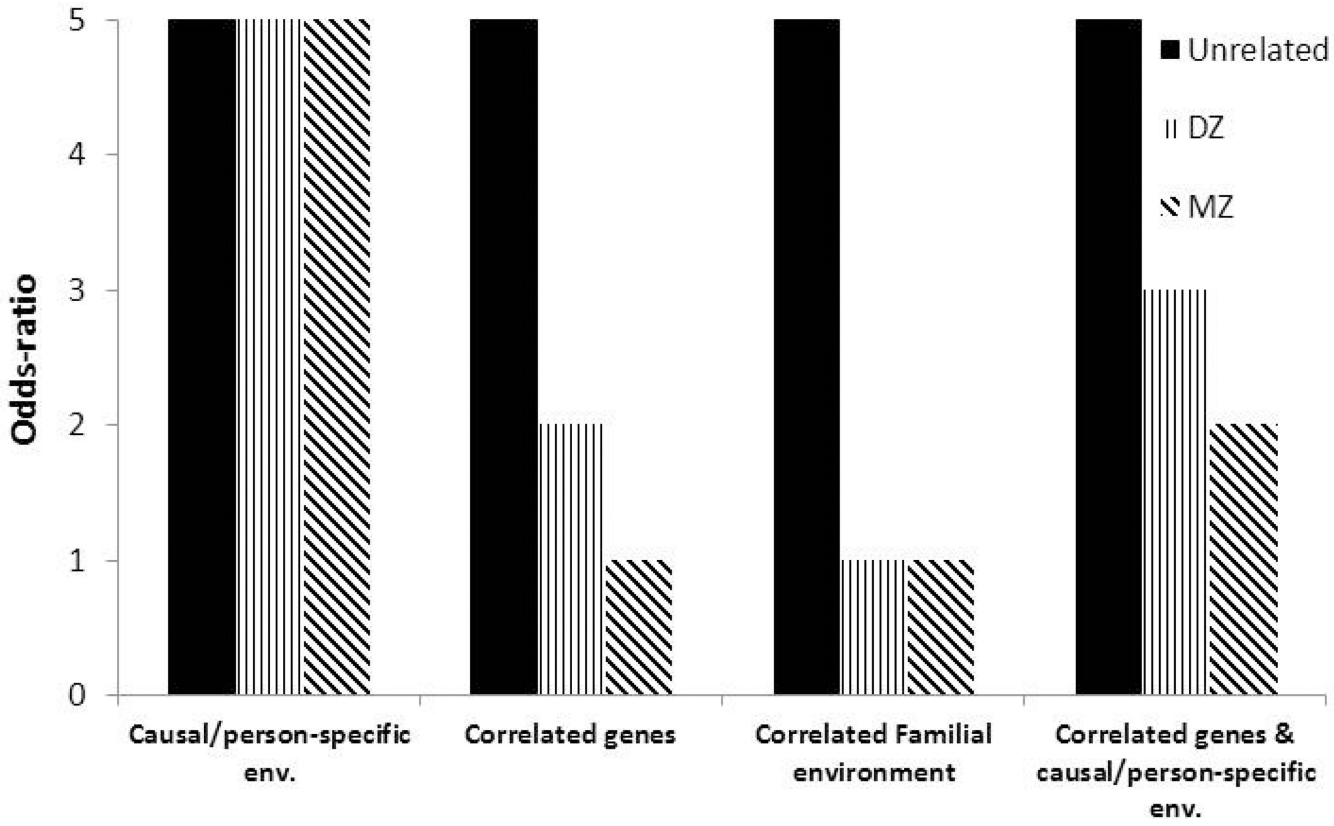

FIGURE 3.

Hypothetical results expected from a discordant twin study, for discordant pairs of MZ, DZ and unrelated individuals, which can be used to infer the nature of the association between cannabis use and outcomes. If the association is entirely due to causal or individual-specific factors then the magnitude of association is invariant to degree of relatedness. In contrast, if genes or family environment play a role, then matching discordant pairs of individuals for these factors results in an attenuation of the association.