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ORIGINAL ARTICLE

Genetic predisposition to schizophrenia associated with increased use of cannabis

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Cannabis is the most commonly used illicit drug worldwide. With debate surrounding the legalization and control of use, investigating its health risks has become a pressing area of research. One established association is that between cannabis use and schizophrenia, a debilitating psychiatric disorder affecting ~1% of the population over their lifetime. Although considerable evidence implicates cannabis use as a component cause of schizophrenia, it remains unclear whether this is entirely due to cannabis directly raising risk of psychosis, or whether the same genes that increases psychosis risk may also increase risk of cannabis use. In a sample of 2082 healthy individuals, we show an association between an individual's burden of schizophrenia risk alleles and use of cannabis. This was significant both for comparing those who have ever versus never used cannabis ($P = 2.6 \times 10^{-4}$), and for quantity of use within users ($P = 3.0 \times 10^{-3}$). Although directly predicting only a small amount of the variance in cannabis use, these findings suggest that part of the association between schizophrenia and cannabis is due to a shared genetic aetiology. This form of gene–environment correlation is an important consideration when calculating the impact of environmental risk factors, including cannabis use.

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INTRODUCTION

During the last quarter of the 20th century, cannabis use has increased to become the most widely used illicit drug in the world.[1] It is well established that cannabis use is much higher among schizophrenic patients than in the general population.[2] Cannabis intoxication can lead to an acute transient psychotic episode and produce short-term exacerbations of pre-existing psychotic symptoms,[3–5] an association that has been confirmed through the experimental administration of tetrahydrocannabinol.[6,7] Meta-analyses of prospective studies have found that cannabis use increases the likelihood of developing a psychotic illness by a factor of roughly two.[8–11] A dose response effect has been demonstrated,[12–14] and use in adolescence has been associated with the greatest risk.[15] Given the large health burden from schizophrenia and other psychotic disorders,[16] the view that cannabis use is a component cause of schizophrenia has heavily influenced discussion over the legislation surrounding cannabis use.

However, the relationship between schizophrenia and cannabis use may be more complicated than it initially seems. Despite a clear association between the two, the possibility of reverse causation has not been entirely excluded. Some small studies have suggested that it is in fact psychosis that is a risk factor for cannabis use, as those on a psychotic spectrum are more likely to experiment with drugs.[17,18] The strongest evidence comes from Ferdinand *et al.*[19] who found that the association was bidirectional, as cannabis-naive children with prodromal psychotic episodes had greater incidence of later cannabis use. However, a similarly sized study failed to replicate this finding.[20] There is also the possibility of attempts by patients at self-medication, as it has been suggested that cannabis use can reduce negative and affective symptoms in patients with an established psychotic disorder.[21–23]

The issue is further complicated by tentative evidence for interactions between cannabis use and genetic risk variants for schizophrenia.[24] Schizophrenia is known to be highly heritable with up to 80% of the variance explained by additive genetic effects,[25] and as sample sizes have increased a growing number of genetic risk variants have been identified.[26,27] Interactions between risk variants and cannabis use might explain why some individuals experience psychosis while others do not. However, cannabis use itself has been reported to be heritable,[28–30] although no genetic risk variants have been identified.[31] It is unclear to what extent the heritability of cannabis use results from shared heritability with other behavioural phenotypes such as schizophrenia predicting its use.

Here we test for such genetic overlap directly, and aim to discern the direction of causation between cannabis use and schizophrenia. Within a sample of 2082 healthy individuals, we tested to see whether polygenic risk scores for schizophrenia predict cannabis use. Polygenic risk scores reflect the cumulative burden of risk alleles carried by an individual as identified in a previous genome-wide association study (GWAS),[32] here of 13 833 schizophrenia cases and 18 310 controls.[27] Such an association with cannabis use would suggest that those genetically predisposed to schizophrenia use cannabis more frequently. This would mean that the association between schizophrenia and cannabis use is not simply one of an environmental risk factor, but rather involves gene–environment correlation, as individuals

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choose and shape their own environment based on their own innate preferences.

MATERIALS AND METHODS

The data used in this study come from the Australian Twin Registry. Data were obtained from two studies in which twins and their families participated in semi-structured diagnostic telephone interviews aimed primarily at assessing psychiatric health. Informed consent was obtained from all participants.

Sample 1 consisted of 6265 individuals aged between 23 and 39 years (mean = 29.9 ± 2.5) interviewed between 1996 and 2000. Participants were members of the young adult cohort, a volunteer panel of twins born between 1964 and 1971. The interview was based on a modified version of the SSAGA (Semi-Structured Assessment of the Genetics of Alcoholism[33]). Detailed information about the sample recruitment, the study procedure and the measures can be found elsewhere.[34] Sample 2 comprised 9688 individuals aged between 18 and 91 years (mean = 46.3 ± 11.3) interviewed between 2001 and 2005. Participants were members of the older and younger adult cohort of Australian twin pairs (born between 1895 and 1964, and between 1964 and 1971, respectively). A subset of this sample was ascertained based on large sibship size, or having a relative with nicotine or alcohol dependence. The interview used for this sample was also based on a modified version of the SSAGA. Further details about the sample and assessment can be found in Heath *et al.*[35]

A subset of the participants ($N = 1866$; 11.7%) participated in both studies, in which case we used data from the last assessment. The combined phenotypic sample consisted of 14 087 individuals, of whom 7172 were genotyped. In both studies, twins were asked the same items about cannabis use: (1) did you ever use marijuana?, (2) how old were you the very first time you tried marijuana (not counting the times you took it as prescribed)? and (3) how many times in your life have you used marijuana (do not count times when you used a drug prescribed for you and took the prescribed dose). Ever use was measured on a dichotomous scale (ever versus never), whereas age at initiation and quantity of use were open questions. Table 1 shows the prevalence of cannabis use for individuals included in the present study.

Genotype data were obtained using three different Illumina single nucleotide polygmorphism (SNP) genotyping platforms (317K, HumanCNV370-Quadv3, Human CNV370v1 and Human610-Quad). Standard quality control procedures were applied as outlined previously,[36] including checks for ancestry outliers, Hardy–Weinberg equilibrium ($P < 10^{-6}$), Mendelian errors, call rate, genotypic missingness (>5%), individual missingness (>5%) and minor allele frequency (< 0.01). Individuals were pruned on relatedness, removing one individual from each pair with relatedness >0.05, as determined from genetic data. The final sample therefore comprised 2082 'unrelated' individuals (see Table 1 for sample details).

Polygenic risk scores were constructed using the *P*-values and $\log_{10}$ odds ratios from the most recent large GWAS of schizophrenia, a meta-analysis of the Psychiatric Genomics Consortium's studies with additional Swedish samples totalling 13 833 cases and 18 310 controls.[27] SNPs were pruned for linkage disequilibrium using *P*-value informed clumping in PLINK,[37] using a cutoff of $R^2 = 0.25$ within 200 kb window. The major histocompatibility complex region of the genome was excluded, due to its complex linkage disequilibrium structure. After linkage disequilibrium pruning, 147 830 SNPs remained. Multiple scores were generated for each individual using the PLINK score option and based on top SNPs from the schizophrenia GWAS using varying significance thresholds ($P = 0.0001$, 0.001, 0.01. 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 and 1.0). Polygenic risk scores were tested for association with a binary ever versus never used cannabis and two quantitative traits for quantity of use and age at first use, in logistic and linear regressions, respectively. These analyses were corrected for the first 10 ancestry-informative principal components, genotyping platform, sex, age, age squared and sex by age. Analysis was performed in STATA.[38]

Table 1. Summary statistics of sample for cannabis use traits

	Users	*Non-users*
N	1011	1071
Mean age (s.e.)	41.3 (0.23)	53.0 (0.37)
Percentage female (%)	46.5	56.0
Mean age at initiation (s.e.)	19.6 (0.06)	—
Mean number of uses over lifetime (s.e.)	62.7 (4.56)	—

RESULTS

After pruning, 2082 unrelated individuals remained in our sample with both genotype and phenotype measures. Within the sample, 1011 individuals (48.6%) had ever used cannabis, of whom 997 had data on quantity of use. Mean number of usages of cannabis over lifetime was 62.7 (95% CI 53.8–71.6), and the mean age of initiation of use was 20.1 (95% CI 19.7–20.5). Males showed higher rates of use than females, 53.5% compared with 43.9% ($P < 0.001$), although no significant difference in age at initiation. Table 1 shows the summary statistics for the sample.

Polygenic risk scores for schizophrenia showed positive associations for ever versus never use of cannabis across all *P*-value thresholds, with the strongest association for those SNPs with *P*-values of 0.01 or below in the original schizophrenia GWAS (see Figure 1, $R^2 = 0.47\%$, $P = 2.6 \times 10^{-4}$). Significant associations were also seen in the analysis of quantity of cannabis use for 9 of the 10 SNP cutoffs, with the top association seen for those SNPs with $P \leqslant 0.05$ for schizophrenia ($R^2 = 0.85\%$, $P = 0.003$). No association was seen with age at initiation of use, although the association with quantity of use remained significant when number of years of usage was accounted for (results not shown).

As a secondary analysis, polygenic risk score for schizophrenia risk alleles with $P \leqslant 0.01$ (the threshold with the greatest association in the primary analysis) was examined within 990 twin pairs (608 dizygotic and 382 monozygotic) where data on cannabis use of both twins was available. Taking the mean polygenic risk score within each twin pair, an ordinal regression was performed to predict whether neither ($n = 272$), one ($n = 273$) or both twins ($n = 445$) were cannabis users. After correcting for age, sex and zygosity, a significant association was observed ($P = 0.001$). Those twin pairs where both reported using cannabis had the greatest burden of schizophrenia risk alleles, pairs with only one user were found to have an intermediate level and the

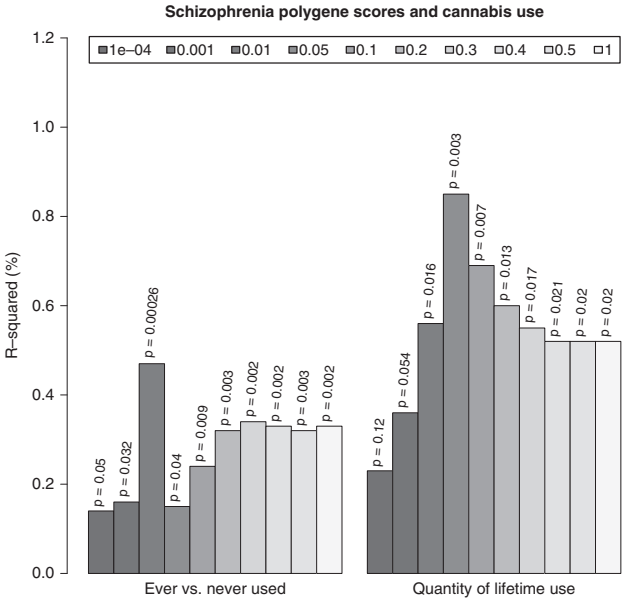

Figure 1. Results of polygenic risk scores for schizophrenia predicting variance explained (R^2) in cannabis use as both a binary trait of ever versus never, and as a quantitative trait of lifetime use within only users. Polygenic scores were created using different cutoffs for the inclusion of risk variants for schizophrenia, ranging from $P = 0.0001$ to 1.0.

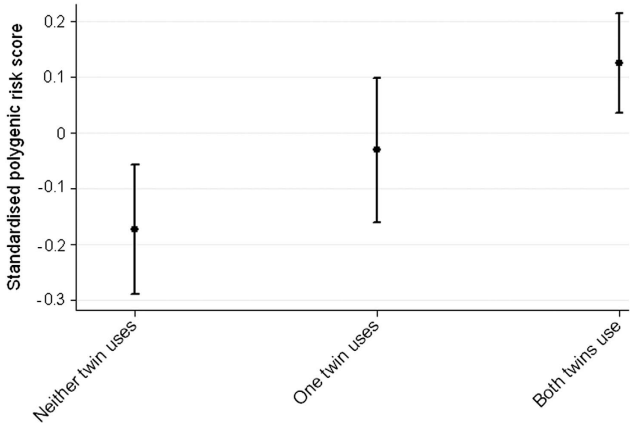

Figure 2. Mean standardized schizophrenia polygenic risk scores for pairs of twins when neither ($n = 272$), one ($n = 273$) or both twins ($n = 445$) had reported use of cannabis. An ordinal regression reported a significant association ($P = 0.001$).

lowest burden was found in pairs where neither twin reported use (see Figure 2).

DISCUSSION

Our results show that to some extent the association between cannabis and schizophrenia is due to a shared genetic aetiology across common variants. They suggest that individuals with an increased genetic predisposition to schizophrenia are both more likely to use cannabis and to use it in greater quantities. This is not to say that there is no causal relationship between use of cannabis and risk of schizophrenia, but it does establish that at least part of the association may be due to causal relationship in the opposite direction. Although the variance in cannabis use explained by schizophrenia polygenic risk scores is small, it is in line with other cross-phenotype analyses, largely due to the polygenic risk scores for schizophrenia predicting only ~7% of the variation for schizophrenia itself. Previous associations between polygenic risk scores for schizophrenia and other psychiatric illnesses, such as bipolar disorder, major depression and autism,[39] have shown effects of similar sizes. Further research will be needed to see whether the genetic overlap observed here is specific to cannabis use or is present across illicit drug use and addiction phenotypes, data for which was not widely available in this sample. For now, these findings have important implications for the current perception of cannabis use as a risk factor for schizophrenia, and other psychotic disorders.

However, it is worth noting that this association, if true, does not rule out the possibility of cannabis independently being a risk factor for schizophrenia. A bidirectional association between cannabis use and psychosis has previously been suggested.[40] Further, one caveat to interpreting the direction of causation concerns the discovery sample used to identify schizophrenia risk alleles. The schizophrenia GWAS sample will likely include many more cannabis users among cases than controls. This may lead to an excess of causal SNPs associated with cannabis use, as opposed to schizophrenia itself, identified as schizophrenia risk alleles. Only if the discovery schizophrenia sample was comprised entirely of non-cannabis users could causation be inferred without any risk of confounding. This is an important consideration as to whether polygenic risk scores overestimate individuals' un-modifiable genetic risk by including their genetic predisposition to modifiable environmental risk factors.

These results highlight the blurring between behavioural phenotypes and environment, and have wider implications for how we perceive supposedly environmental risks for disease. Individuals select their own environments based on their innate and learned preferences, and have their environments react to their own behaviour. Further, parents pass down both genes and environment to their children. All of these can contribute to gene–environment correlation, particularly with respect to behavioural traits. Several studies have shown that supposedly environmental risk factors such as urbanicity, religiosity and stressful life events have heritable components to them.[41–43] The existence of heritability for supposedly environmental risk factors does not mean they are inevitable, only that causality is more complicated to discern. Future studies will need to explore the matching of cases and controls on environmental risk variants to fully disentangle causation. This can be supplemented exploring the generation of polygenic risk scores for environmental risk factors, and their role in predicting disease status. The wider availability of genetic data in richly phenotyped samples should allow for the integration of genetics into an epidemiological framework, and so the discovery of gene–environment correlations where they exist.

With ongoing debate over the legalization of cannabis and the potential health risks it poses, understanding the association between its use and schizophrenia is a priority. It has previously been suggested that, even assuming an entirely causal relationship, the required reduction in the number of cannabis users to prevent one case of schizophrenia is in the thousands.[44] Our findings here highlight the possibility that this association might be bidirectional in causation, and that the risks of cannabis use could be overestimated. This is an important subtlety to consider when calculating the economic and health impact of cannabis use.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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