



LUND UNIVERSITY

The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study.

Giordano, Giuseppe Nicola; Ohlsson, Henrik; Sundquist, Kristina; Sundquist, Jan; Kendler, Ken

Published in:
Psychological Medicine

DOI:
[10.1017/S0033291714001524](https://doi.org/10.1017/S0033291714001524)

2015

[Link to publication](#)

Citation for published version (APA):

Giordano, G. N., Ohlsson, H., Sundquist, K., Sundquist, J., & Kendler, K. (2015). The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study. *Psychological Medicine*, 45(2), 407-414. <https://doi.org/10.1017/S0033291714001524>

Total number of authors:
5

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

**The Association between Cannabis Abuse and Subsequent Schizophrenia: A
Swedish National Co-Relative Control Study**

Giuseppe N. Giordano PhD MD (1), Henrik Ohlsson PhD (1), Kristina Sundquist MD PhD
(1,2), Jan Sundquist MD PhD (1,2), Kenneth S. Kendler (3,4,5)

- 1- Center for Primary Health Care Research, Lund University, Malmö, Sweden.
- 2- Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA.
- 3- Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA.
- 4- Department of Psychiatry, Virginia Commonwealth University, Richmond VA, USA.
- 5- Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA.

Corresponding author: Kenneth S. Kendler, MD, Virginia Institute for Psychiatric and Behavioral Genetics of VCU, Box 980126, Richmond, VA 23298-0126;
E-mail: kendler@vcu.edu

Key words: Schizophrenia, cannabis, causality, co-relative design, cocaine

ABSTRACT

Background - While cannabis abuse (CA) is associated with schizophrenia, the causal nature of this association is less clear, with prodromal effects further complicating its interpretation.

Methods – From Swedish national registry databases, we employed a co-relative case-control design using full-sibling, half-sibling and first cousin comparisons, alongside a general Swedish population sample. Using ICD codes, 5,456 individuals with an initial diagnosis of schizophrenia (2000-2010) were matched with five schizophrenia-free controls. We further identified first cousin, half-sibling and full-sibling pairs discordant for CA and statistically extrapolated results for discordant monozygotic twins (MZ).

Results - Within the general Swedish population, CA was strongly associated with later schizophrenia (Odds ratio (OR) =10.44 (95% CI) 8.99-12.11). This association was substantially attenuated both by increasing temporal delays between CA exposure and schizophrenia diagnosis and by controlling for increasing degrees of familial confounding. Extrapolated discordant MZ pairs suggested that fully controlling for confounding familial factors reduced the association between CA and later schizophrenia to more modest levels (ORs of approximately 3.3 and 1.6 with three- and seven-year temporal delays, respectively). Opiate, sedative, cocaine/stimulant and hallucinogen abuse were also strongly associated with subsequent schizophrenia in the general population. After controlling for familial confounding, only cocaine/stimulant exposure remained associated.

Conclusions - CA has an appreciable causal impact on future risk for schizophrenia. However, population-based estimates of cannabis-schizophrenia comorbidity substantially over-estimate their causal association. Predictions of the cases of schizophrenia that might be prevented by reduced cannabis consumption based on population associations are, therefore, likely to be considerably over-estimated.

A long history of empirical evidence shows an association between cannabis use and symptoms of psychosis (see reviews: (D'Souza, 2007, Minozzi *et al.*, 2010)). Three main inferences may be drawn from this extensive body of research. First, cannabis intoxication may lead to transient psychotic episodes (Mathers and Ghodse, 1992, Negrete *et al.*, 1986, Sewell *et al.*, 2009, Thornicroft, 1990); second, cannabis use seems commonplace among individuals who are vulnerable to, or have pre-existing symptoms of, psychosis and/or schizophrenia (Degenhardt *et al.*, 2003, Dixon, 1999, Koskinen *et al.*, 2010, Linszen *et al.*, 1994) Third, though there is empirical evidence to support the theory that cannabis use is a component cause of schizophrenia (Andreasson *et al.*, 1987, Arseneault *et al.*, 2002, McGrath *et al.*, 2010, van Os *et al.*, 2002, Veling *et al.*, 2008, Weiser *et al.*, 2002, Zammit *et al.*, 2002), the 'etiologic' hypothesis remains controversial (Fergusson *et al.*, 2006, McLaren *et al.*, 2010, Moore *et al.*, 2007, Sevy *et al.*, 2010). This paper focuses on the third point and investigates the degree to which the association between cannabis use and schizophrenia is causal.

Evidence supporting causality, as per 'Hill's Postulates' (Goodman and Phillips, 2005, Hill and Hill, 1991), includes specificity of association (van Os *et al.*, 2002, Zammit *et al.*, 2002), and a dose-related response (Arseneault *et al.*, 2002, Di Forti *et al.*, 2009, McGrath *et al.*, 2010, Veling *et al.*, 2008), with heavy cannabis users (cannabis abusers) having a six-fold increase in risk of future diagnosis of schizophrenia (Andreasson *et al.*, 1987, Zammit *et al.*, 2002).

Of all the suggested causal criteria, however, only *temporality* is labelled "essential", i.e. exposure must occur prior to disease onset (Goodman and Phillips, 2005, Hill and Hill, 1991). Prodromal effects common to schizophrenia could make temporality difficult to establish: affected individuals may suffer from a variety of non-specific symptoms (anxiety, depression, concentration problems, etc.) (Cornblatt *et al.*, 2003), which occur months to years prior to the manifestation of full schizophrenic illness (Klosterkotter *et al.*, 2001). During this time, individuals may use cannabis either as a result of the prodromal illness or in an attempt to treat their emerging symptoms.

One recent review assessed current evidence of association between cannabis use and psychosis/schizophrenia alongside Hill's causal criteria and concluded that "...[this observed] association may reflect a causal relationship" (McLaren *et al.*, 2010). However, the same review recognised the critical need for future research "... [to] control for important environmental and biological confounding factors...".

Given the consistent evidence for strong familial/genetic contributions to both schizophrenia and cannabis use and misuse (Kendler *et al.*, 2000, Kendler and Prescott, 1998, Sullivan *et al.*, 2003, Tsuang *et al.*, 1996, Verweij *et al.*, 2010), a substantial concern should be that some or all of the association between cannabis use and schizophrenia arises from familial confounding. However, to date, only one prospective study has attempted to control for such confounders by employing a sibling-pair analysis (McGrath *et al.*, 2010). Sibling-pairs are a natural experiment; they each share 50% of their parents' genes, often share a similar pre-natal environment and, share similar environmental factors as they grow up (Lawlor and Mishra, 2009). Investigating sibling-pairs, who are discordant for cannabis use, alongside a general population sample, permits an assessment of the degree to which observed associations between cannabis use and schizophrenia are confounded by familial (genetic and/or shared environmental) factors.

An extension of this methodology is the co-relative control design, which includes other relatives, in particular half-sibling and first-cousin-pair comparisons; half-siblings share on average 25% of their genes, and cousins 12.5%. Shared environmental influences also decrease across the three co-relative groups, the presumption being that cousin-pairs are the group likely to spend the least time together growing up. The use of a co-relative design, therefore, may provide a more convincing case as to the nature and extent of familial confounding, particularly if an expected gradient is observed, as familial confounding is increasingly controlled.

The aim of this study is to investigate the causal nature of the association between cannabis *abuse* and a future diagnosis of schizophrenia. We utilise longitudinal national data, containing independent observations of cannabis abuse prior to later hospital diagnosis of schizophrenia. We test the *etiologic* hypothesis, that cannabis abuse is one direct cause of schizophrenia employing a co-relative control design and then proceed to consider the specificity of this association and temporal issues surrounding potential prodromal effects.

Methods

Our study used linked data from multiple Swedish nationwide registries and healthcare data. Linking was achieved via the unique individual Swedish 10-digit personal ID number assigned at birth or immigration to all Swedish residents. Our databases utilized the following: the Total Population Register, containing annual data on family status; the Multi-Generation Register, providing information on family relations; the Swedish Hospital Discharge Register, containing all hospitalizations for Swedish inhabitants from 1964-2010;

the Outpatient Care Register, containing information from all outpatient clinics from 2001 to 2010; the Swedish Crime Register, which included national complete data on all convictions from 1973-2011; the Swedish Mortality Register, containing causes of death. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409). Our methods for identifying cannabis abuse and schizophrenia are given in the appendix. Of note, our definition of schizophrenia excluded diagnoses of simple schizophrenia, schizoaffective disorder and acute schizophrenia.

Sample

First, we identified all individuals in Sweden diagnosed with schizophrenia over the period 2000-2010. From these, we identified all individuals under 50 years of age at the time of their initial schizophrenia diagnosis (N = 5,456). Each individual was then matched to five controls based on gender, age and country of birth, and without a diagnosis of schizophrenia from 1987-2010. Our main exposure variable was cannabis abuse (CA). In both cases and controls, CA was defined only if the individual was registered as a cannabis abuser *prior* to the date of their first diagnosis of schizophrenia. We investigated the association between CA and individual schizophrenia risk in the general Swedish population using conditional logistic regression.

Second, we compared the results from the Swedish general population with results from a co-relative design. By means of the Swedish Multi-Generation Register, we identified all first cousin, paternal and maternal half-sibling and full-sibling pairs who were born within 10 years of one another. We separated paternal and maternal half-siblings because, although they shared their degree of genetic resemblance, Swedish maternal half-siblings were much more likely to live together while growing up than paternal half-siblings (Frisell *et al.*, 2012b).

Statistical analysis

To adjust for an array of potentially confounding genetic and environmental factors, we used conditional logistic regression to examine all co-relatives pairs discordant for CA. In these analyses, only pairs discordant for schizophrenia are informative. If the individual with CA had a schizophrenia diagnosis, the CA registration had to be recorded *prior* to the schizophrenia diagnosis. Pairs where one member had a registration of schizophrenia prior to year 2000 were excluded.

To consider potential prodromal effects, we also investigated the time between CA and schizophrenia diagnosis at 1, 3, 5 and 7-year intervals. MZ twin pairs discordant for CA exposure would be of particular interest in these analyses as they provide complete control for genetic and familial-environmental confounding. However, fewer than five MZ twin pairs met our definition of discordance. Therefore, we estimated values for discordant MZ pairs based on the observed results from other relationships, i.e. by fitting a regression line to the beta-coefficients from the five analyses (general population, cousins, paternal half-siblings, maternal half-siblings and siblings). We assumed values of additive genetic effects (A) from genetic expectations. The shared environmental estimates (C) were calculated from the entire Swedish population born during the period 1970 to 1985 from a dataset for all possible relative-pairs. Based on age difference, we calculated the percentage of possible time spent in the same household up to age 15. For example, a full sibling pair born 5 years apart that spent 10 years in the same household was given the value 1; whereas a pair born 5 years apart that spent 5 years in the same household was given the value 0.5. The A and C mean estimates for each relative pair group were used for the extrapolation: Population A:0, C:0; Full cousins A:0.125, C:0; Paternal half siblings: A:0.25 C:0.05; Maternal half siblings A:0.25 C:0.87; Full siblings: A:0.5 C:0.95; and MZ Twins: A:1 C:1.

We conducted two further sensitivity analyses to test the robustness of the results from our main analyses: i) Individuals had to have two separate registrations for both CA and later schizophrenia; ii) Individuals with diagnoses of *any* drug psychoses and/or bipolar disorder were excluded from schizophrenia cases (see appendix for ICD codes). We also tested the specificity of the association by investigating the association between CA and major affective disorder defined as bipolar or major depressive disorder (see appendix for ICD codes). Finally, we tested for substance specificity by investigating associations between abuse of other drug classes and later schizophrenia. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc, 2008).

Results

From all schizophrenia cases derived from the Swedish general population, 10.28% were recorded as cannabis abusers prior to diagnosis, compared with 1.17% among controls. The mean number of days between registration for CA and subsequent diagnosis of schizophrenia was 2,701 (SD: 2,355) – approximately 7 years, three months.

'General population' sample

As seen in table 1, row 1, in the general population, there was a large increased risk of diagnosis of schizophrenia if an individual had a prior registration of CA (odds ratio (OR) = 10.44, 95% confidence interval (CI) 8.99-12.11). As the required time between CA and schizophrenia diagnosis was increased (columns 2-5), this risk was attenuated, though remained substantial and significant at 7 years (OR = 4.24 (CI) 3.54-5.07).

Co-relative control samples

Table 1, rows 2-5 demonstrate the effect of the removal of familial confounding on the association between CA and a future schizophrenia diagnosis. As the degree of sharing of genetic and environmental factors increased (from first cousin to full-sibling pairs), the association between CA and schizophrenia decreased (OR full-siblings = 5.07 (CI) 4.17-6.16).

As in the general population, the co-relative risk was attenuated as the required delay between CA and a schizophrenia diagnosis was increased. The risk for schizophrenia remained significant although modest at 7 years, even in full-sibling pairs (OR = 1.98 (CI) 1.59-2.48).

Table 1, row 6 contained our extrapolated estimates for MZ twins discordant for CA. Controlling for 100% of genetic and familial-environmental factors, we estimated ORs between CA and schizophrenia ranging from 3.92 with no time lag to 1.67 after a seven year lag.

Sensitivity and specificity analyses

As seen in tables 2 and 3, after requiring two separate registrations of CA prior to two separate later diagnoses of schizophrenia, the observed association increased modestly in the general population but was similar or slightly attenuated in maternal half and full-sibling pairs and in our extrapolated discordant MZ twin pairs.

Having excluded all individuals with diagnoses of bipolar disorder (Lichtenstein *et al.*, 2009) and/or *any* drug-induced psychosis prior to *and* after initial SCZ diagnosis, the association between CA and schizophrenia was slightly attenuated in the general population but little changed among close relatives and our estimated MZ pairs.

CA registration was significantly associated with a later diagnosis of major affective illness in the population (OR 2.98 (CI) 2.75 - 3.17). This association was decreased but

remained significant in full sibling pairs (OR = 1.63 (CI) 1.49-1.77) but was fully attenuated in our extrapolated discordant MZ twins pairs.

Table 3 shows the observed associations between abuse of opiates, sedatives, cocaine/stimulants and hallucinogens and subsequent schizophrenia after excluding CA cases. In the general population, abuse of all four drug classes was strongly associated with schizophrenia, especially sedatives and hallucinogens. However, these associations were substantially attenuated in relative pairs. In our extrapolated discordant MZ twins, only cocaine/stimulant abuse remained associated with future schizophrenia risk.

Discussion

The aim of this study was to investigate the causal nature of the association between CA and the future diagnosis of schizophrenia utilizing national-level data and a co-relative control design. As the risk for CA and schizophrenia runs strongly in families (Kendler *et al.*, 2000, Kendler and Prescott, 1998, Sullivan *et al.*, 2003, Tsuang *et al.*, 1996, Verweij *et al.*, 2010), results from a co-relative design could provide a critical evaluation of the nature of the causal relationship between CA and schizophrenia.

Within the general Swedish population, CA was more strongly associated with later schizophrenia (OR = 10.44) than has been observed in most prior studies (Arseneault *et al.*, 2002, Di Forti *et al.*, 2009, McGrath *et al.*, 2010, Veling *et al.*, 2008, Zammit *et al.*, 2002). However, previous studies have suggested that the relationship between cannabis use is dose-dependent and these prior studies nearly all examined only cannabis use. Because our sample of cannabis abusers had high enough levels of cannabis use to experience adverse legal or medical consequences, the association with schizophrenia would likely be stronger than that observed in studies only assessing cannabis use. Interestingly, after allowing for the same 5-year prodromal period as Zammit *et al.* (2002), our study produced similar results within the Swedish general population (OR = 5.95) to those identified as cannabis 'abusers' within Swedish conscripts (OR = 6.70).

Allowing seven years from initial CA registration to later diagnosis, the risk for schizophrenia in discordant full-sibling pairs remained almost two-fold. Our extrapolated MZ estimates suggested that if familial factors were fully controlled for, the positive association between CA and later schizophrenia remained (OR = 1.67). The results of this study, therefore, lend support to the *etiologic* hypothesis, that cannabis abuse is one direct cause of later schizophrenia (Andreasson *et al.*, 1987, Arseneault *et al.*, 2002, McGrath *et al.*,

2010, van Os *et al.*, 2002, Veling *et al.*, 2008, Weiser *et al.*, 2002, Zammit *et al.*, 2002). The strength of the association from our full-sibling analysis is similar to that derived from the meta-analysis performed by Arseneault *et al.* (2004); however, it is important to note that the latter's outcome definition is broader than the one used in this study, including schizophreniform and other psychotic symptoms.

Our results also suggest that a large majority of the CA-schizophrenia association observed in the general population is not causal and results from confounding due to shared familial factors. The pattern of ORs observed in table 1 gives some insight into the nature of these familial factors. The monotonic decline in ORs with increasing genetic resemblance in co-relative pairs suggests that shared genetic risk factors contribute substantially to the CA-schizophrenia association. However, the consistently lower ORs seen in maternal versus paternal half-siblings suggest that familial environmental factors also influence the co-occurrence of CA and schizophrenia.

The results of our sensitivity analyses strengthen our main findings. The 'double registration' analysis increased the rigor of both CA and schizophrenia diagnoses and found broadly similar patterns of association. The 'purified' schizophrenia analysis decreased the general population association (OR = 7.99), but produced little overall change in the co-relative sample (compared with Table 1). Our first specificity analysis of the association between CA and major affective illness showed at the population level a significant association, albeit less robust than that seen between CA and schizophrenia. However, when controlling for familial confounding, especially with our extrapolated MZ twin pairs, the CA-affective illness association disappeared. These results suggest that, in contrast to the CA-schizophrenia relationship, the CA-affective illness association is not likely to be causal but rather results from confounding due to shared familial risk factors.

Past research investigating poly-drug use implicated cannabis as the substance most likely to be associated with a later diagnosis of schizophrenia (Arseneault *et al.*, 2002, van Os *et al.*, 2002, Zammit *et al.*, 2002). Our 'other substance' specificity tests (Table 3) showed that in the general population, associations between abuse of opiates, sedatives, cocaine/stimulants and hallucinogens and risk for subsequent schizophrenia was very similar to those seen for cannabis. These results were surprising given the general lack of evidence of psychotogenic potential for opiates and sedatives (Brown and Stoudemire, 1998, Dalmau *et al.*, 1999). However, an examination of our co-relative results, including our extrapolated MZ twins, suggests that the associations for opiates, sedatives, and hallucinogens were

likely non-causal, arising rather from familial confounding. By contrast, our analyses suggest that exposure to cocaine and non-cocaine stimulants (at the level sufficient to be registered for abuse in Sweden), has a modest causal impact on future schizophrenia risk. This result is consistent with prior studies showing that stimulant abusers had an increased risk for psychosis (Chen *et al.*, 2003, Mitchell and Vierkant, 1991) and a subsequent diagnosis of schizophrenia (Callaghan *et al.*, 2012, Post, 1975).

In aggregate, our results support the hypothesis that cannabis abuse of sufficient severity to be detected in Swedish registries has an appreciable causal impact on future risk for schizophrenia. However, our findings also suggest that raw estimates of the cannabis-schizophrenia association substantially over-estimate their causal association. An examination of our Table 1 suggests that fully correcting for familial confounding reduces the CA-schizophrenia association by approximately two-thirds. Though these results reflect those found in the meta-analysis performed by Arseneault *et al.* (2004), the latter's broader outcome definition may have led to an over-estimation of cases of schizophrenia that might be prevented by reduced cannabis consumption, based on population associations.

Strengths and limitations

A major strength of our study is its annual sampling of a national population from 1987-2010, enabling us to perform the first co-relative study of cannabis abuse and later schizophrenia. Our medical data are nearly 100% complete for exposure and outcome diagnoses. Despite this, there are several limitations of our study that should be noted.

First, by utilizing registry data, we relied on a hospital-based diagnosis of schizophrenia. Many consider the gold-standard to be a 'research-based' diagnosis. However, an evaluation of Swedish diagnostic procedures concluded that schizophrenic psychoses in Swedish Register data had '... high positive predictive power to a standard research DSM-IV diagnosis' (Ekholm *et al.*, 2005).

Second, we identified cannabis abuse from medical and legal records, utilising ICD and conviction codes to capture prevalence within our study population. While this method has the important advantage of not requiring accurate respondent recall and self-reporting, the risk for misclassification bias remains. Furthermore, we have assumed that those admitted to hospital or convicted for cannabis use represented a sub-sample of heavy cannabis users, which are labelled 'cannabis abusers' in this study (i.e. it is likely that there were many more people who used/abused cannabis than those who were registered as CA.)

Therefore, some risk remains that CA identification in the current sample may be contaminated by evidence of prodromal schizophrenia. Because our subjects experienced adverse medical or legal consequences of their cannabis use, our results are not directly comparable to studies that examine cannabis use or even heavy cannabis.

Third, it has been shown that in sibling and twin-pair comparisons, estimates could be more biased by non-shared confounders than in unpaired (general population) estimates (Frisell *et al.*, 2012a). However, it is unlikely that the effects of non-shared bias would have the same influence across the four relative groups of our co-relative control design. Furthermore, that our results showed a decreasing gradient of association as familial factors increased provides a convincing case as to the nature and extent of familial confounding of the association between CA and schizophrenia. We further extrapolated our MZ twin estimates from the regression lines of our co-relative models. Though we weighted these for genetic (A) and shared environmental (C) factors, the extrapolated results will not be as robust as those derived from our actual sample and, therefore, should be interpreted accordingly. Also, ORs greater than one in our sibling or simulated MZ pairs need not imply a causal link between CA and schizophrenia. Such results could arise, totally or in part, due to environmental experiences not shared with the sibling that increase risk both for CA and schizophrenia.

Fourth, only information pertaining to first registration for CA and first admission for schizophrenia were available in the registries. We, therefore, do not know when the abuse or illness actually started. We explored this question by examining various temporal delays between CA and first schizophrenia admission to rule out the possibility that CA arose during the psychotic prodrome. As the delay becomes longer, the number of false positive associations (excluded cases where CA arose as a result of the prodrome and did not causally contribute to schizophrenia) probably declines but the number of false negatives (excluded cases where CA did causally contribute to schizophrenia) also probably increases. We cannot determine what delay provides the most accurate picture of the causal association.

Conclusion

In the Swedish population, cannabis abuse was strongly associated with subsequent schizophrenia. However, controlling for familial confounding and prodromal effects substantially reduced later schizophrenia risk, intimating that a large proportion of the observed association is non-casual. However, as shown in our full-sibling comparisons, the

results of this study provide empirical evidence lending further support to the hypothesis that cannabis abuse is one component cause of schizophrenia. Current and future policies should consider this, as well as the other reported deleterious health outcomes associated with cannabis use, when debating the legal status of this substance.

Financial support - Funding for this study was provided by NIDA Grant R01 DA030005, the Swedish Research Council to Kristina Sundquist (K2012-70X-15428-08-3), the Swedish Research Council for Health, Working Life and Welfare (In Swedish: Forte; Reg.nr: 2013-1836) to Kristina Sundquist, the Swedish Research Council to Jan Sundquist (2012-2378) as well as ALF funding from Region Skåne awarded to Jan Sundquist and Kristina Sundquist.

Conflict of interest: None

References

- Andreasson, S., Engstrom, A., Allebeck, P. & Rydberg, U.** (1987). Cannabis and schizophrenia - a longitudinal-study of swedish conscripts. *Lancet* **2**, 1483-1486.
- Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A. & Moffitt, T. E.** (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal* **325**, 1212-1213.
- Arseneault, L., Cannon, M., Witton, J. & Murray, R. M.** (2004). Causal association between cannabis and psychosis: examination of the evidence. *British Journal of Psychiatry* **184**, 110-117.
- Brown, T. M. & Stoudemire, A.** (1998). *Psychiatric side effects of prescription and over-the-counter medications: recognition and management*. American Psychiatric Pub: Chicago.
- Callaghan, R. C., Cunningham, J. K., Allebeck, P., Arenovich, T., Sajeev, G., Remington, G., Boileau, I. & Kish, S. J.** (2012). Methamphetamine use and schizophrenia: a population-based cohort study in California. *American Journal of Psychiatry* **169**, 389-96.
- Chen, C. K., Lin, S. K., Sham, P. C., Ball, D., Loh, E. W., Hsiao, C. C., Chiang, Y. L., Ree, S. C., Lee, C. H. & Murray, R. M.** (2003). Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychological Medicine* **33**, 1407-14.
- Cornblatt, B. A., Lencz, T., Smith, C. W., Correll, C. U., Auther, A. M. & Nakayama, E.** (2003). The schizophrenia prodrome revisited: A neurodevelopmental perspective. *Schizophrenia Bulletin* **29**, 633-651.
- D'Souza, D. C.** (2007). Cannabinoids and psychosis. *Integrating the Neurobiology of Schizophrenia* **78**, 289-326.
- Dalmau, A., Bergman, B. & Brismar, B.** (1999). Psychotic disorders among inpatients with abuse of cannabis, amphetamine and opiates. Do dopaminergic stimulants facilitate psychiatric illness? *Eur Psychiatry* **14**, 366-71.
- Degenhardt, L., Hall, W. & Lynskey, M.** (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence* **71**, 37-48.
- Di Forti, M., Morgan, C., Dazzan, P., Pariante, C., Mondelli, V., Marques, T. R., Handley, R., Luzzi, S., Russo, M., Paparelli, A., Butt, A., Stilo, S. A., Wiffen, B., Powell, J. & Murray, R. M.** (2009). High-potency cannabis and the risk of psychosis. *British Journal of Psychiatry* **195**, 488-491.
- Dixon, L.** (1999). Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. *Schizophrenia Research* **35**, S93-S100.
- Eckholm, B., Eckholm, A., Adolfsson, R., Vares, M., Osby, U., Sedvall, G. C. & Jonsson, E. G.** (2005). Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. *Nordic Journal of Psychiatry* **59**, 457-464.
- Fergusson, D. M., Poulton, R., Smith, P. F. & Boden, J. M.** (2006). Drugs - Cannabis and psychosis. *British Medical Journal* **332**, 172-175.
- Frisell, T., Oberg, S., Kuja-Halkola, R. & Sjolander, A.** (2012a). Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology* **23**, 713-20.
- Frisell, T., Pawitan, Y., Langstrom, N. & Lichtenstein, P.** (2012b). Heritability, assortative mating and gender differences in violent crime: results from a total population sample using twin, adoption, and sibling models. *Behavior Genetics* **42**, 3-18.
- Goodman, K. & Phillips, C.** (2005). Hill's Criteria of Causation. In *Encyclopedia of Statistics in Behavioral Sciences* (ed. E. BS and H. DC), pp. 818-820. John Wiley & Sons: Chichester, UK.
- Hill, A. B. & Hill, I. D.** (1991). *Principles of medical statistics*. Edward Arnold: London.

- Kendler, K. S., Karkowski, L. M., Neale, M. C. & Prescott, C. A.** (2000). Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Archives of General Psychiatry* **57**, 261-269.
- Kendler, K. S. & Prescott, C. A.** (1998). Cannabis use, abuse, and dependence in a population-based sample of female twins. *American Journal of Psychiatry* **155**, 1016-22.
- Klosterkotter, J., Hellmich, M., Steinmeyer, E. M. & Schultze-Lutter, F.** (2001). Diagnosing schizophrenia in the initial prodromal phase. *Archives of General Psychiatry* **58**, 158-164.
- Koskinen, J., Lohonen, J., Koponen, H., Isohanni, M. & Miettunen, J.** (2010). Rate of Cannabis Use Disorders in Clinical Samples of Patients With Schizophrenia: A Meta-analysis. *Schizophrenia Bulletin* **36**, 1115-1130.
- Lawlor, D. & Mishra, G.** (2009). *Family Matters: Designing, Analysing And Understanding Family Based Studies In Life Course Epidemiology*. Oxford University Press: Oxford, England.
- Lichtenstein, P., Yip, B. H., Bjork, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F. & Hultman, C. M.** (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**, 234-239.
- Linszen, D. H., Dingemans, P. M. & Lenior, M. E.** (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry* **51**, 273-279.
- Mathers, D. C. & Ghodse, A. H.** (1992). Cannabis and psychotic illness. *British Journal of Psychiatry* **161**, 648-653.
- McGrath, J., Welham, J., Scott, J., Varghese, D., Degenhardt, L., Hayatbakhsh, M. R., Alati, R., Williams, G. M., Bor, W. & Najman, J. M.** (2010). Association Between Cannabis Use and Psychosis-Related Outcomes Using Sibling Pair Analysis in a Cohort of Young Adults. *Archives of General Psychiatry* **67**, 440-447.
- McLaren, J. A., Silins, E., Hutchinson, D., Mattick, R. P. & Hall, W.** (2010). Assessing evidence for a causal link between cannabis and psychosis: A review of cohort studies. *International Journal of Drug Policy* **21**, 10-19.
- Minozzi, S., Davoli, M., Bargagli, A. M., Amato, L., Vecchi, S. & Perucci, C. A.** (2010). An overview of systematic reviews on cannabis and psychosis: Discussing apparently conflicting results. *Drug and Alcohol Review* **29**, 304-317.
- Mitchell, J. & Vierkant, A. D.** (1991). Delusions and hallucinations of cocaine abusers and paranoid schizophrenics: a comparative study. *Journal of Psychology* **125**, 301-10.
- Moore, T. H. M., Zammit, S., Lingford-Hughes, A., Barnes, T. R. E., Jones, P. B., Burke, M. & Lewis, G.** (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**, 319-328.
- Negrete, J. C., Knapp, W. P., Douglas, D. E. & Smith, W. B.** (1986). Cannabis affects the severity of schizophrenic symptoms - results of a clinical survey. *Psychological Medicine* **16**, 515-520.
- Post, R. M.** (1975). Cocaine psychoses: a continuum model. *American Journal of Psychiatry* **132**, 225-31.
- SAS Institute Inc** (2008). *SAS ONLINE DOC Version 9.3*. SAS Institute Inc: Cary, NC.
- Sevy, S., Robinson, D. G., Napolitano, B., Patel, R. C., Gunduz-Bruce, H., Miller, R., McCormack, J., Lorell, B. S. & Kane, J.** (2010). Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia. *Schizophrenia Research* **120**, 101-107.
- Sewell, R. A., Ranganathan, M. & D'Souza, D. C.** (2009). Cannabinoids and psychosis. *International Review of Psychiatry* **21**, 152-162.
- Sullivan, P. F., Kendler, K. S. & Neale, M. C.** (2003). Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of General Psychiatry* **60**, 1187-92.

- Thornicroft, G.** (1990). Cannabis and psychosis - is there epidemiologic evidence for an association? *British Journal of Psychiatry* **157**, 25-33.
- Tsuang, M. T., Lyons, M. J., Eisen, S. A., Goldberg, J., True, W., Meyer, J. M. & Eaves, L. J.** (1996). Genetic influences on abuse of illicit drugs: a study of 3,297 twin pairs. *American Journal of Medical Genetics* **67**, 473-477.
- van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R. & Verdoux, H.** (2002). Cannabis use and psychosis: A longitudinal population-based study. *American Journal of Epidemiology* **156**, 319-327.
- Veling, W., Mackenbach, J. P., van Os, J. & Hoek, H. W.** (2008). Cannabis use and genetic predisposition for schizophrenia: a case-control study. *Psychological Medicine* **38**, 1251-1256.
- Verweij, K. J., Zietsch, B. P., Lynskey, M. T., Medland, S. E., Neale, M. C., Martin, N. G., Boomsma, D. I. & Vink, J. M.** (2010). Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. *Addiction* **105**, 417-430.
- Weiser, M., Knobler, H. Y., Noy, S. & Kaplan, Z.** (2002). Clinical characteristics of adolescents later hospitalized for schizophrenia. *American Journal of Medical Genetics* **114**, 949-955.
- Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I. & Lewis, G.** (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *British Medical Journal* **325**, 1199-1201.

Appendix

Discordance for schizophrenia was defined as one member of a relative-pair having a hospital diagnosis of schizophrenia (during 2000-2010) whilst the co-relative did not. Cannabis abuse (CA) discordance was defined as one member of a relative-pair having at least one CA registration, whilst the co-relative did not.

Cannabis abuse codes:

Medical registries: ICD10: F12.x (excluding F12.5 and F12.7); ICD9: 3052.x, 3043.x
Convictions register: Code 8

Schizophrenia diagnosis

Medical register:

ICD10: F20.0, F20.1, F20.2, F20.3, F20.5, F20.8, F20.9 – excluded codes F20.4 and F20.6
 ICD9: 295.3, 295.1, 295.2, 295.6, 295.5 – excluded codes 295.0, 295.4, 295.7 and 295.8

Sensitivity tests

Bipolar/major depression disorders

ICD10: F30.x, F31.x, F32.x, F33.x
 ICD9: 3004, 2980, 2961, 2980, 2969, 311, 2966, 2960, 2981, 2962, 2963, 2964
 Drug induced psychosis
 ICD 10: F11.5, F12.5, F13.5, F14.5, F15.5, F16.5, F19.5
 ICD9: 2921

Other substances

Medical registries

Opioids ICD10: F11.x; ICD9: 3055.x, 3040.x
Sedatives ICD10: F13.x; ICD9: 3054.x, 3041.x
Cocaine ICD10: F14.x; ICD9: 3056.x, 3042.x
Stimulants ICD10: F15.x; ICD9: 3057.x, 3044.x
Hallucinogens ICD10: F16.x; ICD9: 3053.x, 3045.x

Convictions register:

Opioids - 9, 10, 11, 12 and 13

Sedatives - 17, 19

Cocaine/stimulants - 1, 2, 3, 4, 5, 6, 7,

Hallucinogens 14, 15, 16

Table 1: Odds ratios (OR) with 95% confidence intervals (CI) describing the risk of hospital diagnosis of schizophrenia after prior registration for cannabis abuse in i) a general population sample and ii) a co-relative sample, allowing the time between exposure and disease to vary from 1, 3, 5 and 7 years

	OR (95 % CI)	1 year gap	3 year gap	5 year gap	7 year gap
i) General population sample	10.44 (8.99; 12.11) (<i>N=5,456</i>)	9.19 (7.89;10.70) (<i>N=5,388</i>)	7.69 (6.57;9.00) (<i>N=5,306</i>)	5.95 (5.04; 7.02) (<i>N=5,210</i>)	4.24 (3.54; 5.07) (<i>N=5,119</i>)
	OR (95 % CI)	1 year gap	3 year gap	5 year gap	7 year gap
ii) Co-relative sample					
First-cousin pairs	9.40 (8.12; 10.87) (<i>N=2,079</i>)	8.37 (7.22; 9.70) (<i>N=1,836</i>)	7.19 (6.19; 8.35) (<i>N=1,605</i>)	5.85 (5.03; 6.81) (<i>N=1,343</i>)	4.05 (3.46; 4.73) (<i>N=989</i>)
Paternal half-sibling pairs	9.15 (6.39; 13.11) (<i>N=342</i>)	8.42 (5.87; 12.09) (<i>N=328</i>)	7.82 (5.44; 11.23) (<i>N=298</i>)	6.12 (4.24; 8.84) (<i>N=239</i>)	4.18 (2.86; 6.11) (<i>N=173</i>)
Maternal half-siblings pairs	6.00 (4.20; 8.58) (<i>N=245</i>)	5.85 (4.04; 8.46) (<i>N=226</i>)	4.70 (3.23; 6.84) (<i>N=188</i>)	3.42 (2.32; 5.05) (<i>N=146</i>)	2.58 (1.72; 3.85) (<i>N=118</i>)
Full-sibling pairs	5.07 (4.17; 6.16) (<i>N=728</i>)	4.47 (3.66; 5.47) (<i>N=635</i>)	3.71 (3.02;4.55) (<i>N=546</i>)	2.80 (2.27;3.46) (<i>N=441</i>)	1.98 (1.59;2.48) (<i>N=346</i>)
MZ twins (extrapolated)	3.92	3.38	3.31	2.63	1.67

Table 2: Odds ratios (OR) with 95% confidence intervals (95% CI) describing the risk of hospital diagnosis of schizophrenia after prior registration for cannabis abuse in i) a general population sample and ii) a co-relative sample.

	2 registrations for schizophrenia and cannabis	Purified schizophrenia	Bipolar and major depression
i) General population sample	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
	13.57 (10.49; 17.55) <i>(N=3,179)</i>	7.99 (6.76; 9.44) <i>(N=4,398)</i>	2.98 (2.75; 3.17) <i>(N=42,945)</i>
ii) Co-relative sample	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
First-cousin pairs	9.88 (8.16; 11.96) <i>(N=1,262)</i>	9.88 (8.16; 11.96) <i>(N=1,262)</i>	2.48 (2.35; 2.61) <i>(N=6,623)</i>
Paternal half-sibling pairs	12.29 (7.50; 20.16) <i>(N=231)</i>	6.89 (4.60; 10.32) <i>(N=217)</i>	1.73 (1.51; 1.98) <i>(N=953)</i>
Maternal half-siblings pairs	5.91 (3.76; 9.28) <i>(N=152)</i>	5.56 (3.63; 8.51) <i>(N=164)</i>	1.69 (1.47; 1.94) <i>(N=877)</i>
Full-sibling pairs	4.37 (3.45; 5.51) <i>(N=446)</i>	4.66 (3.72; 5.83) <i>(N=526)</i>	1.63 (1.49; 1.77) <i>(N=2,139)</i>
MZ twins (extrapolated)	3.23	3.53	0.80

Table 3: Odds ratios (OR) with 95% confidence intervals (95% CI) describing the risk of hospital diagnosis of schizophrenia after prior registration for different types of drug abuse in i) a general population sample and ii) a co-relative sample (cannabis cases excluded)

	Opiates	Sedatives	Cocaine/Stimulants	Hallucinogens
i) General population sample	9.04 (5.60; 14.59) (N=5,456)	12.74 (9.52;17.04) (N=5,456)	9.61 (7.71;11.97) (N=5,456)	26.67 (15.36; 46.29) (N=5,456)
ii) Co-relative sample	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
First-cousin pairs	3.25 (2.39; 4.42) (N=225)	7.33 (5.91; 9.11) (N=775)	8.56 (6.91; 10.35) (N=993)	9.87 (6.82; 14.28) (N=337)
Paternal half-sibling pairs	1.80 (0.96; 3.38) (N=42)	3.50 (2.07; 5.91) (N=81)	8.50 (5.06; 14.27) (N=154)	7.00 (2.74; 17.87) (N=41)
Maternal half-siblings pairs	8.25 (2.92; 23.29) (N=37)	4.65 (2.75; 7.85) (N=96)	10.64 (5.73; 19.74) (N=128)	17.50 (4.21; 72.8) (N=37)
Full-sibling pairs	1.49 (1.01; 2.19) (N=107)	3.34 (2.51; 4.43) (N=269)	4.36 (3.21; 5.93) (N=268)	5.73 (3.31;9.92) (N=101)
MZ twins (extrapolated)	<1.00	<1.00	1.9	<1.00