# Combined patterns of tobacco and cannabis use in adolescence and their association with psychotic experiences: a longitudinal analysis

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# Key Points

**Question:** How do patterns of adolescent cigarette and cannabis use relate to subsequent onset of psychotic experiences?

**Findings:** In this birth cohort study of 3,328-4,101 adolescents there was strong evidence that both cannabis and cigarette use were associated with subsequent psychotic experiences prior to adjusting for confounders. However, after adjusting, the associations for cigarette-only use attenuated substantially, whereas those for cannabis use were unchanged.

**Meaning:** Whilst individuals who use either cannabis or cigarettes during adolescence have an increased risk of developing psychotic experiences, epidemiological evidence for these being causal is substantially more robust for cannabis than it is for tobacco.

# Abstract

Importance

There has been increasing concern about potentially causal effects of tobacco use on psychosis, but epidemiological studies have been less robust in attempts to minimise effects of confounding than studies of cannabis use have been.

Objective

To examine the association of patterns of cigarette and cannabis use with preceding and subsequent psychotic experiences, and compare patterns of confounding across these patterns.

****Design, Setting, and Participants****

A cohort study of adolescents from the Avon Longitudinal Study of Parents and Children birth cohort initially consisting of 14,062 children. Data were collected periodically from September 6, 1990, with collection ongoing, and analyzed from August 8, 2016 to June 14, 2017. Cigarette and cannabis use data were summarised using longitudinal latent class analysis to identify longitudinal classes of substance use, and associations between classes and psychotic experiences at 18 years were assessed.

Exposures

Depending on the analysis model, exposures were longitudinal classes of substance use or psychotic experiences at age 12 years.

Main Outcomes and Measures

Logistic regression was used to examine the relationships between substance use longitudinal classes and subsequent onset of psychotic experiences.

Results

Longitudinal classes were derived using 5,300 (56.1% female) individuals who had at least 3 measures of cigarette and cannabis use between ages 14-19 years. Prior to adjusting for a range of potential confounders, there was strong evidence that early-onset cigarette-only use (4.3%), early-onset cannabis use (3.2%), and late-onset cannabis use (11.9%), but not later-onset cigarette-only use (14.8%) latent classes were associated with increased psychotic experiences compared to non-users (65.9%) (omnibus *P*<0.001). After adjusting for confounders, the association for early-onset cigarette-only use attenuated substantially (unadjusted odds ratio (OR) = 3.03, 95%CI 1.13, 8.14; adjusted OR = 1.78, 95%CI 0.54, 5.88), whereas those for early-onset (adjusted OR = 3.70, 95%CI 1.66, 8.25) and late-onset (adjusted OR = 2.97, 95%CI 1.63, 5.40) cannabis use were unchanged.

Conclusions and relevance

Our findings indicate that whilst individuals who use either cannabis or cigarettes during adolescence have an increased risk of developing subsequent psychotic experiences, the epidemiological evidence for this being causal is substantively more robust for cannabis than it is for tobacco.

# Introduction

Cannabis and tobacco are frequently used together, so teasing out their causal effects on mental health is difficult but important, as this can advance understanding of causal mechanisms and help target preventive interventions.

Individuals who use cannabis regularly have a 2-3-fold increased risk of developing a psychotic outcome.1 Tobacco use is also associated with an increased incidence of psychotic disorders2-5 in cohort studies, and (less consistently) with subclinical psychotic symptoms,6-8 with hypothesised casual mechanisms including nicotine increasing dopamine release and inducing D2-receptor supersensitivity.5,9

However, whilst a recent systematic review reported a meta-analysis estimate for daily smoking and psychosis that was similar to that for regular cannabis use, the estimate was based on results unadjusted for confounders,5 unlike that for cannabis.1 Whilst concern about confounding leading to over-estimation of causal effects on psychosis also exists for cannabis,1 support for a causal effect of cannabis also comes from experimental studies showing an increase in psychotic experiences following exposure to intravenous delta-9-THC.10 In contrast, experimental studies of nicotine administration do not support the acute onset of psychotic experiences.11

The strongest evidence in support of a causal effect of tobacco on psychosis is that a genetic locus strongly associated with heaviness of smoking (within the nicotinic receptor *CHRNA5-A3-B4* gene cluster) is one of the loci most strongly associated with schizophrenia.12 This, however, is also theoretically consistent with either confounding by shared genetic effects (biological pleiotropy), or, perhaps less plausibly, ‘reverse causality’ (i.e., biological risk of schizophrenia causing smoking behaviour).

Similarly, associations between genetic risk for psychosis and both cannabis use and heaviness of cigarette use are also consistent with causal, reverse-causal, and pleiotropic explanations.13-15

As most people who use cannabis also smoke cigarettes, teasing out potentially causal effects of cannabis from those of tobacco is difficult, particularly as individuals usually mix their cannabis with tobacco, even when classing themselves as non-smokers.16 Measurement error can lead to incorrect estimates of causal effects (see Gage et al. 201416 and Munafò et al. 201217 for examples of the impact of measurement error on confounding and main effects), and is particularly likely when using single-time point assessments of exposure status. Thus, other methods for teasing out causal effects of cannabis as distinct from tobacco are required.

One approach that can help inform causal inference is to use behavioural patterns of cannabis and tobacco use over time to identify classes of individuals with different substance use profiles across a developmental period rather than relying on patterns of use at one point in time.18 Such methods capture additional information that may enable persistent users of cannabis and tobacco to be distinguished from those who may have experimented briefly.

In this study, we used longitudinal latent class analysis (LLCA) to identify subgroups of individuals based on similar patterns of cigarette and cannabis use behaviour over time, to: i) examine the association of different classes with subsequent onset of psychotic experiences, ii) compare patterns of confounding across these classes, and iii) examine the effect of childhood psychotic experiences on adolescent patterns of cigarette and cannabis use.

# Methods

## Participants

The sample comprised individuals within the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. The initial cohort consisted of 14,062 children born to women residing in the former Avon Health Authority area with expected delivery dates between April 1991-December 199219,20 (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary>). All subjects provided written informed consent, and ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

## Measures

### Cigarette and cannabis use

Measures of cigarette and cannabis use were collected at 6 time points between ages 14 and 19 years (see eMethods for further details). As very few individuals used cannabis without tobacco16 (see eTable-1), data at each time point were summarised as individuals who didn’t report cigarettes or cannabis use, individuals who reported cigarette use only, and individuals who reported cannabis use (with or without cigarettes).

### Psychotic experiences

The semi-structured Psychosis-Like Symptom Interview (PLIKSi)21,22 was used to assess psychotic experiences at ages 12 years and 18 years. The PLIKSi allows rating of 12 psychotic experiences including hallucinations, delusions and thought interference.

The primary psychotic experience measures at ages 12 and 18 years were binary variables relating to whether an individual had at least one definite psychotic experience compared to suspected or no psychotic experiences. As sensitivity analyses we also repeated analyses using narrower (definite psychotic experiences versus none; psychotic disorder versus none) and broader (definite or suspected psychotic experiences versus none) cut-offs for defining the measure (see eMethods).

### Potential confounders

Potential confounders examined included: sex, family history of schizophrenia or depression, family history of drug use, maternal/paternal smoking during pregnancy, maternal education, maternal/paternal social class, IQ (age 8 years), childhood trauma and victimisation (ages 7-9 years), emotional/behavioural problems (Strengths and Difficulties Questionnaire (SDQ) score age 9 years), and alcohol use (age 12 years). For more information see eMethods.

## Statistical analysis

### Longitudinal Latent class analysis

LLCA was used to derive distinct behaviour patterns in the repeated measures data relating to cigarette and/or cannabis use as previously described.23,24 The aim of LLCA is to identify the number latent classes that adequately explain the relationship between the observed variables. Individuals were included in the analysis if they had data present for 3 or more time points. Starting with one class, additional classes were added and the model fit assessed until the optimal number of classes was achieved. Model fit was assessed using the following parameters: proportion of individuals in each class, sample size adjusted Bayesian Information Criterion (SSABIC) and Lo-Mendell-Rubin likelihood ratio test (LMR-LRT). LLCA was performed using MPlus version 7.31.25

### Association analyses

#### Psychotic experiences as exposure

Multinomial regression was used to assess whether psychotic experiences at age 12 years were associated with subsequent latent class membership, before and after adjustment for potential confounders, using a manual implementation of the bias-adjusted three-step method (see eMethods and Heron et al. 201526 for more detail).

Analyses were also conducted on a restricted sample omitting 455 individuals who used cannabis or cigarettes at age 12 years.

#### Psychotic experiences as outcome

Logistic regression was used to assess whether latent class membership was associated with subsequent psychotic experiences at age 18 years, before and after adjustment for potential confounders. For these analyses derivation of classes was restricted to data from the first to fourth time point (approximate ages 14 to 17 years). Otherwise the method used to derive classes was as described above. Restricting data to four time-points had minimal impact on latent class structure and proportions (eFigure-1 and eTable-2).

Analyses were also conducted on a restricted sample omitting 149 individuals with definite psychotic experiences at age 12 years.

Adjusting for family history of schizophrenia or depression, family history of drug use, paternal smoking during pregnancy, social class, IQ, victimisation, childhood trauma, and alcohol use had almost no effect on results for either model described above (eTable-3), but reduced the analysis sample size substantially. We therefore only adjusted for sex, maternal education, maternal smoking during pregnancy, and child SDQ in our final adjusted model.

## Missing data

Percentage of missing data increased with time (eTable-4). The analysis sample were more likely to be female, and come from more advantaged backgrounds (see Table 1 and eTable-5 for sample demographics).

# Results

Data were available for 5,300 individuals. Based on model fit statistics (eTable-6), there was good agreement that a 5-class solution adequately described the heterogeneity within the data.

The 5-class model comprised of individuals with a higher probability of early-onset cigarette-only use (4.3%), early-onset cannabis use (3.2%), late-onset cigarette-only use (14.8%), late-onset cannabis use (11.9%), and individuals with a very low probability of cigarettes or cannabis use (65.9%; referred to as “non-users”) (Figure 1).

## Patterns of cigarette/cannabis use ages 14-17 and psychotic experiences at age 18 years

Individuals within the early-onset cigarette-only class, but not the late-onset cigarette-only class, were at greater odds of psychotic experiences at age 18 years when compared to non-users (OR = 3.03; 95% CI = 1.13, 8.14 and OR = 0.84; 95% CI 0.31, 2.31 respectively; Table 2).

There was strong evidence that individuals within the early-onset and late-onset cannabis use classes also had increased odds of psychotic experiences (early-onset cannabis use: OR = 3.79; 95% CI 1.73, 8.31; late-onset cannabis use: OR = 3.05; 95% CI 1.69, 5.53).

When adjusting for confounding, the evidence of association between early-onset cigarette-only use and psychotic experiences was attenuated by approximately 60% (adjusted OR = 1.78; 95% CI 0.54, 5.88; Table 3). In contrast, adjusting for confounding had minimal impact on the associations for early-onset cannabis use (adjusted OR = 3.70; 95% CI 1.66, 8.25) or late-onset cannabis use (adjusted OR 2.97; 95% CI 1.63, 5.40).

When comparing the substance using classes against each other (eTable-7) there was strong evidence to rule out equivalence between the effects for late-onset cannabis use and late-onset cigarette-only use on psychotic experiences (OR = 3.63; 95% CI = 1.12, 11.76). There was insufficient evidence to support a difference between the effects of early-onset cannabis and early-onset cigarette-only use on psychotic experiences though this was based on smaller numbers, or to support a difference between late-onset and early-onset cannabis use classes.

Results were similar when excluding individuals with psychotic experiences at age 12 years (eTable-7).

### Sensitivity analyses

Results of associations between class membership and subsequent psychotic experiences were substantively the same when excluding individuals whose psychotic experiences only ever occurred within 2 hours of any drug use (eTable-8), and when examining narrower, or broader, psychotic outcome definitions (eTable-9).

## Psychotic experiences at age 12 years and patterns of cigarette/cannabis use ages 14-19

Definite psychotic experiences at age 12 years were associated with increased odds of subsequent late-onset cigarette-only use (OR = 1.76; 95% CI 1.01, 3.10) and late-onset cannabis use (OR 1.66; 95% CI = 0.94, 2.91) as compared to not using (Table 3 and eTable-10).

There was little evidence that psychotic experiences at age 12 years were associated with increased odds of early-onset cigarette-only or cannabis use; however, these classes had smaller membership (Figure 1 and Table 3). Adjusting for confounders had minimal impact on associations between psychotic experiences at age 12 years and classes of subsequent cannabis/cigarette use.

The effect estimates for all classes were smaller, and evidence of association weaker (particularly for early-onset classes), when restricting the analysis to non-users of cigarettes/cannabis at age 12 years (eTable-11).

# Discussion

Both early-onset and late-onset cannabis use classes were strongly associated with psychotic experiences at age 18 years, and were only minimally attenuated after adjusting for potential confounders. In contrast, there was inadequate evidence to support an association between either early-onset or late-onset cigarette-only use and psychotic experiences in the adjusted analyses. There was also evidence that individuals in the late-onset cannabis use class had higher odds of developing psychotic experiences than those in the late-onset cigarette-only use class, the two most common substance use classes in our data. There was no evidence to support a stronger effect of early-onset cannabis use compared to late-onset cannabis use on psychotic outcomes as proposed by some, though not all studies,1 though the relatively small size of the early-onset class will have limited power to detect small-moderate effects.

Adjusting for a broad range of potential confounders did not alter the estimate of association for either the early- or late-onset cannabis use class, but resulted in an approximately 60% attenuation of the estimate for the early-onset cigarette-only class. This difference in the impact of adjustment for confounders indicates that the association between cannabis use and psychotic experiences is more robust against explanations of residual confounding than that for tobacco use.

In comparison, we found little evidence that psychotic experiences in childhood led to increased cannabis use. As other observational studies have indicated,27-29 the self-medication hypothesis does not appear to adequately explain the association between cannabis use and psychosis. Such a relationship for tobacco use is also not well supported by our data.

The uncertainty around our estimates means we cannot exclude a possible causal effect of cigarette-only use on psychotic experiences. A number of longitudinal studies have reported that tobacco users are at greater risk for later psychotic disorders.2-5,30,31 However, none of these studies adjusted for cannabis use, and whilst adjusting for diagnoses of drug abuse in two of the studies substantially attenuated associations for cigarette smoking4 or snus use,31 this is likely to have been a poor measure of cannabis use and hence may have underestimated its confounding effect. In the only longitudinal study that has adjusted for cannabis use, this substantially attenuated the association for cigarette smoking, with the fully-adjusted model supporting a *protective* effect of smoking on schizophrenia.32

In our previous study using the ALSPAC cohort we reported that the association between cannabis use and psychotic experiences was altered only slightly by adjusting for early/childhood confounders, but that interpretation of results adjusted for tobacco use was problematic due to strong relationship between these measures.16 In the current study we are better able to disentangle differential effects of tobacco use from those of cannabis use through utilization of data at multiple time points to describe patterns of use related to both these substances over time. Our findings here are consistent with another study where adjusting for confounding using fixed-effects regression to deal with unmeasured time-invariant effects resulted in much greater attenuation of association between cigarette smoking and psychotic symptoms than for cannabis use.8

Another approach to strengthen causal inference is Mendelian randomization (MR) whereby genetic variants act as unconfounded proxy measures for exposure status.33 One study reported weak evidence of association between a genetic variant within the *CHRNA5-A3-B4* gene cluster and being prescribed anti-psychotic medication.34 However, despite this association being stronger in smokers than non-smokers (as would be expected if this was due to a causal role of smoking on psychosis), there was little statistical evidence (*P* = 0.60) for this.34

We recently conducted a MR study and found little evidence of a causal association between cigarette smoking initiation and schizophrenia risk,35 while our MR study of cannabis initiation and schizophrenia risk provided evidence for causal pathways operating in both directions.14 However, in both cases our analyses were restricted to smoking /cannabis initiation, and might not reflect the effects of longer-term regular use. The lack of adequate samples and strong genetic instruments for regular cannabis use limit current use of MR studies to further inform causal inference.

**Strengths and limitations**

One of the strengths of our study is that we use a large, well-characterised cohort, albeit of mostly European ancestry, with multiple measures of exposures of interest and psychotic experience data over time, with data on a broad range of potential confounders collected prospectively. Using information across the whole adolescent period rather than from a single time point means our results are much less prone to measurement error. However, there is considerable attrition over time, although the use of a latent class methodology with longitudinal data allows us to maximise use of data for individuals even where participation and question response has been sporadic, and hence minimise potential selection bias to some extent. Whilst use of a latent class methodology confers a number of advantages over using measures at single time points, it was not possible to define a class of individuals who use cannabis without tobacco as most cannabis users smoke cannabis in combination with tobacco.36 Therefore, we cannot rule out whether the associations observed between the cannabis use class and psychotic experiences are exacerbated by the combined use of cannabis and cigarettes. Whilst experimental studies of intravenous delta-9-THC support a causal effect of cannabis on acute psychotic experiences in the absence of tobacco,10 there is some evidence that smoking cannabis with tobacco also increases the amount of THC inhaled per gram.37

Furthermore, we have previously found that a substantial proportion of people who smoke cigarettes most heavily also use cannabis, and thus the cigarette-only class might not include those who have been most heavily exposed to tobacco. As the cannabis use group in our study included occasional (1-3 times in the past 6 months) *and* frequent (daily) users, we were unable to differentiate whether our findings are mainly driven by frequent users; including frequency of substance use data resulted in an unstable model. Our study was also not able to examine longer-term, cumulative cannabis/tobacco use on psychosis outcomes, though these analyses may become tractable in the future.

Whilst psychotic experiences in the population are relatively poor predictors of psychotic disorder,22 they represent the key characteristic of such disorders, and understanding their aetiology almost certainly has relevance to understanding the aetiology of clinically-defined psychosis. However, we were not adequately powered to investigate the effects of cannabis or cigarette use on psychotic disorders, and cannot rule out different effects of these substances on other psychosis-related psychopathology such as negative symptoms. We were also unable to tease out effects of cannabis on chronic, from more acute, psychotic outcomes, though excluding individuals who reported psychotic experiences only ever occurring within 2 hours of using drugs had minimal effect on our results. Nevertheless, given the long half-life of THC the only way of determining whether cannabis use can lead to chronic psychotic disorders that persist long after effects of exogenous cannabinoids is to study regular users of cannabis who subsequently become abstinent.29

The one longitudinal study we are aware of that examined this relationship reported only weak evidence of association between ex-cannabis use and psychotic experiences, though there were relatively few ex-cannabis users.29 Given the age of the participants over the course of our study, we were not able to identify a class of ex-cannabis users to clarify this relationship; however, long-term follow-up of this cohort may enable us to address this question more robustly.

**Conclusion**

All research approaches designed to address causal relationships between substance use and psychosis have particular strengths and limitations, and it is only through triangulation of different approaches that we can best determine causal effects. Our study provides evidence that whilst both adolescent cannabis use and cigarette use are associated with increased risk for subsequent psychotic experiences, the evidence supporting a causal effect of cannabis is substantially more robust than that for tobacco. Associations observed between tobacco use and psychotic experiences are more likely than those for cannabis to be influenced by other characteristics of people who develop psychotic experiences.

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**Author Contributions:** H. Jones and S. Zammit had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Jones, Gage, Heron, Munafò, Zammit.

*Acquisition, analysis, or interpretation of data:* Jones, Gage, Heron, Munafò, Zammit.

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# Figure legend

**Figure 1.** **Five-class model of cigarette/cannabis use patterns from a sample of 5,300 individuals.** The probability axis represents the probability of a class member being a non-user, a cigarette-only user or a cannabis with/without cigarette user at each time point.

# Tables

**Table 1.** Sample demographics for individuals who completed questions related to cigarette and cannabis use per time point

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Age (years) | | | | |
| Time point | Data Source | N | No. (%) Female | Approx. | Mean | Min | Max | Median |
| 1 | Interview | 4,654 | 2,530 (54.4) | 14 | 13.8 | 12.5 | 15.2 | 13.8 |
| 2 | Postal questionnaire | 4,537 | 2,608 (57.5) | 15 | 14.2 | 14 | 16.2 | 14.1 |
| 3 | Interview | 4,421 | 2,421 (54.8) | 16 | 15.4 | 14.3 | 17.5 | 15.3 |
| 4 | Postal questionnaire | 4,169 | 2,478 (59.4) | 17 | 16.7 | 16.4 | 18.1 | 16.6 |
| 5 | Interview | 3,541 | 2,002 (56.5) | 18 | 17.7 | 16.3 | 19.6 | 17.7 |
| 6 | Postal questionnaire | 2,927 | 1,878 (64.2) | 19 | 18.6 | 17.8 | 20 | 18.7 |

**Note:** N, number of respondents per time point; Approx., approximate age used to plot the data; Min, minimum age; Max, maximum age.

**Table 2.** Unadjusted and adjusted associations between cigarette and/or cannabis use and psychotic experiences at age 18 years

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Definite PE  (n = 3328) | | | | | |
|  | Unadjusted | | | Adjusted† | | |
|  | ORa | 95% CI | *P* value | ORa | 95% CI | *P* value |
| **Early-onset cigarette-only** | 3.03 | 1.13, 8.14 | <0.001 | 1.78 | 0.54, 5.88 | <0.001 |
| **Early-onset cannabis** | 3.79 | 1.73, 8.31 | 3.70 | 1.66, 8.25 |
| **Late-onset cigarette-only** | 0.84 | 0.31, 2.31 | 0.73 | 0.27, 1.98 |
| **Late-onset cannabis** | 3.05 | 1.69, 5.53 | 2.97 | 1.63, 5.40 |

**Note:** PE, psychotic experiences; OR, odds ratio; 95% CI, 95% confidence interval; *P* value, omnibus *P* value for association between cigarette/cannabis use classes and psychotic experiences at age 18 years.

a Compared to non-use class.

† Adjusted for sex, maternal education, emotional/behavioural problems (Strengths and Difficulties Questionnaire (SDQ) score age 9 years) and maternal cigarette smoking during pregnancy.

**Table 3.** Unadjusted and adjusted associations between psychotic experiences at age 12 years and subsequent cigarette and/or cannabis use

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Early-onset cigarette | | Early-onset cannabis | | Late-onset cigarette | | Late-onset cannabis | |  |
|  | ORa | 95% CI | ORa | 95% CI | ORa | 95% CI | ORa | 95% CI | *P* value |
| **Unadjusted** |  |  |  |  |  |  |  |  |  |
| Definite PE  (n = 4101) | 1.17 | 0.41, 3.33 | 0.97 | 0.31, 3.00 | 1.76 | 1.01, 3.10 | 1.66 | 0.94, 2.91 | 0.14 |
| **Adjusted†** |  |  |  |  |  |  |  |  |  |
| Definite PE  (n = 4101) | 0.86 | 0.27, 2.81 | 0.93 | 0.28, 3.06 | 1.60 | 0.91, 2.82 | 1.65 | 0.90, 3.05 | 0.25 |

**Note:** PE, psychotic experiences; OR, odds ratio; 95% CI, confidence interval; *P* value , omnibus *P* value for association between psychotic experiences at age 12 years and cigarette/cannabis use classes.

a Compared to non-use class.

† Adjusted for sex, maternal education, emotional/behavioural problems (Strengths and Difficulties Questionnaire (SDQ) score age 9 years) and maternal cigarette smoking during pregnancy.