Examining pathways between genetic liability for schizophrenia and patterns of tobacco and cannabis use in adolescence

Hannah J. Jones, PhD[1,2,3]; Gemma Hammerton, PhD[1,2]; Tayla McCloud, MSc[4]; Lindsey A. Hines, PhD[1]; Caroline Wright, PhD[5]; Suzanne H. Gage, PhD[6]; Peter Holmans, PhD[7]; Peter B Jones MD, PhD, MRCPsych[8]; George Davey Smith, MD, DSc[2]; David E. J. Linden, D.Phil[7]; Michael C. O'Donovan, PhD, FRCPsych[7]; Michael J. Owen, PhD, FRCPsych[7]; James T. Walters, MRCPsych, PhD[7]; Marcus R. Munafò, PhD[2,9]; Jon Heron, PhD[1,2]; Stanley Zammit, MRCPsych, PhD[1,7]

[1]Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, UK

[2]Medical Research Centre (MRC) Integrative Epidemiology Unit (IEU) at the University of Bristol, UK

[3]NIHR Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust, University of Bristol, Bristol, UK

[4]Division of Psychiatry, University College London, London, UK

[5]Population Health Sciences, Bristol Medical School, University of Bristol, UK

[6]Department of Psychological Sciences, University of Liverpool, Liverpool, UK

[7]MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, UK

[8]Department of Psychiatry, University of Cambridge, Cambridge, UK

[9]UK Centre for Tobacco and Alcohol Studies, School of Psychological Science, University of Bristol, UK

Corresponding author: Hannah J. Jones, PhD; Population Health Sciences, Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol, UK (hannah.jones@bristol.ac.uk)

Abstract word count: 246

Main body word count: 4348 (including in-text references)

Abstract

Background

It is not clear to what extent associations between schizophrenia, cannabis use and cigarette use are due to a shared genetic etiology. We therefore examined whether schizophrenia genetic risk associates with longitudinal patterns of cigarette and cannabis use in adolescence, and mediating pathways for any association to inform potential reduction strategies.

Methods

Associations between schizophrenia polygenic scores and longitudinal latent classes of cigarette and cannabis use from ages 14 years to 19 years were investigated in up to 3925 individuals in the Avon Longitudinal Study of Parents and Children. Mediation models were estimated to assess the potential mediating effects of a range of cognitive, emotional, and behavioral phenotypes.

Results

The schizophrenia polygenic score, based on single nucleotide polymorphisms meeting a training-set p-threshold of 0.05, was associated with late-onset cannabis use (OR=1.23; 95% CI=1.08,1.41), but not with cigarette or early-onset cannabis classes. This association was not mediated through lower IQ, victimization, emotional difficulties, antisocial behavior, impulsivity, or poorer social relationships during childhood. Sensitivity analyses adjusting for genetic liability to cannabis or cigarette use, using polygenic scores excluding the *CHRNA5-A3-B4* gene cluster, or basing scores on a 0.5 training-set p-threshold, provided results consistent with our main analyses.

Conclusions

Our study provides evidence that genetic risk for schizophrenia is associated with patterns of cannabis use during adolescence. Investigation of pathways other than the cognitive, emotional, and behavioural phenotypes examined here is required to identify modifiable targets to reduce the public health burden of cannabis use in the population.

Keywords: ALSPAC, polygenic score, cigarette-use, cannabis-use, schizophrenia, mediation

Introduction

Schizophrenia is a highly heritable, severe psychiatric disease with typical symptoms including positive symptoms such as hallucinations, delusions and thought disorder, negative symptoms such as apathy and avolition, and cognitive dysfunction. Genome-wide association studies (GWAS) provide strong evidence of multiple independent loci contributing to the etiology of schizophrenia (Pardiñas et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). However, whilst individual loci have small effects on risk, multi-locus approaches show that cumulatively, even moderately associated alleles explain at least a third of schizophrenia genetic risk (Purcell et al., 2009; Ripke et al., 2013). Based on these alleles, an individual's genetic liability can be quantified using a polygenic score, a valuable tool when investigating shared genetics between disorders and how genetic risk is manifest throughout the life course (Hubbard et al., 2016; Jones et al., 2016).

Cannabis use is more common in individuals with schizophrenia than in the general population (Green, Young, & Kavanagh, 2005), and a large body of evidence from observational (Moore et al., 2007) and experimental (D'Souza et al., 2004) studies support a causal effect of cannabis use on psychosis. However, some recent studies (Carey et al., 2016; Power et al., 2014; Reginsson et al., 2017; Verweij et al., 2017), though not all (Guloksuz et al., 2019), have found that genetic liability to schizophrenia (as captured by polygenic scores) is associated with cannabis use, suggesting that the association between cannabis and schizophrenia might be partly genetically confounded, or represent a pathway from schizophrenia risk to cannabis use. The latter may result from early manifestations of schizophrenia liability that may increase an individual's likelihood to start using cannabis, for example, experiencing difficulties with peers (Cannon et al., 2001; Malmberg, Lewis, David, & Allebeck, 1998). If a bi-directional relationship does exist, then identifying the mechanisms by which schizophrenia genetic risk increases risk of cannabis use could provide important insights about targets to prevent cannabis use in the population, and particularly in those at genetically high risk for schizophrenia where cannabis reduction is likely to lead to the greatest benefit in reducing population levels of schizophrenia.

Schizophrenia is also associated with a higher prevalence of tobacco smoking behaviors compared with the general population (de Leon & Diaz, 2005; Dickerson et al., 2013). As such, the possibility that cigarette smoking might increase risk for schizophrenia has gained attention (Gurillo, Jauhar, Murray, & MacCabe, 2015), although recent work shows that evidence consistent with causal effects on psychotic experiences are much stronger for cannabis use than they are for tobacco use (Jones et al., 2018). Schizophrenia polygenic risk, and a schizophrenia GWAS hit in the *CHRNA5-A3-B4* gene cluster, are associated with cigarette smoking phenotypes, including initiation, dependence and heaviness (Reginsson et al., 2017; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) which, similar to the findings for cannabis use, raises questions regarding a shared genetic etiology and direction of effect between cigarette use and schizophrenia, and the potential to gain insights into mechanisms leading to cigarette use in the population.

We identified, *a priori* to any analyses, a number of potentially modifiable pathways through which genetic risk for schizophrenia could theoretically lead to adolescent substance use. Based on evidence of association with both genetic/familial risk for schizophrenia, and with substance use, these included peer-victimization, poorer social relationships, deficits in cognitive ability and impulsivity, and emotional or behavioral problems during childhood (Courtney, Mejia, & Jacobus, 2017; Varese et al., 2012; Welham, Isohanni, Jones, & McGrath, 2009).

Whilst understanding whether genetic risk for schizophrenia is associated with specific patterns of substance use, and the pathways involved in these relationships, could provide important insights into the etiology of both schizophrenia and substance use disorders, disentangling such associations may be hindered by measurement error in the outcomes, the high correlation between cigarette and cannabis use that makes it difficult to study independent effects of these substances, and by experimental and fluctuating use over time which are difficult to capture with single time-point assessments. To overcome some of these difficulties, we previously used longitudinal latent class analysis (LLCA) of repeated measurements of adolescent cigarette and cannabis use to identify subgroups of individuals based on their use or co-use of cigarettes and cannabis and capture information on persistent use as opposed to

brief experimentation with these substances (Jones et al., 2018). The current study therefore aims to use these latent classes to: i) examine whether schizophrenia genetic risk is associated with patterns of cigarette and cannabis use in adolescence, and ii) examine whether genetic effects on substance use are mediated via cognitive, social, emotional or behavioral pathways during childhood.

Methods

Participants

The sample consisted of participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) (see Supplementary Methods) (Boyd et al., 2013; Fraser et al., 2013). Details of available data are accessible through a searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/data-access/data-dictionary). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (http://www.bristol.ac.uk/alspac/researchers/research-ethics/). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

Genetic data

Genetic data were acquired using the Illumina HumanHap550 quad genome-wide single nucleotide polymorphism (SNP) genotyping platform from 9912 participants. Following quality control assessment and imputation (see Supplementary Methods), genetic data was available for 7977 ALSPAC individuals.

Measures

Polygenic scores

Polygenic scores for schizophrenia were constructed for each ALSPAC individual using data from the most recent schizophrenia GWAS based on 40 675 cases and 64 643 controls (Pardiñas et al., 2018) as a

training set. Following quality control (see Supplementary Methods), polygenic scores were calculated using the PLINK (v1.9) (Chang et al., 2015; Purcell et al., 2007) 'score' command following the methodology described previously (Purcell et al., 2009).

For the primary analysis, scores were constructed using a list of SNPs with a GWAS training set p-value threshold ≤ 0.05,which optimally captures phenotypic variance in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Scores were weighted by the logarithm of the odds ratio (OR) for schizophrenia reported by the training set.

For sensitivity analyses, additional polygenic scores were created based on different GWAS training set p-value thresholds ($P \leq 0.5$, $1e^{-5}$ and $5e^{-8}$ [genome-wide significant]) and after excluding the *CHRNA5-A3-B4* nicotinic receptor gene cluster (chromosome 15: 78- 79.5Mb), a loci which is strongly associated with smoking cigarette quantity and nicotine dependence (Saccone et al., 2009; Tobacco Genetics Consortium, 2010) and also genome-wide significantly associated with schizophrenia (Pardiñas et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Weighted polygenic scores were also constructed for cigarette smoking initiation and cannabis use initiation using results from the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) tobacco and alcohol use GWAS (n = 1 232 091) (Liu et al., 2019) and from a cannabis use GWAS meta-analysis using data from the International Cannabis Consortium (ICC) and UK Biobank (n = 184 765) (Pasman et al., 2018), respectively, using SNPs meeting a p-value threshold ≤ 0.5 in the training set GWAS. As ALSPAC was a part of the GSCAN and ICC GWAS samples (Liu et al., 2019; Stringer et al., 2016), the SNPs and log ORs used to generate and weight the polygenic scores were from results after removal of ALSPAC and, due to data permissions, 23andMe from the GWAS meta-analyses.

Repeated measures of cigarette and/or cannabis use

Repeated measures of cigarette and/or cannabis use in ALSPAC were collected from clinic visits and questionnaires between approximate ages 14 and 19 years. At each time point, individuals were asked questions relating to their current use and frequency of use (see Supplementary Methods for more detail). At each time point, data on cigarette and cannabis use were combined into a 3-category nominal

variable: “Non-users”, “Cigarette-only users” and “Cannabis users (either with or without cigarettes)” as previously described (Jones et al., 2018).

Potential mediators

Potential mediators were selected on the basis that they are all premorbid antecedents of schizophrenia, associated with familial risk of schizophrenia, and/or associated with substance use. These included: IQ (assessed via the Wechsler Intelligence Scale for Children (Wechsler, Golombok, & Rust, 1992) at age 8 years), victimization (from the Bullying and Friendship Interview Schedule (Wolke, Woods, Bloomfield, & Karstadt, 2000) at age 8 years), emotional problems (Strengths and Difficulties Questionnaire [SDQ] (Goodman, 1999) sub-scale score at age 9 years), antisocial behavior (assessed via a short structured interview at age 10 years), impulsivity (number of incorrect items on the stop signal task (150ms delay) (Handley, Capon, Beveridge, Dennis, & Evans, 2004) at age 10 years), friendship quality (based on 5 items from the Cambridge Friendship Questionnaire (Baron-Cohen & Wheelwright, 2003) at age 12 years), and psychotic experiences (Psychosis-Like Symptom Interview [PLIKSi] (Horwood et al., 2008) at age 12 years). For more information, see Supplementary Methods.

Statistical analysis

Longitudinal latent class analysis

Using the repeated, 3-category nominal variable of cigarette and cannabis use described above, LLCA was used to derive distinct behavior patterns of cigarette and/or cannabis use as previously described (Howe et al., 2017; Jones et al., 2018; Taylor et al., 2017) (see Supplementary Methods). Briefly, Individuals were included in the analysis if they had cigarette and cannabis use data present for 3 or more time points. Starting with one class, additional classes were added, and each time the model fit assessed using proportion of individuals in each class, sample size adjusted Bayesian Information Criterion (SSABIC) and Lo-Mendell-Rubin likelihood ratio test (LMR-LRT). The optimal number of classes that explained the variation within the data was achieved. LLCA was performed using MPlus version 8 (Muthén & Muthén, 1998-2017).

Our previous study using the same data found that a 5-class solution adequately describes the combined cigarette and cannabis use data between ages 14 to 19 years (Jones et al., 2018). The classes were defined as: non-users, early-onset cigarette-only users, early-onset cannabis users (with or without cigarette use), late-onset cigarette-only users and late-onset cannabis users (with or without cigarette use)(Jones et al., 2018). Based on the patterns of class membership across time (see Jones *et al*., 2018), early-onset and late-onset substance use are approximately defined as higher probability of use between approximate ages 14-16 years and higher probability of use between approximate ages 16-19 years, respectively (see Supplementary Figure 1).

Association analyses

Multinomial logistic regression was used to assess whether polygenic scores predicted latent class membership. Associations were assessed using a manual implementation of the bias-adjusted three-step method in MPlus (see Supplementary Methods and Heron *et al*. (2015) for more detail). Association analyses were conducted using individuals who had cigarette and cannabis use data present for 3 or more time points and genetic data.

To investigate whether associations between schizophrenia polygenic scores and latent class membership were influenced by genetic overlap between variants associated with both schizophrenia and cannabis or cigarette use, analyses were also adjusted for the cigarette smoking initiation and cannabis use initiation polygenic scores.

As it was not possible to incorporate information on frequency of substance use in our 5-class latent class approach as this resulted in an unstable model (Jones et al., 2018), we examined whether schizophrenia polygenic scores were associated with frequency of cannabis or cigarette use using data from single time-points. To aid future meta-analyses, the association between schizophrenia polygenic scores and cannabis and cigarette ever versus never use were also investigated. The association between schizophrenia polygenic scores and ever/never use and frequency of use were assessed using logistic regression and ordered logistic regression, respectively, in Stata statistical software (version 15; StataCorp LLC).

Mediation analysis

Mediation models were used to assess the direct effects of polygenic risk for schizophrenia on latent class membership and indirectly through each potential mediator. Mediation models were run in MPlus using a maximum likelihood estimator, and standard errors for indirect effects were calculated using a non-parametric bootstrapping approach with 100 replications. As two of the mediators were dichotomous measures, a counterfactual approach was implemented to allow for incorporation of the dichotomous mediators with effect estimates that are easily interpretable (Valeri & VanderWeele, 2013). However, it is noted that for the models incorporating continuous mediators, this approach simplifies to product of coefficient strategy as we did not allow for an interaction between exposure and mediator.

Class reparameterization

As the main analyses were performed using multinomial logistic regression, the effect estimates are interpreted as the strength of association between the exposure and each outcome class in relation to a reference class, rather than the effect of the exposure on class membership in the whole population. To address whether this influenced our results, we repeated all analyses after reparametrizing the longitudinal latent classes (maintaining uncertainty in class membership) to examine, primarily, the effects for late-onset cannabis use as compared to all other classes combined in a logistic regression. Effects from these analyses therefore represent odds for membership in late-onset cannabis use class compared to membership in any other latent class.

Results

There was strong evidence that genetic risk for schizophrenia differed across the combined cigarette use and cannabis use latent classes (omnibus p = 0.004; Table 1). The schizophrenia polygenic score based on SNPs meeting a training sample p-threshold of 0.05 was associated with late-onset cannabis use as compared to non-use (OR = 1.23; 95% CI = 1.08, 1.41). There was also weak evidence of association with

decreased odds of late-onset cigarette-only use (OR = 0.87; 95% CI = 0.76, 1.00) as compared to non-use, but little evidence of association with increased odds of early-onset cigarette-only use (OR = 1.13; 95% CI = 0.94, 1.36) or early-onset cannabis use (OR = 1.08; 95% CI = 0.87, 1.33). These associations persisted after adjusting for cigarette smoking initiation and cannabis use initiation polygenic scores (Table 1) which both showed evidence of association with the cigarette use and cannabis use latent classes (omnibus $p < 0.001$; Supplementary Table 1).

Results were similar when excluding the *CHRNA5-A3-B4* gene cluster, and when using a more relaxed p-value threshold for inclusion of SNPs into the schizophrenia polygenic score (p-value threshold ≤ 0.5). However, evidence was weaker when using polygenic scores based on more stringent p-value thresholds ($p \leq 1e^{-5}$ or $p \leq 5e^{-8}$) for SNP inclusion, that capture very little variance in liability to schizophrenia (Supplementary Tables 2 and 3).

Results were also similar following reparameterization of classes with evidence of an increased genetic liability for schizophrenia (p-value threshold ≤ 0.05) being associated with a 1.2-fold increase in odds (95% CI = 1.05, 1.37) of late-onset cannabis use as compared to all other classes combined (Supplementary Table 4).

Evidence of association between the schizophrenia polygenic score and ever/never substance use as well as frequency of substance use was generally stronger for cannabis use than for cigarette use, and also stronger for measures of frequency of use in late adolescence and early adulthood than for measures of use in early adolescence (Supplementary Tables 5 and 6).

There was weak evidence that genetic risk for schizophrenia was associated with lower quality of friendships (higher score indicates a lower friendship quality) (Beta = 0.06; 95% CI = -0.01, 0.13), and lower IQ score in childhood (Beta = -0.05; 95% CI = -0.07, -0.02), but less so with emotional symptoms, victimization, antisocial behavior or impulsivity (Supplementary Figures 2 and 3). There was evidence that higher IQ and engagement in antisocial behavior were associated with an increased odds of late-onset cannabis use (IQ: OR = 1.39; 95% CI = 1.18, 1.64; antisocial behavior: OR = 1.62; 95% CI = 1.02,

2.56). There was weaker evidence that a higher emotional symptoms score was associated with a reduction in late-onset cannabis use (OR = 0.91; 95% CI = 0.82, 1.01) (Supplementary Figure 2).

In the mediation analysis, there was weak evidence that the effect of schizophrenia polygenic score on IQ score at age 8 years acts to reduce the effect of schizophrenia genetic risk on late-onset cannabis use (indirect effect through IQ at age 8 years: OR = 0.99; 95% CI = 0.97, 1.00), but little evidence that any other mediators affected this pathway (Table 2). Results were also similar following reparameterization of classes (Supplementary Table 7).

Discussion

We examined whether genetic risk for schizophrenia was associated with cigarette and cannabis use during adolescence within a general population cohort and, where appropriate, tested for mediating effects of a range of factors measured prior to our outcome measures. Our primary outcome measures were latent classes summarizing the use of cigarettes and cannabis between ages 14 and 19 years. As previously reported (Jones et al., 2018), our data was best summarized by 5 classes comprising individuals with early-onset cigarette-only use, late-onset cigarette-only use, early-onset cannabis use, late-onset cannabis use, and no use of either substance. In our primary analysis, using a training sample p-threshold of 0.05 that optimally captures variance in schizophrenia liability, we found that schizophrenia polygenic risk was most strongly associated with late-onset cannabis use. Early-onset cigarette and cannabis use class estimates were compatible with the late-onset cannabis use estimate. However, these estimates were less precise as the classes were substantially smaller and therefore analyses had lower power. Interestingly, we found that schizophrenia polygenic risk was also associated with a decreased odds of late-onset cigarette only use, however, this weak association did not survive after class reparameterization.

Our findings are consistent with other studies showing that schizophrenia polygenic risk is associated with cannabis use (Carey et al., 2016; Power et al., 2014; Reginsson et al., 2017; Verweij et al., 2017).

Furthermore, results from both our primary results and sensitivity analyses provide evidence that genetic risk of schizophrenia is more strongly associated with cannabis use than with cigarette use.

One interpretation of our findings is that genetic risk for schizophrenia confers a risk of substance use that is more specific for some drug classes than others, perhaps due to pleiotropic effects on more substance-specific biological pathways than ones that are common across addictive behaviors. However, as almost all individuals within the cannabis use class also use tobacco this class could just index a more severe phenotype. Therefore, genetic risk for schizophrenia could confer a risk of multiple substance use, for example through dopaminergic or opioid function that are biological pathways strongly implicated across all addictive behaviours (Koob & Volkow, 2016).

It is also possible that the association with late-onset cannabis use is not due to pleiotropic effects of addiction-related biological pathways, but due to behavioral manifestations of schizophrenia genetic risk leading to adolescent use of cannabis. To explore this possibility we examined if the strongest association we observed in our primary analysis, between schizophrenia genetic risk and late-onset cannabis use, was mediated by lower childhood IQ, emotional problems, victimization, engagement in antisocial behavior, impulsivity or poorer social relationships, all of which are characteristics associated with increased risk of schizophrenia incidence or cannabis use (Courtney et al., 2017; Varese et al., 2012; Welham et al., 2009). Our results suggested that little to none of this association was mediated through these pathways, and indeed that 'direct' effects of schizophrenia genetic risk on late-onset cannabis use may be stronger than first observed. However, this does not exclude the possibility that other variables that we did not test mediate this relationship.

Whilst the cognitive, emotional, and behavioral characteristics we examined did not mediate the relationship between schizophrenia genetic risk and cannabis use, identifying mediating phenotypes expressed in childhood or adolescence is important not just for understanding the mechanisms underlying addictive behavior, but also to inform potential targets for early intervention to prevent substance use and harmful consequences of this. The mediators we examined were measured in childhood, to ensure they occurred prior to substance use, hence minimizing bias in our models.

However, a potential limitation of this is that our results might not adequately reflect the relationship of schizophrenia genetic risk with those same characteristics in adolescence, when they might have a more immediate effect on substance use behavior.

The association we observe here between schizophrenia genetic risk and cannabis use suggests either that the association between cannabis use and psychosis observed consistently in epidemiological studies (Gage, Hickman, & Zammit, 2016; Moore et al., 2007) is, at least in part, due to pleiotropy, or that cannabis has a causal effect on schizophrenia (and therefore risk variants for cannabis use will also be identified as risk variants for schizophrenia (Gage, Davey Smith, Ware, Flint, & Munafò, 2016) in adequately-powered GWASs where there would be many more cannabis users among cases than controls). In fact, despite the finding from this and other studies that schizophrenia genetic risk is associated with cannabis use, there is little evidence that shared genetic effects confound associations between cannabis use and risk of psychotic outcomes in epidemiological studies. For example, in a recent study we found strong evidence that classes of cannabis use were associated with subsequent risk of psychotic experiences, and that this was not attenuated after adjusting for family history of schizophrenia (Jones et al., 2018) or schizophrenia genetic risk score (Supplementary Table 8).

One approach that has been used to examine causal effects of cannabis use on schizophrenia and assess the presence of genetic confounding (horizontal pleiotropy) is Mendelian randomization (MR). Evidence consistent with a causal effect of schizophrenia risk on likelihood of cannabis initiation, as well as weak evidence of a causal effect from cannabis initiation to schizophrenia has been reported (Gage, Jones, et al., 2016; Pasman et al., 2018). Similarly analyses have reported a bidirectional relationship between a measure of lifetime cigarette smoking (capturing smoking duration, heaviness and cessation) (Wootton et al., 2018) and schizophrenia risk. However, when there is little understanding of the biological effects of the genetic instruments used in MR analyses, bidirectional relationships such as these can be difficult to interpret (Davey Smith & Hemani, 2014), and therefore neither MR studies to date, nor our results here, lead to substantially stronger conclusions about the causal effects of cannabis and cigarettes on psychosis than those from more traditional epidemiology designs.

Whilst our findings cannot address whether cannabis use has a causal effect on schizophrenia, our results show that schizophrenia genetic liability does not lead to increased cannabis use through the mechanisms examined here, and that the investigation of other pathways is required to identify potentially modifiable targets to reduce the public health burden of cannabis use in the population.

Strengths and limitations

One of the strengths of our study is that we use a large, population-based cohort, with multiple measures of cigarette and cannabis use data over the whole adolescent period, and thus our results are much less prone to measurement error than if we had used single time-point measures of substance use, although it likely still exists to some extent. Furthermore, using a latent class approach with longitudinal data allows us to maximize use of data for individuals even where participation and question response has been sporadic, and hence minimize potential selection bias, despite the considerable levels of attrition over time. We also used the largest, most recent published GWASs of schizophrenia, cigarette use and cannabis use as training sets for derivation of our polygenic scores. Nevertheless, there are a number of limitations with our study.

Whilst our use of latent classes derived from information on the combined use of cigarettes and cannabis use is useful for teasing out independent effects of schizophrenia genetic risk on these outcomes, 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 (Amos, Wiltshire, Bostock, Haw, & McNeill, 2004), even when they self-report as being cigarette non-smokers (Gage et al., 2014). Furthermore, we have previously found that a substantial proportion of the people who smoke cigarettes most heavily also use cannabis (Gage et al., 2014), and thus the cigarette-only class might not include those who have been most heavily exposed to tobacco. Therefore, we cannot rule out whether the associations observed between schizophrenia genetic risk and the late-onset cannabis use class is driven by heavier cigarette use in these individuals than in those within the early-onset cigarette only or late-onset cigarette only classes (although this would not be consistent with our sensitivity analyses).

Another limitation is that it was not possible to incorporate information on frequency of substance use per time point within the combined cannabis and cigarette use model due to model instability. We therefore also examined frequency of cigarette use and cannabis use using single time-point measures and found no consistent evidence of association with genetic liability of schizophrenia, with the exception of increase odds of cannabis use frequency at ages 17 to 19 years.

Furthermore, although we attempted to minimize genetic confounding by adjusting for cigarette and cannabis initiation polygenic scores, heterogeneity between training set GWAS samples (i.e. differing ages of participants) and substance use measures (i.e. measures combined experimental and regular users into a single group) may have reduced their power to detect genetic associations. Furthermore, polygenic scores for cigarette and cannabis use initiation explain only a small proportion of the variance for these phenotypes in independent samples. Hence, adjusting for cigarette and cannabis initiation polygenic scores may have not adequately removed confounding effects resulting from pleiotropy. It is also possible that our mediation effects are underestimated due to residual confounding.

Finally, as our cohort only included data up to 19 years of age, it was not possible to examine effects of schizophrenia genetic risk on longer-term patterns, or long-term cumulative use of cannabis or cigarettes. Addressing these model limitations may become more tractable in the future.

Conclusion

In conclusion, our study provides evidence that genetic risk for schizophrenia is associated with patterns of cannabis use during adolescence, and that this is not mediated through other measured phenotypic manifestations of genetic risk for schizophrenia during childhood, including lower IQ, victimization, increased emotional difficulties, antisocial behavior, impulsivity, or poorer social relationships. Evidence of association between genetic risk for schizophrenia and cigarette use was weaker. Further studies need to examine longer-term patterns of use of these substances over time to minimize measurement error in allocation of substance use classes, and to establish the mechanisms by which these associations arise to inform substance use reduction strategies.

Acknowledgments

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

Financial support

The UK Medical Research Council (MRC) and Wellcome (grant number 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website. Measures used were specifically funded by the MRC (grant number G0800612/86812) and the Wellcome Trust (grant numbers 076467/Z/05/Z, 086684, 092731). GWAS data were generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. This study was supported by MRC (grant number MR/M006727/1) and the National Institute for Health Research (NIHR) Biomedical Research Centre at the University Hospitals Bristol National Health Service Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health. HJJ, GH and MRM are members of the Medical Research Council Integrative Epidemiology Unit at the University of Bristol funded by the MRC (grant numbers MC_UU_00011/1, MC_UU_00011/7). GH is funded by a Sir Henry Wellcome Postdoctoral Fellowship (grant number 209138/Z/17/Z). CW is funded by a Cancer Research UK Population Research Postdoctoral Fellowship (grant number C60153/A23895).

Conflict of Interest

Professor O'Donovan received a consultancy fee from Roche in July 2015. All other authors have declared no conflicts of interest.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Amos, A., Wiltshire, S., Bostock, Y., Haw, S., & McNeill, A. (2004). 'You can't go without a fag ... you need it for your hash' - a qualitative exploration of smoking, cannabis and young people. *Addiction, 99*(1), 77-81. doi:DOI 10.1111/j.1360-0443.2004.00531.x

Baron-Cohen, S., & Wheelwright, S. (2003). The friendship questionnaire: an investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders, 33*(5), 509-517. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14594330

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., . . . Davey Smith, G. (2013). Cohort Profile: the 'children of the 90s' - the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology, 42*, 111-127. doi:10.1093/ije/dys064

Cannon, M., Walsh, E., Hollis, C., Kargin, M., Taylor, E., Murray, R. M., & Jones, P. B. (2001). Predictors of later schizophrenia and affective psychosis among attendees at a child psychiatry department. *British Journal of Psychiatry, 178*, 420-426. doi:DOI 10.1192/bjp.178.5.420

Carey, C. E., Agrawal, A., Bucholz, K. K., Hartz, S. M., Lynskey, M. T., Nelson, E. C., . . . Bogdan, R. (2016). Associations between polygenic risk for psychiatric disorders and substance involvement. *Frontiers in Genetics, 7*. doi:10.3389/fgene.2016.00149

Chang, C. C., Chow, C. C., Tellier, L. C. A. M., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience, 4*. doi:10.1186/s13742-015-0047-8

Courtney, K. E., Mejia, M. H., & Jacobus, J. (2017). Longitudinal studies on the etiology of cannabis use disorder: a review. *Current addiction reports, 4*(2), 43-52. doi:10.1007/s40429-017-0133-3

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., . . . Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology, 29*(8), 1558-1572. doi:10.1038/sj.npp.1300496

Davey Smith, G., & Hemani, G. (2014). Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Human Molecular Genetics, 23*(R1), R89-98. doi:10.1093/hmg/ddu328

de Leon, J., & Diaz, F. J. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research, 76*(2-3), 135-157. doi:10.1016/j.schres.2005.02.010

Dickerson, F., Stallings, C. R., Origoni, A. E., Vaughan, C., Khushalani, S., Schroeder, J., & Yolken, R. H. (2013). Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999-2011. *Psychiatric Services, 64*(1), 44-50. doi:10.1176/appi.ps.001432012

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., . . . Lawlor, D. A. (2013). Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology, 42*, 97-110. doi:10.1093/ije/dys066

Gage, S. H., Davey Smith, G., Ware, J. J., Flint, J., & Munafò, M. R. (2016). G = E: what GWAS can tell us about the environment. *Plos Genetics, 12*(2). doi:10.1371/journal.pgen.1005765

Gage, S. H., Hickman, M., Heron, J., Munafo, M. R., Lewis, G., Macleod, J., & Zammit, S. (2014). Associations of cannabis and cigarette use with psychotic experiences at age 18: findings from

454 the Avon Longitudinal Study of Parents and Children. *Psychological Medicine, 44*(16), 3435-
455 3444. doi:10.1017/S0033291714000531
456 Gage, S. H., Hickman, M., & Zammit, S. (2016). Association between cannabis and psychosis:
457 epidemiologic evidence. *Biological Psychiatry, 79*(7), 549-556.
458 doi:10.1016/j.biopsych.2015.08.001
459 Gage, S. H., Jones, H. J., Burgess, S., Bowden, J., Davey Smith, G., Zammit, S., & Munafò, M. R. (2016).
460 Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample
461 Mendelian randomization study. *Psychological Medicine*, 1-10.
462 doi:10.1017/S0033291716003172
463 Goodman, R. (1999). The extended version of the strengths and difficulties questionnaire as a guide to
464 child psychiatric caseness and consequent burden. *Journal of Child Psychology and Psychiatry,*
465 *and Allied Disciplines, 40*(5), 791-799. doi:Doi 10.1017/S0021963099004096
466 Green, B., Young, R., & Kavanagh, D. (2005). Cannabis use and misuse prevalence among people with
467 psychosis. *British Journal of Psychiatry, 187*, 306-313. doi:DOI 10.1192/bjp.187.4.306
468 Guloksuz, S., Pries, L. K., Delespaul, P., Kenis, G., Luykx, J. J., Lin, B. C. D., . . . van Os, J. (2019). Examining
469 the independent and joint effects of molecular genetic liability and environmental exposures in
470 schizophrenia: results from the EUGEI study. *World Psychiatry, 18*(2), 173-182.
471 doi:10.1002/wps.20629
472 Gurillo, P., Jauhar, S., Murray, R. M., & MacCabe, J. H. (2015). Does tobacco use cause psychosis?
473 Systematic review and meta-analysis. *Lancet Psychiatry, 2*(8), 718-725. doi:10.1016/S2215-
474 0366(15)00152-2
475 Handley, S. J., Capon, A., Beveridge, M., Dennis, I., & Evans, J. S. T. (2004). Working memory, inhibitory
476 control and the development of children's reasoning. *Thinking & Reasoning, 10*(2), 175-195.
477 doi:10.1080/13546780442000051
478 Heron, J. E., Croudace, T. J., Barker, E. D., & Tilling, K. (2015). A comparison of approaches for assessing
479 covariate effects in latent class analysis. *2015, 6*(4), 15. doi:10.14301/llcs.v6i4.322
480 Horwood, J., Salvi, G., Thomas, K., Duffy, L., Gunnell, D., Hollis, C., . . . Harrison, G. (2008). IQ and non-
481 clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort. *British Journal*
482 *of Psychiatry, 193*, 185-191. doi:10.1192/bjp.bp.108.051904
483 Howe, L. J., Trela-Larsen, L., Taylor, M., Heron, J., Munafò, M. R., & Taylor, A. E. (2017). Body mass index,
484 body dissatisfaction and adolescent smoking initiation. *Drug and Alcohol Dependence, 178*, 143-
485 149. doi:10.1016/j.drugalcdep.2017.04.008
486 Hubbard, L., Tansey, K. E., Rai, D., Jones, P., Ripke, S., Chambert, K. D., . . . Zammit, S. (2016). Evidence of
487 common genetic overlap between schizophrenia and cognition. *Schizophrenia Bulletin, 42*(3),
488 832-842. doi:10.1093/schbul/sbv168
489 Jones, H. J., Gage, S. H., Heron, J., Hickman, M., Lewis, G., Munafo, M. R., & Zammit, S. (2018).
490 Association of combined patterns of tobacco and cannabis use in adolescence with psychotic
491 experiences. *JAMA Psychiatry, 75*(3), 240-246. doi:10.1001/jamapsychiatry.2017.4271
492 Jones, H. J., Stergiakouli, E., Tansey, K. E., Hubbard, L., Heron, J., Cannon, M., . . . Zammit, S. (2016).
493 Phenotypic manifestation of genetic risk for schizophrenia during adolescence in the general
494 population. *JAMA Psychiatry, 73*(3), 221-228. doi:10.1001/jamapsychiatry.2015.3058
495 Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *Lancet*
496 *Psychiatry, 3*(8), 760-773. Retrieved from <Go to ISI>://WOS:000382276500025
497 Liu, M. Z., Jiang, Y., Wedow, R., Li, Y., Brazel, D. M., Chen, F., . . . Vrieze, S. (2019). Association studies of
498 up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol
499 use. *Nature Genetics, 51*(2), 237-244. doi:10.1038/s41588-018-0307-5
500 Malmberg, A., Lewis, G., David, A., & Allebeck, P. (1998). Premorbid adjustment and personality in
501 people with schizophrenia. *British Journal of Psychiatry, 172*, 308-313; discussion 314-305.
502 Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9715332
503 Moore, T. H. M., Zammit, S., Lingford-Hughes, A., Barnes, T. R. E., Jones, P. B., Burke, M., & Lewis, G.
504 (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic
505 review. *Lancet, 370*(9584), 319-328. doi:Doi 10.1016/S0140-6736(07)61162-3
506 Muthén, L. K., & Muthén, B. O. (1998-2017). *MPlus user's guide. Eighth Edition*. Los Angeles, CA: Muthén
507 & Muthén.

Pardiñas, A. F., Holmans, P., Pocklington, A. J., Escott-Price, V., Ripke, S., Carrera, N., . . . Walters, J. T. R. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature Genetics, 50*(3), 381-389. doi:10.1038/s41588-018-0059-2

Pasman, J. A., Verweij, K. J. H., Gerring, Z., Stringer, S., Sanchez-Roige, S., Treur, J. L., . . . Vink, J. M. (2018). GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nature Neuroscience, 21*(9), 1161 - 1170. doi:10.1038/s41593-018-0206-1

Power, R. A., Verweij, K. J. H., Zuhair, M., Montgomery, G. W., Henders, A. K., Heath, A. C., . . . Martin, N. G. (2014). Genetic predisposition to schizophrenia associated with increased use of cannabis. *Molecular Psychiatry, 19*(11), 1201-1204. doi:10.1038/mp.2014.51

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., . . . Sham, P. C. (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet, 81*, 559-575. doi:10.1086/519795

Purcell, S., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., . . . International Schizophrenia Consortium. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature, 460*, 748-752. doi:10.1038/nature08185

Reginsson, G. W., Ingason, A., Euesden, J., Bjornsdottir, G., Olafsson, S., Sigurdsson, E., . . . Stefansson, K. (2017). Polygenic risk scores for schizophrenia and bipolar disorder associate with addiction. *Addiction Biology*. doi:10.1111/adb.12496

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J. L., Kähler, A. K., Akterin, S., . . . Sullivan, P. F. (2013). Genome-wide association analysis identifies 14 new risk loci for schizophrenia. *Nature Genetics, 45*(10), 10.1038/ng.2742. doi:10.1038/ng.2742

Saccone, N. L., Wang, J. C., Breslau, N., Johnson, E. O., Hatsukami, D., Saccone, S. F., . . . Bierut, L. J. (2009). The CHRNA5-CHRNA3-CHRNB4 nicotinic receptor subunit gene cluster affects risk for nicotine dependence in African-Americans and in European-Americans. *Cancer Research, 69*(17), 6848-6856. doi:10.1158/0008-5472.CAN-09-0786

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*, 421-427. doi:10.1038/nature13595

Stringer, S., Minica, C. C., Verweij, K. J. H., Mbarek, H., Bernard, M., Derringer, J., . . . Vink, J. M. (2016). Genome-wide association study of lifetime cannabis use based on a large meta-analytic sample of 32330 subjects from the International Cannabis Consortium. *Translational Psychiatry, 6*. doi:10.1038/tp.2016.36

Taylor, M., Collin, S. M., Munafò, M. R., MacLeod, J., Hickman, M., & Heron, J. (2017). Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: findings from a UK birth cohort. *Journal of Epidemiology and Community Health*. doi:10.1136/jech-2016-208503

Tobacco Genetics Consortium. (2010). Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nature Genetics, 42*(5), 441-447. doi:10.1038/ng.571

Valeri, L., & VanderWeele, T. J. (2013). Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychological Methods, 18*(2), 137-150. doi:10.1037/a0031034

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., . . . Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort Studies. *Schizophrenia Bulletin, 38*(4), 661-671. doi:10.1093/schbul/sbs050

Verweij, K. J. H., Abdellaoui, A., Nivard, M. G., Cort, A. S., Ligthart, L., Draisma, H. H. M., . . . Vink, J. M. (2017). Short communication: Genetic association between schizophrenia and cannabis use. *Drug and Alcohol Dependence, 171*, 117-121. doi:10.1016/j.drugalcdep.2016.09.022

Wechsler, D., Golombok, S., & Rust, J. (1992). *Wechsler Intelligence Scale for Children – Third Edition UK Manual*. Sidcup, UK: The Psychological Corporation.

Welham, J., Isohanni, M., Jones, P., & McGrath, J. (2009). The antecedents of schizophrenia: a review of birth cohort studies. *Schizophrenia Bulletin, 35*(3), 603-623. doi:10.1093/schbul/sbn084

Wolke, D., Woods, S., Bloomfield, L., & Karstadt, L. (2000). The association between direct and relational bullying and behaviour problems among primary school children. *Journal of Child Psychology and Psychiatry, 41*(8), 989-1002. doi:Doi 10.1017/S0021963099006381

Wootton, R. E., Richmond, R. C., Stuijfzand, B. G., Lawn, R. B., Sallis, H. M., Taylor, G. M. J., . . . Munafò, M. R. (2018). Causal effects of lifetime smoking on risk for depression and schizophrenia: evidence from a Mendelian randomisation study. *bioRxiv*.

Tables

Table 1. Associations between polygenic score for schizophrenia and subsequent cigarette and/or cannabis use as compared to non-use (N = 3925)

P-value threshold for inclusion of SNPs into polygenic score (P_T)	Early cigarette only users (4.3%) [1] OR (95% CI) [2]	Early cannabis with/without cigarette users (3.4%) [1] OR (95% CI) [2]	Late cigarette only users (15.2%) [1] OR (95% CI) [2]	Late cannabis with/without cigarette users (11.8%) [1] OR (95% CI) [2]	*P*
Unadjusted					
P_T = 0.05	1.13 (0.94, 1.36)	1.08 (0.87, 1.33)	0.87 (0.76, 1.00)	1.23 (1.08, 1.41)	0.004
Adjusted [3]					
P_T = 0.05	1.11 (0.91, 1.34)	1.07 (0.86, 1.33)	0.85 (0.74, 0.99)	1.22 (1.07, 1.40)	0.006

Note: SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval; P, omnibus P-value for association between polygenic score and cigarette/cannabis use classes

[1] Class proportions for latent class membership based on the estimated model

[2] Compared to non-use class (class proportion for latent class membership based on the estimated model: 65.3%).

[3] Adjusted for polygenic scores for cigarette smoking initiation and cannabis use initiation (P_T = 0.5).

Table 2. Total effect, direct effect and indirect effect of schizophrenia polygenic score (P_T = 0.05) on late-onset cannabis with/without cigarette use as compared to non-use through a range of potential mediators

Mediator	N	Total Effect OR (95% CI)	Direct Effect OR (95% CI)	Indirect Effect via mediator OR (95% CI)
Standardized measure of IQ at age 8 years	3468	1.23 (1.06,1.44)	1.25 (1.07,1.46)	0.99 (0.97,1.00)
Victimization at age 8 years	3371	1.22 (1.07,1.38)	1.22 (1.07,1.38)	1.00 (1.00,1.01)
Emotional symptoms at age 9 years	3522	1.20 (1.04,1.39)	1.20 (1.04,1.39)	1.00 (0.99,1.00)
Antisocial behavior at age 10 years	3533	1.26 (1.09,1.46)	1.26 (1.09,1.46)	1.00 (1.00,1.01)
Impulsivity at age 10 years	3344	1.22 (1.06,1.41)	1.22 (1.06,1.41)	1.00 (1.00,1.00)
Friendship quality at age 12 years	3542	1.27 (1.09,1.48)	1.27 (1.09,1.48)	1.00 (0.99,1.00)
Psychotic experiences at age 12 years	3572	1.26 (1.12,1.42)	1.26 (1.12,1.42)	1.00 (1.00,1.00)

Note: OR, odds ratio; 95% CI, 95% confidence interval; P_T, p-value threshold for inclusion of SNPs into polygenic score. Within the mediation models, higher emotional, impulsivity and friendship quality scores indicate more emotional problems, a higher level of impulsivity and worse friendship quality, respectively.

Supplementary material -- Examining pathways between genetic liability for schizophrenia and patterns of tobacco and cannabis use in adolescence

Supplementary Methods

Participants

The sample consisted of participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) longitudinal birth cohort which recruited 14,541 pregnant women residing in the former Avon Health Authority area with an expected delivery date between April 1991 and December 1992. Of the initial 14,541 pregnancies, 14,062 were live births and 13,988 were alive at 1 year (Boyd *et al.*, 2013, Fraser *et al.*, 2013). When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally resulting in an additional 913 children being enrolled. The total sample size for analyses using any data collected after the age of 7 years is therefore 15,454 pregnancies, resulting in 15,589 fetuses. Of these 14,901 were alive at 1 year of age. Collection of a range of measures from ALSPAC mothers and their children is still ongoing and details of available data are accessible through a fully searchable data dictionary and variable search tool (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (http://www.bristol.ac.uk/alspac/researchers/research-ethics/). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

Genetic data

Avon Longitudinal Study of Parents and Children (ALSPAC) participants genetic data were acquired using the Illumina HumanHap550 quad genome-wide single nucleotide polymorphism (SNP) genotyping platform from 9912 participants. Individuals were excluded from further analysis on the basis of gender mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%), evidence of cryptic relatedness (>10% of alleles identical by descent), and being of non-European ancestry (assessed by multidimensional scaling analysis including HapMap 2 individuals). SNPs with a minor allele frequency (MAF) of < 1%, Impute2 information quality metric of < 0.8, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (p value < 5 x 10^{-7}) were removed. Imputation of the target data was performed using Impute V2.2.2 against the 1000 genomes reference panel (Phase 1, Version 3; all polymorphic SNPs excluding singletons), using 2,186 reference haplotypes (including non-Europeans). Following quality control assessment and imputation and restricting to 1 young person per family, genetic data was available for 7,977 ALSPAC individuals.

Polygenic scores

Polygenic scores for schizophrenia were constructed for each ALSPAC individual using data from the most recent schizophrenia GWAS based on 40,675 cases and 64,643 controls (Pardiñas *et al.*, 2018) as a training set. Polygenic scores were calculated using the PLINK (v1.9)(Chang *et al.*, 2015, Purcell *et al.*, 2007) 'score' command following the methodology described by the International Schizophrenia Consortium (ISC) (Purcell *et al.*, 2009). Prior to construction of scores, SNPs were removed from the analysis if they had a minor allele frequency less than 0.01, an imputation quality less than 0.8 or if there was allelic mismatch between samples. Due to the high linkage disequilibrium (LD) within the extended major histocompatibility complex (MHC; chromosome 6: 25-34Mb) only a single SNP was included to represent this region. SNPs were pruned for LD using the PLINK 'clump' command to remove SNPs in LD ($r^2 > 0.25$) with a more significant SNP in the training set. Windows of 500kb were used to assess inter-SNP LD for pruning.

Repeated measures of cigarette and/or cannabis use

Measures taken at approximate age 14 years, 16 years and 18 years were collected as part of ALSPAC assessment clinics using a computerized interview. Measures taken at approximate age 15 years, 17 years and 19 years were collected via ALSPAC postal questionnaires. For each time point, individuals were deemed as cigarette users if they were current smokers who smoked at least 1-3 in the previous 6 months (age 14 years), who smoked less that once a week, weekly or daily (age 15 and 16 years), had smoked less that once a week, weekly or daily in the last 30 days (age 16, 18 and 19 years). Individuals were deemed as non-cigarette users if they had never smoked a cigarette, if they had only tried cigarettes once or twice (age 15 and 17 years) or if they had not smoked in the last 6 months (age 14 years) or last 30 days (age 16, 18 and 19 years). For each time point, individuals were deemed as cannabis users if they had used or taken cannabis at least 1-3 times in the past 6 months (age 14 years), currently take cannabis less than weekly, weekly or daily (age 15, 16 and 17 years) or at least monthly or less in the last 12 months (age 18 and 19 years). Individuals were deemed as non-cannabis users if they had never tried cannabis, if they had only ever tried cannabis once or twice or if they used to sometimes use or take cannabis but had since stopped.

For generation of longitudinal latent classes, cigarette and cannabis use data were then combined into a 3-category nominal variable for each time point: "Non-users", "Cigarette-only users" and "Cannabis users (either with or without cigarettes)" as previously described (Jones *et al.*, 2018).

To assess the associations between polygenic scores for schizophrenia and frequency of cigarette and cannabis use, responses to one or more questions at each time point were used to derive two 3-level ordinal variables for cigarette use and cannabis use: "Non-user", "Occasional user" (typically less than once per week) and "Frequent user" (typically once a week or more) as previously described (Howe *et al.*, 2017, Taylor *et al.*, 2017).

Association analyses

Multinomial logistic regression was used to assess whether polygenic scores predicted latent class membership. Associations were assessed using a manual implementation of the bias-adjusted three-step method in MPlus (see Heron *et al.* (2015) for more detail and example of code). The latent classes were first derived without the presence of the predictor. The resulting logit parameters defining the relationship between modal and latent classes were used as constraints allowing odds ratios (ORs) and confidence intervals (CIs) for the associations to be calculated without influencing latent class membership. Association analyses were conducted using individuals who had cigarette and cannabis use data present for 3 or more time points and genetic data.

Potential mediators

A number of potential mediators were examined: IQ at age 8 years (assessed via the Wechsler Intelligence Scale for Children (Wechsler *et al.*, 1992); this measure was standardized [mean =0, standard deviation = 1] before use), victimization at age 8 years (a dichotomous measure relating to whether individual experienced relational or overt victimization, assessed via a modified version of the Bullying and Friendship Interview Schedule (Wolke *et al.*, 2000) at age 8 years), Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1999) score at age 9 years relating to emotional symptoms (total scores assessed via parental-completed questionnaire when child was age 9 years with higher score indicating emotional difficulties), antisocial behavior (a dichotomous measure relating to whether individual engaged in any antisocial activities, assessed via a short structured interview at age 10 years), impulsivity (assessed using the number of incorrect stop signal trials at a 150ms delay during the stop signal task (Handley *et al.*, 2004) administered at age 10 years with a higher score indicating a higher level of impulsivity), friendship quality score (total score based on 5 items from the Cambridge Friendship Questionnaire (Baron-Cohen and Wheelwright, 2003) at age 12 years with a higher score indicating worse friendship quality), and psychotic experiences (a dichotomous measure relating to whether individual experienced hallucinations (visual and auditory), delusions (spied on, persecution, thoughts read, reference, control, grandiosity, other) and experiences of thought interference (broadcasting, insertion and withdrawal), assessed via the semi-structured Psychosis-Like Symptom Interview (PLIKSi) (Horwood *et al.*, 2008) at age 12 years).

Supplementary References

Baron-Cohen, S. & Wheelwright, S. (2003). The friendship questionnaire: an investigation of adults with Asperger syndrome or high-functioning autism, and normal sex differences. *Journal of Autism and Developmental Disorders* **33**, 509-17.
Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S. & Davey Smith, G. (2013). Cohort Profile: the 'children of the 90s' - the index offspring of the Avon Longitudinal Study of Parents and Children. *International Journal of Epidemiology* **42**, 111-27.
Chang, C. C., Chow, C. C., Tellier, L. C. A. M., Vattikuti, S., Purcell, S. M. & Lee, J. J. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**.
Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., Henderson, J., Macleod, J., Molloy, L., Ness, A., Ring, S., Nelson, S. M. & Lawlor, D. A. (2013). Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology* **42**, 97-110.

Goodman, R. (1999). The extended version of the strengths and difficulties questionnaire as a guide to child psychiatric caseness and consequent burden. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **40**, 791-799.
Handley, S. J., Capon, A., Beveridge, M., Dennis, I. & Evans, J. S. T. (2004). Working memory, inhibitory control and the development of children's reasoning. *Thinking & Reasoning* **10**, 175-195.
Heron, J. E., Croudace, T. J., Barker, E. D. & Tilling, K. (2015). A comparison of approaches for assessing covariate effects in latent class analysis. *2015* **6**, 15.
Horwood, J., Salvi, G., Thomas, K., Duffy, L., Gunnell, D., Hollis, C., Lewis, G., Menezes, P., Thompson, A., Wolke, D., Zammit, S. & Harrison, G. (2008). IQ and non-clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort. *British Journal of Psychiatry* **193**, 185-91.
Howe, L. J., Trela-Larsen, L., Taylor, M., Heron, J., Munafò, M. R. & Taylor, A. E. (2017). Body mass index, body dissatisfaction and adolescent smoking initiation. *Drug and Alcohol Dependence* **178**, 143-149.
Jones, H. J., Gage, S. H., Heron, J., Hickman, M., Lewis, G., Munafo, M. R. & Zammit, S. (2018). Association of combined patterns of tobacco and cannabis use in adolescence with psychotic experiences. *JAMA Psychiatry* **75**, 240-246.
Pardiñas, A. F., Holmans, P., Pocklington, A. J., Escott-Price, V., Ripke, S., Carrera, N., Legge, S. E., Bishop, S., Cameron, D., Hamshere, M. L., Han, J., Hubbard, L., Lynham, A., Mantripragada, K., Rees, E., MacCabe, J. H., McCarroll, S. A., Baune, B. T., Breen, G., Byrne, E. M., Dannlowski, U., Eley, T. C., Hayward, C., Martin, N. G., McIntosh, A. M., Plomin, R., Porteous, D. J., Wray, N. R., Caballero, A., Geschwind, D. H., Huckins, L. M., Ruderfer, D. M., Santiago, E., Sklar, P., Stahl, E. A., Won, H., Agerbo, E., Als, T. D., Andreassen, O. A., Bækvad-Hansen, M., Mortensen, P. B., Pedersen, C. B., Børglum, A. D., Bybjerg-Grauholm, J., Djurovic, S., Durmishi, N., Pedersen, M. G., Golimbet, V., Grove, J., Hougaard, D. M., Mattheisen, M., Molden, E., Mors, O., Nordentoft, M., Pejovic-Milovancevic, M., Sigurdsson, E., Silagadze, T., Hansen, C. S., Stefansson, K., Stefansson, H., Steinberg, S., Tosato, S., Werge, T., GERAD1 Consortium, CRESTAR Consortium, Collier, D. A., Rujescu, D., Kirov, G., Owen, M. J., O'Donovan, M. C. & Walters, J. T. R. (2018). Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature Genetics* **50**, 381-389.
Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., Maller, J., Sklar, P., de Bakker, P. I., Daly, M. J. & Sham, P. C. (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559-75.
Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., Sklar, P. & International Schizophrenia Consortium (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748-52.
Taylor, M., Collin, S. M., Munafò, M. R., MacLeod, J., Hickman, M. & Heron, J. (2017). Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: findings from a UK birth cohort. *Journal of Epidemiology and Community Health*.
Wechsler, D., Golombok, S. & Rust, J. (1992). *Wechsler Intelligence Scale for Children – Third Edition UK Manual*. The Psychological Corporation: Sidcup, UK.
Wolke, D., Woods, S., Bloomfield, L. & Karstadt, L. (2000). The association between direct and relational bullying and behaviour problems among primary school children. *Journal of Child Psychology and Psychiatry* **41**, 989-1002.

Supplementary Tables

Supplementary Table 1. Associations between polygenic score for cigarette smoking initiation and cannabis use initiation and subsequent cigarette and/or cannabis use as compared to non-use (N = 3925)

P_T	Early cigarette only users	Early cannabis with/without cigarette users	Late cigarette only users	Late cannabis with/without cigarette users	
	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	*P*
Cigarette smoking initiation polygenic score associations					
0.5	1.68 (1.34, 2.10)	1.33 (1.03, 1.71)	1.46 (1.25, 1.70)	1.23 (1.05, 1.45)	<0.001
Cannabis use initiation polygenic score associations					
0.5	1.16 (0.94, 1.44)	1.15 (0.93, 1.42)	1.13 (0.98, 1.32)	1.42 (1.24, 1.62)	<0.001

Note: SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval; P, omnibus P-value for association between polygenic score and cigarette/cannabis use classes; P_T, p-value threshold for inclusion of SNPs into the cigarette use and cannabis use polygenic scores.

[1] Compared to all other classes combined.

Supplementary Table 2. Associations between polygenic risk score for schizophrenia minus the CHRNA5-CHRNA3-CHRNB4 gene cluster on chromosome 15 and cigarette and/or cannabis use as compared to non-use

P_T	Early cigarette only users	Early cannabis with/without cigarette users	Late cigarette only users	Late cannabis with/without cigarette users	
	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	*P*
0.5	1.13 (0.93, 1.37)	1.08 (0.88, 1.32)	0.87 (0.75, 1.00)	1.25 (1.09, 1.44)	0.004
0.05	1.13 (0.94, 1.36)	1.08 (0.87, 1.33)	0.87 (0.76, 1.00)	1.23 (1.08, 1.41)	0.004
$1e^{-5}$	1.00 (0.82, 1.22)	1.20 (0.98, 1.47)	0.93 (0.81, 1.08)	1.03 (0.90, 1.18)	0.344
$5e^{-8}$	0.96 (0.75, 1.23)	1.14 (0.92, 1.41)	1.10 (0.94, 1.29)	1.00 (0.87, 1.16)	0.632

Note: OR, odds ratio; 95% CI, 95% confidence interval; P, omnibus P-value for association between polygenic risk score and substance use classes; P_T, p-value threshold for inclusion of SNPs into the schizophrenia polygenic score.

[1] Compared to non-use class.

Supplementary Table 3. Associations between polygenic score for schizophrenia and cigarette and/or cannabis use as compared to non-use

P_T	Early cigarette only users	Early cannabis with/without cigarette users	Late cigarette only users	Late cannabis with/without cigarette users	
	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	*P*
0.5	1.13 (0.93, 1.37)	1.08 (0.88, 1.32)	0.87 (0.75, 1.00)	1.25 (1.09, 1.44)	0.003
$1e^{-5}$	0.99 (0.81, 1.21)	1.19 (0.97, 1.47)	0.94 (0.81, 1.09)	1.03 (0.91, 1.18)	0.377
$5e^{-8}$	0.95 (0.74, 1.21)	1.14 (0.92, 1.41)	1.12 (0.95, 1.31)	1.01 (0.87, 1.16)	0.562

Note: SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval; P, omnibus P-value for association between polygenic score and cigarette/cannabis use classes; P_T, p-value threshold for inclusion of SNPs into the schizophrenia polygenic score.

[1] Compared to non-use class.

Supplementary Table 4. Logistic regression associations between polygenic score for schizophrenia and cigarette and/or cannabis use after reparameterization of classes into a 2-category outcome (N = 3925)

P_T	Early cigarette only users	Early cannabis with/without cigarette users	Late cigarette only users	Late cannabis with/without cigarette users	
	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	OR (95% CI) [1]	*P*
Unadjusted					
0.05	1.07 (0.88, 1.31)	1.10 (0.88, 1.36)	0.89 (0.77, 1.02)	1.20 (1.05, 1.37)	0.032
Adjusted [2]					
0.05	1.06 (0.86, 1.3)	1.09 (0.87, 1.35)	0.87 (0.75, 1.01)	1.19 (1.04, 1.37)	0.040

Note: SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval; P, omnibus P-value for association between polygenic score and cigarette/cannabis use classes; P_T, p-value threshold for inclusion of SNPs into the schizophrenia polygenic score.

[1] Compared to all other classes combined.

[2] Adjusted for polygenic scores for cigarette smoking initiation and cannabis use initiation (P_T = 0.5).

Supplementary Table 5. Associations between polygenic score for schizophrenia and cannabis and cigarette use (ever versus never) at single time-points

P_T	OR (95% CI) for cigarette ever versus never use					
	14 years (N = 4567)	**15 years (N = 4150)**	**16 years (N = 1896)**	**17 years (N = 3579)**	**18 years (N = 3043)**	**19 years (N = 2402)**
0.5	1.10 (1.02, 1.18)	1.08 (1.01, 1.16)	0.94 (0.86, 1.04)	1.12 (1.05, 1.20)	1.13 (1.05, 1.21)	1.08 (1.00, 1.17)
0.05	1.08 (1.01, 1.17)	1.10 (1.03, 1.18)	0.95 (0.86, 1.05)	1.09 (1.02, 1.16)	1.11 (1.03, 1.19)	1.05 (0.97, 1.14)
$1e^{-5}$	1.07 (0.99, 1.15)	1.07 (0.99, 1.14)	1.03 (0.94, 1.14)	1.06 (1.00, 1.14)	1.06 (0.98, 1.13)	1.04 (0.96, 1.13)
$5e^{-8}$	1.07 (0.99, 1.15)	1.06 (0.98, 1.13)	1.00 (0.91, 1.10)	1.02 (0.95, 1.09)	1.06 (0.99, 1.14)	0.98 (0.91, 1.07)
P_T	**OR (95% CI) for cannabis ever versus never use**					
	14 years (N = 4551)	**15 years (N = 4164)**	**16 years (N = 3957)**	**17 years (N = 3580)**	**18 years (N = 3015)**	**19 years (N = 2405)**
0.5	1.18 (1.03, 1.35)	1.13 (1.02, 1.26)	1.17 (1.09, 1.25)	1.16 (1.08, 1.25)	1.19 (1.10, 1.28)	1.17 (1.08, 1.27)
0.05	1.15 (1.00, 1.31)	1.12 (1.01, 1.25)	1.18 (1.10, 1.27)	1.13 (1.05, 1.22)	1.14 (1.06, 1.23)	1.13 (1.04, 1.23)
$1e^{-5}$	1.19 (1.04, 1.36)	1.09 (0.98, 1.22)	1.09 (1.01, 1.17)	1.08 (1.01, 1.17)	1.02 (0.95, 1.10)	1.1 0 (1.01, 1.19)
$5e^{-8}$	1.12 (0.98, 1.28)	1.06 (0.96, 1.18)	1.05 (0.97, 1.12)	1.02 (0.95, 1.1)	1.02 (0.95, 1.10)	1.01 (0.93, 1.10)

Note: P_T, p-value threshold for inclusion of SNPs into the schizophrenia polygenic score; OR, odds ratio; 95% CI, 95% confidence interval.

Supplementary Table 6. Associations between polygenic score for schizophrenia and frequency of cannabis and cigarette use (non-use, occasional use, frequent use) at single time-points

P_T	OR (95% CI) for increasing frequency of cigarette use					
	14 years (N = 3578)	**15 years (N = 3403)**	**16 years (N = 3400)**	**17 years (N = 3105)**	**18 years (N = 2714)**	**19 years (N = 2166)**
0.5	1.14 (0.91, 1.41)	0.96 (0.83, 1.12)	1.02 (0.93, 1.12)	1.06 (0.97, 1.16)	1.06 (0.98, 1.16)	1.09 (1.00, 1.20)
0.05	1.15 (0.92, 1.43)	0.95 (0.81, 1.10)	1.05 (0.95, 1.15)	1.07 (0.98, 1.17)	1.04 (0.95, 1.13)	1.08 (0.98, 1.18)
$1e^{-5}$	1.01 (0.81, 1.26)	0.94 (0.81, 1.10)	1.01 (0.92, 1.11)	0.97 (0.89, 1.06)	1.01 (0.93, 1.1)	1.08 (0.98, 1.18)
$5e^{-8}$	1.04 (0.84, 1.30)	0.97 (0.84, 1.13)	1.01 (0.92, 1.10)	1.00 (0.91, 1.09)	1.02 (0.94, 1.11)	1.02 (0.93, 1.12)
P_T	**OR (95% CI) for increasing frequency of cannabis use**					
	14 years (N = 3557)	**15 years (N = 3388)**	**16 years (N = 3373)**	**17 years (N = 3098)**	**18 years (N = 2690)**	**19 years (N = 2160)**
0.5	1.19 (0.99, 1.44)	1.00 (0.80, 1.25)	1.10 (0.98, 1.24)	1.23 (1.10, 1.39)	1.11 (1.01, 1.23)	1.22 (1.09, 1.37)
0.05	1.13 (0.94, 1.37)	1.01 (0.81, 1.27)	1.11 (0.98, 1.25)	1.21 (1.08, 1.36)	1.10 (1.00, 1.22)	1.20 (1.07, 1.34)
$1e^{-5}$	1.19 (0.99, 1.44)	1.04 (0.82, 1.31)	1.08 (0.96, 1.21)	1.02 (0.91, 1.15)	1.06 (0.96, 1.17)	1.04 (0.93, 1.17)
$5e^{-8}$	1.11 (0.92, 1.34)	0.99 (0.79, 1.24)	1.06 (0.94, 1.19)	1.00 (0.89, 1.13)	1.00 (0.91, 1.10)	0.94 (0.84, 1.06)

Note: P_T, p-value threshold for inclusion of SNPs into the schizophrenia polygenic score; OR, odds ratio; 95% CI, 95% confidence interval.

Supplementary Table 7. Total effect, direct effect and indirect effect of schizophrenia polygenic score (P_T = 0.05) on late-onset cannabis with/without cigarette use as compared to all other classes combined (after class reparameterization) through a range of potential mediators

Mediator	N	Total Effect OR (95% CI)	Direct Effect OR (95% CI)	Indirect Effect via mediator OR (95% CI)
IQ at age 8 years	3468	1.20 (1.03,1.39)	1.22 (1.05,1.41)	0.98 (0.97,1.00)
Victimization at age 8 years	3371	1.18 (1.04,1.33)	1.18 (1.04,1.33)	1.00 (1.00,1.01)
Emotional symptoms at age 9 years	3522	1.18 (1.02,1.36)	1.18 (1.02,1.36)	1.00 (0.99,1.00)
Antisocial behavior at age 10 years	3533	1.22 (1.06,1.40)	1.21 (1.05,1.40)	1.00 (1.00,1.01)
Impulsivity at age 10 years	3344	1.17 (1.02,1.35)	1.17 (1.02,1.35)	1.00 (1.00,1.00)
Friendship quality at age 12 years	3542	1.22 (1.06,1.41)	1.22 (1.06,1.41)	1.00 (0.99,1.00)
Psychotic experiences at age 12 years	3572	1.22 (1.08,1.37)	1.22 (1.08,1.38)	1.00 (1.00,1.00)

Note: OR, odds ratio; 95% CI, 95% confidence interval; P_T, p-value threshold for inclusion of SNPs into polygenic score. Within the mediation models, higher emotional, impulsivity and friendship quality scores indicate more emotional problems, a higher level of impulsivity and worse friendship quality, respectively.

Supplementary Table 8. Unadjusted and adjusted associations between cigarette and/or cannabis use and psychotic experiences at age 18 years (N = 2923)

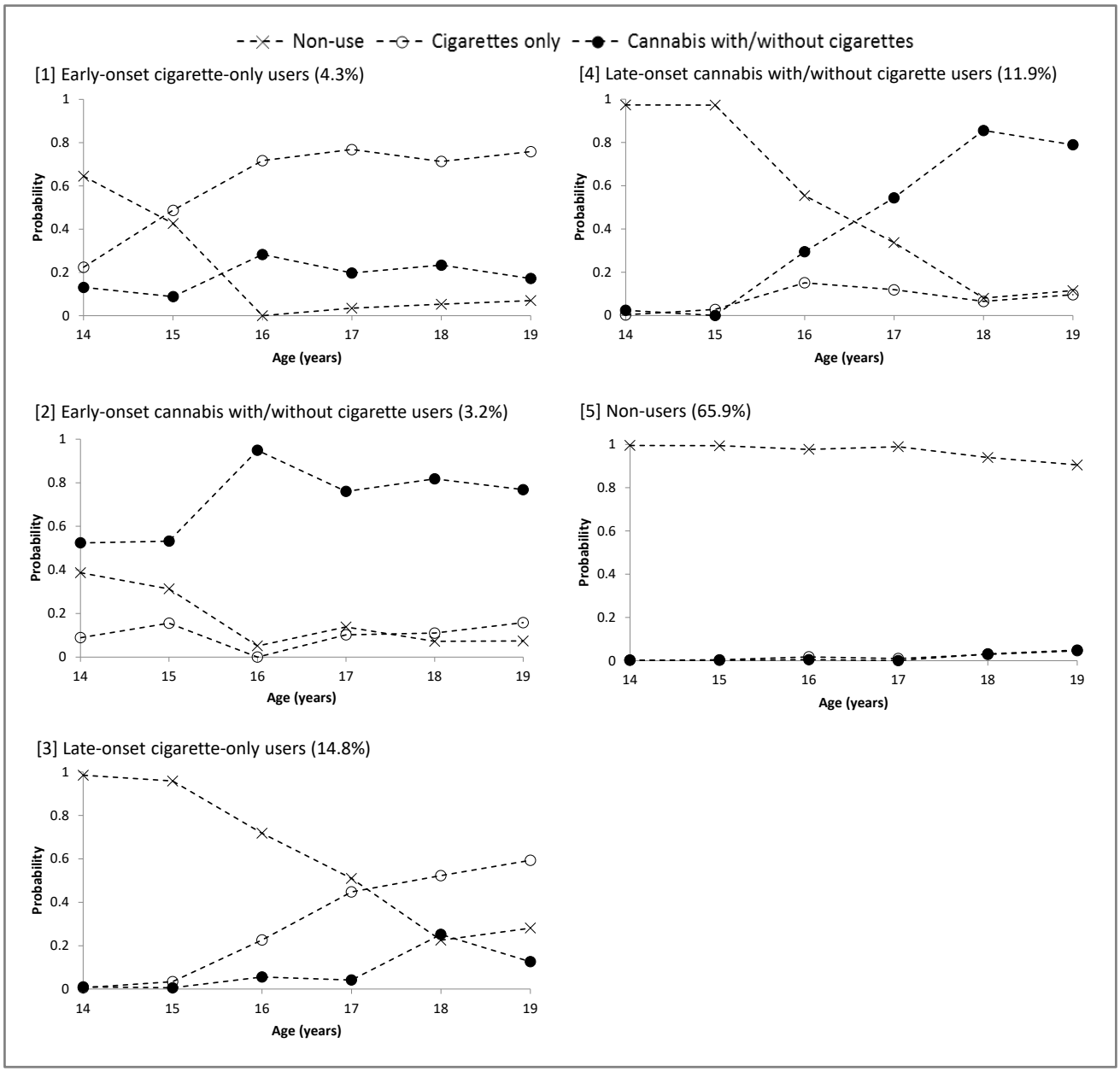
	Definite PE (4.48% definite PEs versus 95.52% suspected PEs or none)			
	Unadjusted		Adjusted [1]	
	OR (95% CI) [2]	*P*	OR (95% CI) [2]	*P*
Early-onset cigarette-only	2.98 (1.14, 7.78)	<0.001	2.96 (1.14, 7.69)	<0.001
Early-onset cannabis	3.28 (1.35, 7.97)		3.28 (1.35, 7.95)	
Late-onset cigarette-only	0.58 (0.16, 2.05)		0.59 (0.17, 2.06)	
Late-onset cannabis	2.76 (1.49, 5.11)		2.75 (1.48, 5.10)	

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

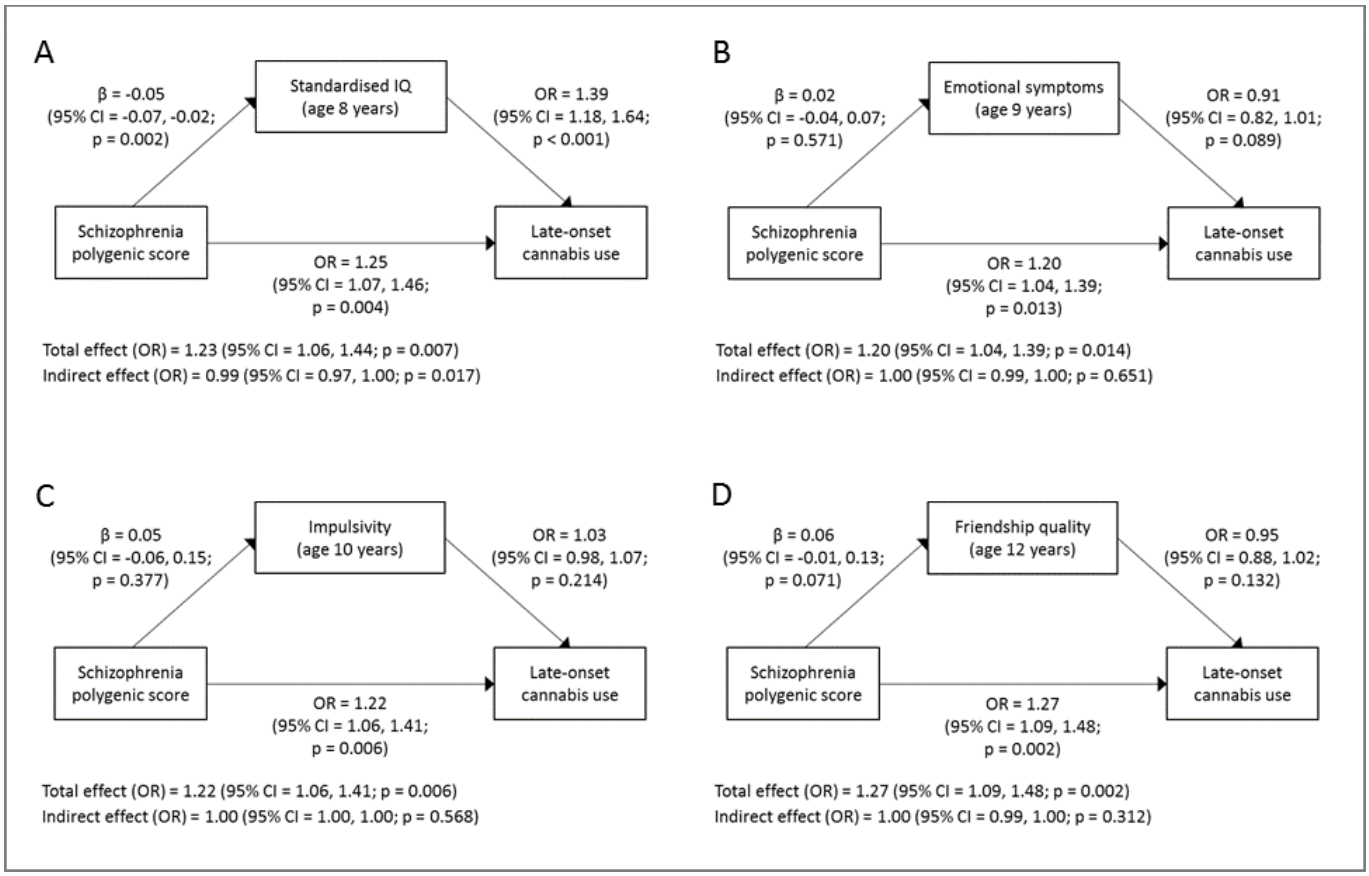
[1] Adjusted for schizophrenia polygenic risk score (P_T = 0.05).

[2] Compared to non-use class.

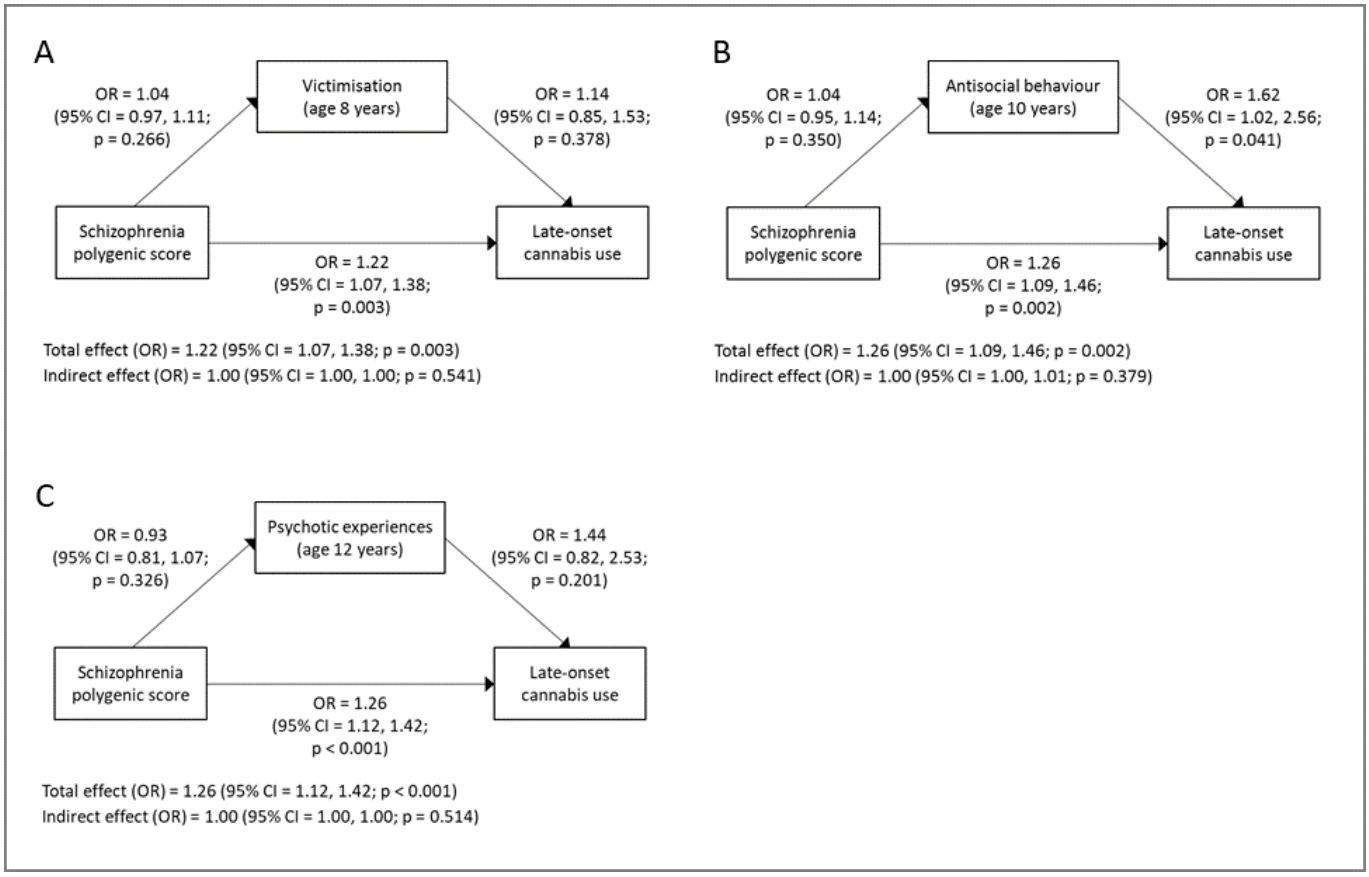
Supplementary Figures



Supplementary Figure 1. Five-class model of cigarette/cannabis use patterns from a sample of 5,300 individuals (Jones *et al*., 2018). 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. Class proportions are show as percentages (%) after each class description.



Supplementary Figure 2. Total effect, direct effect and indirect effects of schizophrenia polygenic score (P_T = 0.05) on late-onset cannabis with/without cigarette use as compared to non-use through the following continuous mediators: a) IQ, b) emotional symptoms, c) impulsivity, and d) friendship quality. Note that higher emotional, impulsivity and friendship quality scores indicate more emotional problems, a higher level of impulsivity and worse friendship quality, respectively.



Supplementary Figure 3. Total effect, direct effect and indirect effects of schizophrenia polygenic score (P_T = 0.05) on late-onset cannabis with/without cigarette use as compared to non-use through dichotomous measures of a) experiencing victimization, b) participating in antisocial behavior, and c) experiencing psychotic experiences.