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

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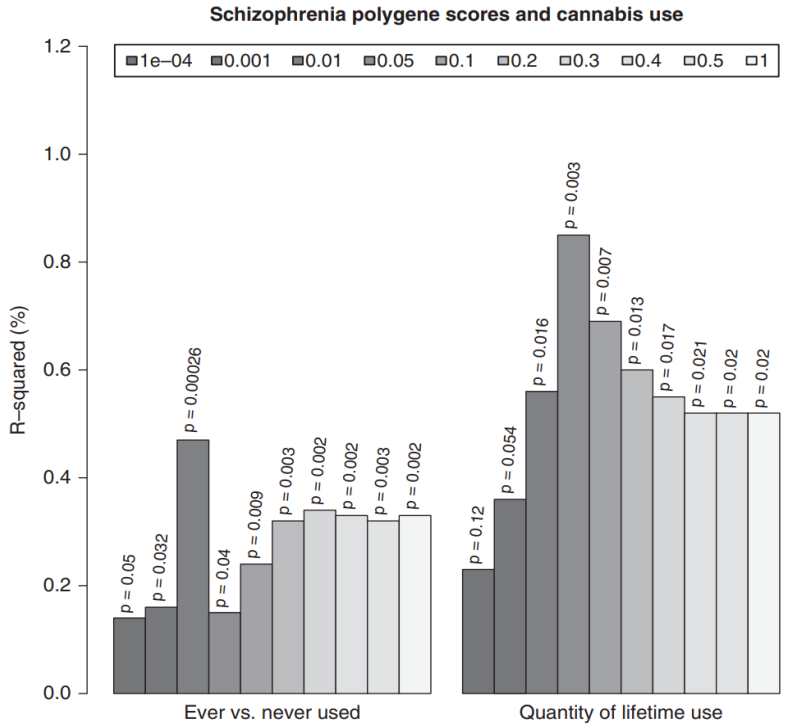
Background

- Both cannabis use and cigarette use have been implicated as causal risk factors for psychosis (Moore et al., 2007; D'Souza et al., 2004; Gurillo, Jauhar, Murray, & MacCabe, 2015)

- Recent studies have found that genetic liability to schizophrenia is associated with
  - Cannabis use (Carey et al., 2016; Power et al., 2014; Reginsson et al., 2018; Verweij et al., 2017, Hiemstra et al., 2018)
  - Cigarette use (Reginsson et al., 2018)

Perhaps the association between substance use and schizophrenia is genetically confounded?

Or perhaps results represent a pathway from schizophrenia risk to substance use?



Power et al., Molecular Psychiatry, 2014

Aims

- Disentangling associations between schizophrenia and cannabis and tobacco use is made difficult by
  - the high correlation between cannabis and tobacco use
  - experimental and fluctuating use over time

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  - ➢ the high correlation between cannabis and tobacco use
  - ➢ experimental and fluctuating use over time

- Use **repeated measures** to jointly **delineate longitudinal patterns of cigarette and cannabis use** during adolescence to examine:
  i. whether schizophrenia genetic liability is associated with recurrent patterns of cigarette and cannabis use
  ii. whether genetic effects on substance use are mediated via cognitive, social, emotional or behavioural pathways during childhood


Psychological Medicine

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Original Article

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

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Measures

- Repeated measures of cigarette and cannabis use in ALSPAC were collected between ages 14 and 19 years
  - ➢ Current cigarette use (1-3 times a month) vs. no use (never used or not used in last month)
  - ➢ Current cannabis use (at least monthly or less in last year) vs. no use (never used or only tries once or twice)

    → 3 category variable: "Non-use", "Cigarette-only use" and "Cannabis use (with or without cigarettes)"

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Outcomes: Longitudinal latent classes of distinct behaviour patterns of cigarette and/or cannabis use
(data present for ≥3 time points, n = 5,300)

Exposure: Schizophrenia polygenic scores ($P_T = 0.05$)
(Pardiñas et al., 2018 GWAS, 40 675 cases and 64 643 controls)

Mediators: IQ (age 8y), bullying (age 8y), emotional problems (parental report; age 9y), antisocial behaviour (age 10y), impulsivity (age 10y), friendship quality (age 12y), and psychotic experiences (age 12y)

Methods

- Longitudinal latent class analysis. Model fit assessed using:
  - the proportion of individuals in each class
  - sample size adjusted Bayesian Information Criterion (SSABIC)
  - Lo-Mendell-Rubin likelihood ratio test (LMR-LRT)

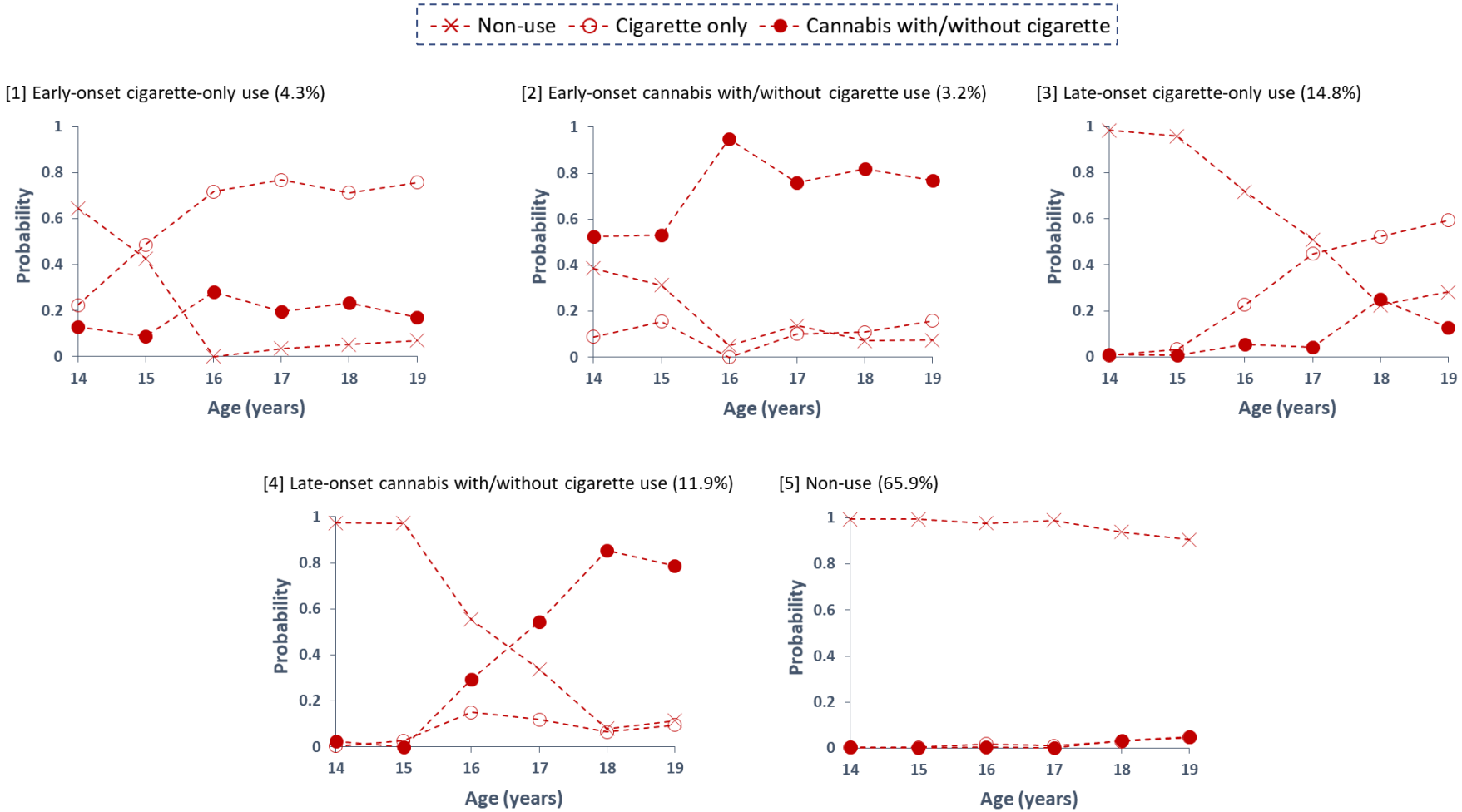
- Multinomial logistic regression was used to assess whether polygenic scores predicted latent class membership
  - bias-adjusted three-step method (n = 3925)
  - Adjusted for polygenic scores for cigarette smoking initiation and cannabis use initiation ($P_T = 0.5$)

- Mediation analysis
  - counterfactual approach was implemented to allow for incorporation of the dichotomous mediators *(Valeri & VanderWeele, 2013)*
  - simplifies to the product of coefficient strategy for continuous mediators

- All analyses performed using **MPlus version 8**

Longitudinal Latent Classes

Longitudinal latent classes of repeated measures of cigarette and cannabis use during adolescence (14-19 years, N=5,300). The data were best described by **5 classes:**



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Jones et al., JAMA Psychiatry, 2018

Results

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%)[a] OR (95% CI)[b]	Early cannabis with/ without cigarette users (3.4%)[a] OR (95% CI)[b]	Late cigarette only users (15.2%)[a] OR (95% CI)[b]	Late cannabis with/ without cigarette users (11.8%)[a] OR (95% CI)[b]	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

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

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

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

Jones et al., Psychological Medicine, 2020

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Adjusted[c]					
$P_T = 0.05$	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 the association between polygenic score and cigarette/cannabis use classes.
[a]Class proportions for latent class membership based on the estimated model.
[b]Compared to non-use class (class proportion for latent class membership based on the estimated model: 65.3%).
[c]Adjusted for polygenic scores for cigarette smoking initiation and cannabis use initiation ($P_T = 0.5$).

Jones et al., Psychological Medicine, 2020

Results, mediation

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

		Total Effect	Direct Effect	Indirect Effect via mediator
Mediator	*N*	OR (95% CI)	OR (95% CI)	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 the 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.

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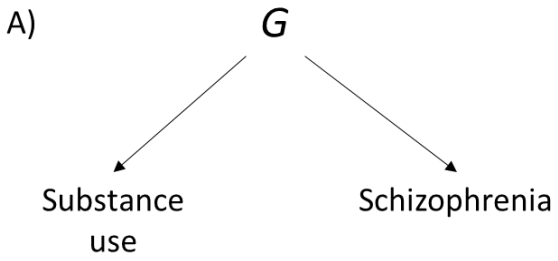
Jones et al., Psychological Medicine, 2020

Conclusions

Genetic liability to schizophrenia (as captured by polygenic scores) is associated with late-onset cannabis use but not with other smoking phenotypes in adolescence in ALSPAC.

Possible explanations for these results are:

A) schizophrenia and cannabis use have a shared genetic aetiology (horizontal pleiotropy)



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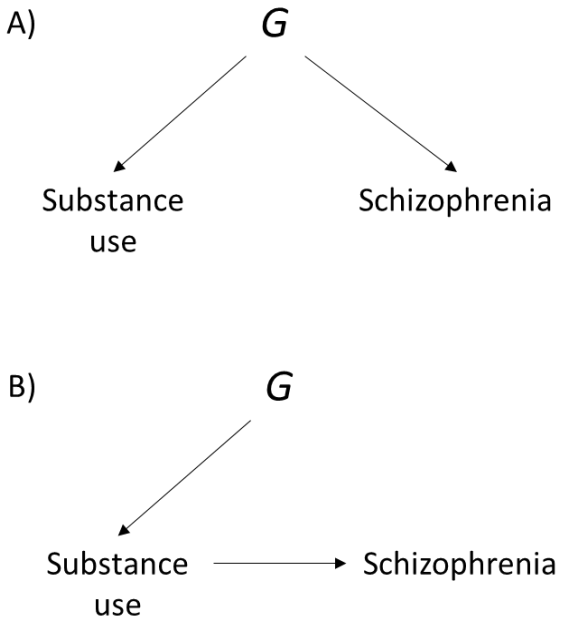
A) schizophrenia and cannabis use have a shared genetic aetiology (horizontal pleiotropy)

B) cannabis use has a causal effect on schizophrenia - schizophrenia polygenic score contains cannabis use variants (vertical pleiotropy)



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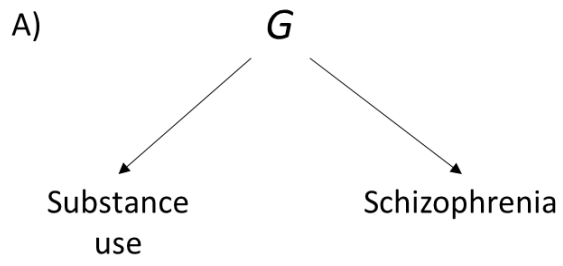
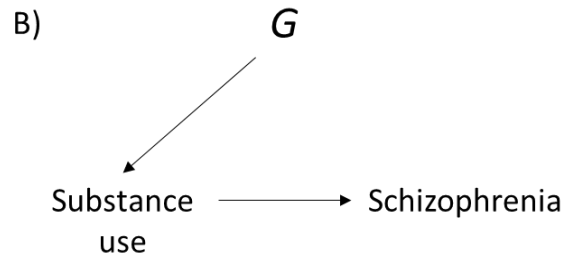
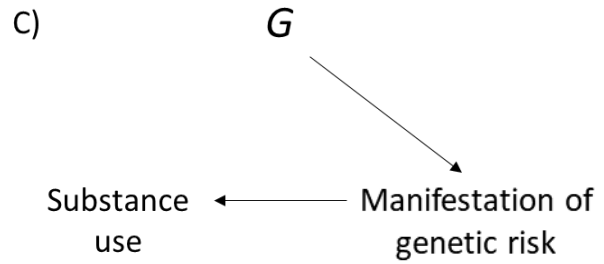
C) polygenic risk of schizophrenia leads to cannabis use through secondary mechanisms (vertical pleiotropy)







Limitations and Future Work

- Generalisability

- Polygenic scores for cigarette and cannabis use initiation explain only a small proportion of variance
  - *May have not adequately removed confounding effects*

- Not possible to define a class of individuals who use cannabis without tobacco
  - *Effects of cannabis independent of tobacco???*

- Not possible to incorporate information on the frequency of cannabis and cigarette use
  - *Model instability*

- No strong evidence of mediation through cognitive, emotional, and behavioural phenotypes
  - *Mediators were measured in childhood*
  - *Other variables that mediate this relationship???*

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- Peter Jones (University of Cambridge)
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- David Linden (Cardiff University)
- Michael O'Donovan (Cardiff University)
- Michael Owen (Cardiff University)
- James Walters (Cardiff University)
- Marcus Munafò (University of Bristol)
- Jon Heron (University of Bristol)
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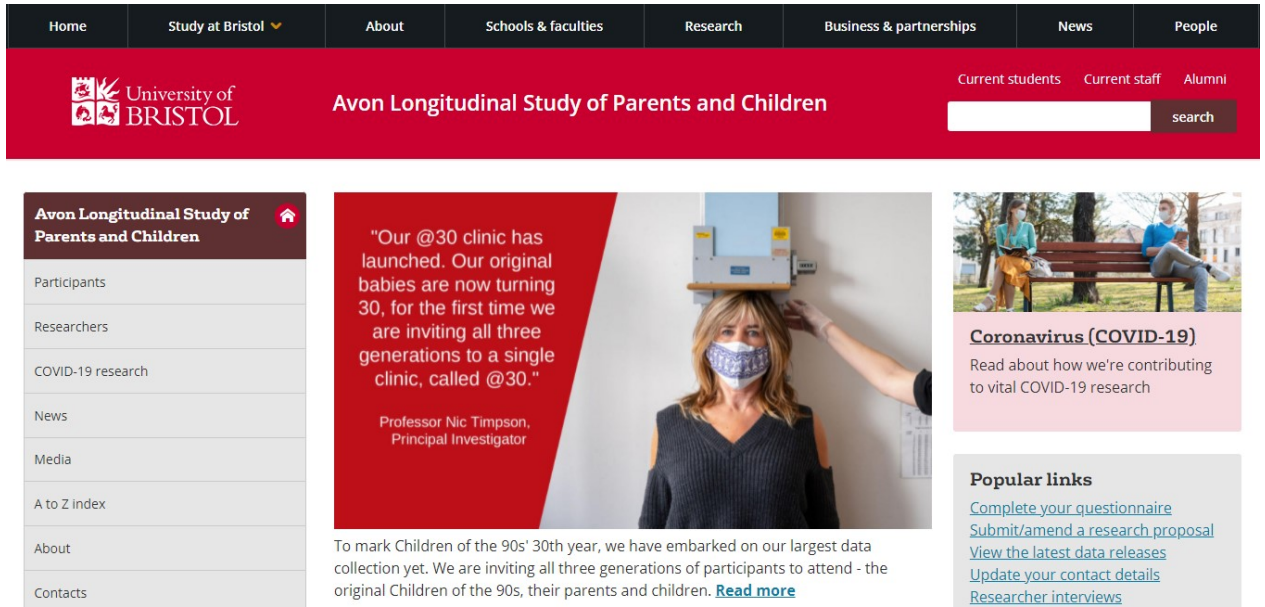
http://www.bristol.ac.uk/alspac/



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