

Adolescent substance use and risk of psychosis in NFBC 1986

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Conflicts of interest

- Juho Vainion säätiö
- Emil Aaltosen säätiö
- Suomen kulttuurirahasto
- Oulun yliopiston apuraharahasto
- Oulun lääketieteellinen tutkimussäätiö
- Alkoholitutkimussäätiö
- Olvi-säätiö

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Publications:

Mustonen, A., Niemelä, S., Nordström, T., Murray, G. K., Mäki, P., Jääskeläinen, E., & Miettunen, J. (2018). Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. *The British Journal of Psychiatry*, *212*(4), 227-233.

Mustonen, A., Ahokas, T., Nordström, T., Murray, G. K., Mäki, P., Jääskeläinen, E., ... & Niemelä, S. (2018). Smokin hot: adolescent smoking and the risk of psychosis. *Acta Psychiatrica Scandinavica*, *138*(1):5-14

Mustonen, A., Niemelä, S., McGrath, J. J., Murray, G. K., Nordström, T., Mäki, P., ... & Scott, J. G. (2018). Adolescent inhalant use and psychosis risk—a prospective longitudinal study. *Schizophrenia research*, *201*, 360-366.

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Research group

- Professor **Jouko Miettunen** (University of Oulu)
- Associate professor **Solja Niemelä** (University of Turku)
- Associate professor **James Scott** (QIMR, UQ, Brisbane, AU)
- PhD **Tanja Nordström** (University of Oulu)
- Professor **John McGrath** (UQ, Brisbane, AU, Aarhus University)
- Professor **Pirjo Mäki** (University of Oulu)
- Academy research fellow, docent **Erika Jääskeläinen** (University of Oulu)
- MD, PhD **Graham Murray** (University of Cambridge, UK)

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Background

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Epidemiological evidence

- Cannabis use as a risk factor of psychotic disorders has been extensively studied (Marconi et al. 2016, Hasan et al. 2020)
 - Current evidence suggests **daily** cannabis use and use of **high potency cannabis products** associates with risk of psychotic disorders with dose-response effect
 - Earlier onset of psychotic disorder
- Similarly, cigarette smoking is linked to increased risk of psychotic disorders (Gurillo et al. 2015)
 - Particularlry **daily and heavy cigarette smoking**
 - Earlier onset of psychotic disorder
- No longitudinal studies on inhalant use and psychotic disorders

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Epidemiological evidence

- There are several prospective cohort studies in different samples that have studied adolescent substance use and risk psychosis outcomes
- Only very few studies have adjusted for baseline psychotic experiences
- Temporal order of the association unclear
 - Self-medication hypothesis
 - Causal
 - Something else?

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Why substance use in adolescence should be of a special interest?

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Epidemiology of adolescent substance use in Finland

- Cannabis use is becoming more prevalent in general population
 - 10% of 15-16 year olds report cannabis use past 12 months
 - Attitudes are becoming more favourable
 - Change in perception of risk associated with cannabis use
 - Easier access
- The prevalence of (daily) cigarette smoking has decreased markedly over years (6-7% report daily cigarette smoking past 30 days)
- The prevalence of any lifetime inhalant use has also decreased (5-6%)
- Polarisation of adolescent substance use

Raitasalo, K., & Härkönen, J. (2019). Nuorten päihteiden käyttö ja rahapelaaminen: ESPAD-tutkimus 2019.

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Neurobiology of adolescent substance use

- Adolescence is critical period of brain development with excess maturation and "fine-tuning" processes especially in prefrontal cortex
- Substance use in adolescence can interfere these maturation processes
- Animal studies suggest adolescent exposure to different substances has distinct effect to the brain compared to adult exposure

Hamidullah, S., Thorpe, H. H., Frie, J. A., Mccurdy, R. D., & Khokhar, J. Y. (2020). Adolescent Substance Use and the Brain: Behavioral, Cognitive and Neuroimaging Correlates. *Frontiers in Human Neuroscience*, 14, 298.

Blest-Hopley, G., Colizzi, M., Giampietro, V., & Bhattacharyya, S. (2020). Is the adolescent brain at greater vulnerability to the effects of cannabis? A narrative review of the evidence. *Frontiers in Psychiatry*, 11, 859.

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Neurobiology of adolescent substance use

- Frequent substance use in adolescence has been associated with structural and functional changes in brain
- Adolescent substance use has been associated with abnormal GABA, glutamate and dopamine signaling
 - Postulated neurobiological basis for psychotic disorders

Hamidullah, S., Thorpe, H. H., Frie, J. A., Mccurdy, R. D., & Khokhar, J. Y. (2020). Adolescent Substance Use and the Brain: Behavioral, Cognitive and Neuroimaging Correlates. *Frontiers in Human Neuroscience*, 14, 298.

Blest-Hopley, G., Colizzi, M., Giampietro, V., & Bhattacharyya, S. (2020). Is the adolescent brain at greater vulnerability to the effects of cannabis? A narrative review of the evidence. *Frontiers in Psychiatry*, 11, 859.

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The study protocol

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Research questions

1. Is adolescent substance use associated with risk of psychotic disorders?
 - I. Cannabis use and risk of psychosis
 - II. Daily cigarette smoking and risk of psychosis
 - III. Inhalant use and risk of psychosis
2. Are these associations independent of baseline psychotic experiences and other potential confounders?

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Methods

- Northern Finland Birth Cohort 1986
- A follow-up study commenced when the participants were 15-16 years old (2001-2002)
- Sample size 6058-6542 individuals
- Data on *substance use* and *psychotic experiences* (PROD-screen) were collected from follow-up study
- *Psychosis diagnoses* were obtained from national registers until the end of 2015 (until the age of 30)
- Cox regression analysis was used to study the association between 1) cannabis use 2) daily cigarette smoking 3) inhalant use and risk of psychotic disorders

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Psychosis diagnoses

- schizophrenia
- schizoaffective disorder
- delusional disorder
- bipolar disorder with psychotic features
- major depressive disorder with psychotic features
- brief reactive psychosis
- other psychosis

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Substance use

- We used the following questions in this study
 - Have you ever tried or used any of the following substances? - **Marihuana or hashish?** (never, once, 2–4 times, 5 times or more, I use regularly)
 - 1. Do you currently smoke **cigarettes** daily (at least 1 cigarette/day, no/yes)?
 - 2. How many filtered or unfiltered cigarettes you smoke per day (n). This was categorized into three levels (no daily smoking (ref), 1–9 cigarettes/day and ≥ 10 cigarettes/day).
 - Have you ever tried or used any of the following substances? - **Sniffing thinner, glue, etc. for intoxication** (never, once, 2–4 times, 5 times or more, or I use regularly)

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Psychotic experiences

- The participants were asked about the occurrence of psychotic experiences during the previous 6 months (no/yes) using PROD-screen
- The PROD-questionnaire has 21 items of which 12 are specific items (no/yes) for psychotic experiences
 - “feelings that something strange or inexplicable is taking place within oneself or in the environment”,
 - “feelings that one is being followed or influenced in some special way”,
 - “experience of thoughts running wild” or
 - “difficulty in controlling the speed of thoughts”
- Cut off ≥ 3 symptoms was used in this study to indicate positive status of baseline “psychotic experiences”

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Main findings

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Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis

Antti Mustonen, Solja Niemelä, Tanja Nordström, Graham K. Murray, Pirjo Mäki, Erika Jääskeläinen and Jouko Miettunen

Background

The association between cannabis use and the risk of psychosis has been studied extensively but the temporal order still remains controversial.

Aims

To examine the association between cannabis use in adolescence and the risk of psychosis after adjustment for prodromal symptoms and other potential confounders.

Method

The sample ($n = 6534$) was composed of the prospective general population-based Northern Finland Birth Cohort of 1986. Information on prodromal symptoms of psychosis and cannabis use was collected using questionnaires at age 15–16 years. Participants were followed up for ICD-10 psychotic disorders until age 30 years using nationwide registers.

Results

The risk of psychosis was elevated in individuals who had tried cannabis five times or more (hazard ratio, (HR) = 6.5, 95% CI 3.0–13.9). The association remained statistically significant even when adjusted for prodromal symptoms, other substance use and parental psychosis (HR = 3.0, 95% CI 1.1–8.0).

Conclusions

Adolescent cannabis use is associated with increased risk of psychosis even after adjustment for baseline prodromal symptoms, parental psychosis and other substance use.

Declaration of interest

None.

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Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis

- **Using cannabis 5 times or more** in adolescence associated with increased risk of any **psychotic disorder** until the age of 30 after adjustments for psychotic experiences, other substance use (at age 15-16 years) and parental psychosis (**HR = 3.01, 1.14 – 7.98**)
- Dose-reponse effect
- Experiencing psychotic experiences at baseline and having used cannabis was strongly related to psychosis outcome

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Smokin' hot: adolescent smoking and the risk of psychosis

Mustonen A, Ahokas T, Nordström T, Murray GK, Mäki P, Jääskeläinen E, Heiskala A, Mcgrath JJ, Scott JG, Miettunen J, Niemelä S. Smokin' hot: adolescent tobacco smoking and the risk of psychosis

Objective: Daily smoking has been associated with a greater risk of psychosis. However, we are still lacking studies to adjust for baseline psychotic experiences and other substance use. We examined associations between daily smoking and psychosis risk in a 15-year follow-up while accounting for these covariates in a prospective sample ($N = 6081$) from the Northern Finland Birth Cohort 1986.

Methods: Self-report questionnaires on psychotic experiences (PROD-screen), tobacco smoking and other substance use were completed when the cohort members were 15–16 years old. Tobacco smoking was categorized into three groups (non-smokers, 1–9 cigarettes and ≥ 10 cigarettes/day). Psychosis diagnoses were obtained from national registers until the age of 30 years.

Results: Subjects in heaviest smoking category were at increased risk of subsequent psychosis (unadjusted HR = 3.15; 95% CI 1.94–5.13). When adjusted for baseline psychotic experiences the association persisted (HR = 2.87; 1.76–4.68) and remained significant even after adjustments for multiple known risk factors such as cannabis use, frequent alcohol use, other illicit substance use, parental substance abuse, and psychosis. Furthermore, number of smoked cigarettes increased psychosis risk in a dose-response manner (adjusted OR = 1.05; 1.01–1.08).

Conclusion: Heavy tobacco smoking in adolescence was associated with a greater risk for psychosis even after adjustment for confounders.

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Smokin' hot: adolescent smoking and the risk of psychosis

- **Daily smoking of ≥ 10 cigarettes** in adolescence associated with increased risk of **psychotic disorder** until the age of 30 after adjustments for psychotic experiences and other substance use at 15–16 years, parental psychosis and parental substance use disorder (**HR = 2.00, 1.13 – 3.54**).
- Dose-response effect
- **Early initiation of daily smoking (≤ 13 years)** associated with increased risk of **psychotic disorder** compared to later initiation (**>13 years**) after adjustments (**HR = 2.82, 1.12– 7.18**)

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Adolescent inhalant use and psychosis risk – a prospective longitudinal study

- Using inhalants 5 times or more associated with increased risk of any **psychotic disorder** after adjustment for psychotic experiences and other substance use at 15-16 years, parental substance use disorder and any other psychiatric disorder of the participant (**HR = 3.06, 1.05 – 8.95**)
- Dose-response effect

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Summary of findings

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Summary

- Cannabis use, daily cigarette smoking and inhalant use in adolescence were associated risk of future psychotic disorder
 - Risk increased with a dose-response effect
 - Independent associations of baseline psychotic experiences
 - Independent association of other substance use and parental psychiatric disorders
- Earlier initiation of daily cigarette smoking was associated with greater risk of psychosis

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Summary

- PROD – screen positive individuals with cannabis use were more likely to be diagnosed with psychotic disorders during the follow-up
 - Are they especially vulnerable?
 - Screening of these individuals is advised
- Cumulative incidence of psychosis was highest in the group that reported use multiple substances

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Summary

- The pathogenesis of psychotic disorders is multifactorial
- The ultimate impact of specific risk factor may depend on the underlying vulnerabilities such as genetics
- However, adolescent onset substance use is one of the preventable risk factors and by screening and general and focused interventions we might promote the mental health of these individuals.
 - Based on this study especially adolescents that report psychiatric symptoms, report use of multiple substances with high frequency should be identified

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Ongoing projects

- ADHD symptoms in adolescence and outcome
- Age at first alcohol intoxication and risk of psychiatric disorders
- Adolescent cannabis use, depression and anxiety disorders (Alexander Denissoff)
- Epidemiology, risk factors and outcome of concurrent use of alcohol and benzodiazepines in NFBC 1966 (Juha Penttala)

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Thank you for your
attention. Questions?

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