SMOKIN` HOT: ADOLESCENT TOBACCO SMOKING AND THE RISK OF PSYCHOSIS

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Objective: Daily smoking has been associated with 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 3 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 with 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 greater risk for psychosis even after adjustment for confounders.

Keywords: Epidemiology, Nicotine, Tobacco, Psychoses, Schizophrenia

Significant Outcomes:

Heavy smoking in adolescence is a risk factor for psychosis even after adjusting for baseline prodromal symptoms, other substance use and parental psychosis and substance abuse.

Early initiation of daily smoking is associated with greater risk for subsequent psychosis compared to late initiation.

Limitations:

Information on substance use and psychotic experiences was collected using self-reports.

We were unable adjust for potential confounding due to childhood trauma or familial adversity.

Introduction

The higher rates of smoking tobacco by patients with psychotic disorders (1,2) has generally been assumed to be due to self-medication strategies and some studies have suggested a possible bidirectional association (3-5). However, two meta-analyses have reported strong associations between tobacco smoking and an increased risk of subsequent psychosis diagnosis (6,7). A dose-response effect has also been reported in two large Swedish cohorts (8), in an Israeli conscript cohort (9) and in a Danish cohort of women (10). Furthermore, the association has persisted in prospective samples after adjustment for risk factors such as socioeconomic status and drug use (8-10). With the exception of one study reporting cigarette smoking in young adults reduced later onset of schizophrenia (1), prospective samples (8-10) have provided strong evidence of the association between smoking and psychosis. Although there are longitudinal studies that have examined the temporal order of this association (2,8,11), there are none that have accounted for baseline psychotic experiences which has left the direction of the association questionable. Furthermore, there are no longitudinal samples that have examined this hypothesis in an adolescent population and it is plausible that adolescent substance use could potentially alter the trajectories of brain maturation and mental health.

Aims of the Study

Within our population based birth cohort, our objective was to study whether daily smoking at age 15-16 years is associated with the risk of subsequent ICD-10 psychosis by the age of 30 years using nationwide registers. Information on psychotic experiences of psychosis was ascertained using self-report when the study population was 15-16 years old. We hypothesized that 1) daily smoking in adolescence is an independent risk factor for later psychosis, 2) increases the risk in a dose-response manner and 3) early initiation of daily smoking results in greater risk of psychosis compared to late initiation of daily smoking after adjusting for multiple confounders such psychotic experiences and substance use.

METHODS

Participants

The Northern Finland Birth Cohort (NFBC) 1986 is an ongoing general population-based study including 99% of all births between July 1st 1985 and June 30th 1986 from the two northernmost provinces in Finland. The current sample included all the live born children (n=9,432) (12). In all, 7,344 participated in the follow-up postal questionnaire and 6,798 in the follow-up field study in 2001-2002, when the participants were aged 15-16 years. Consenting participants who answered the questions on smoking habits and psychotic experiences (PROD-screen) were included in the present study. Adolescents who had received a psychosis diagnosis prior to assessment at 15-16 years (n=10), were excluded from the study. The final sample included 6,081 individuals (47.7% boys). For data flow, please see figure 1. Information on psychosis-related diagnoses (n=110) was collected from the national registries until the end of 2015 i.e. by the age of average 30 years. The study was approved by the Ethics committee of the Northern Ostrobothnia Hospital District in Finland (17 May 2006).

Data collection

Data collection commenced prospectively before birth (12). A multidisciplinary follow-up study was conducted when the adolescents were 15-16 years (13). Data on substance abuse was collected in 2001-2002, in two different surveys when the adolescents were 15-16 years old. First, they received a postal questionnaire, which included questions on smoking habits. Thereafter, the participants were invited to a field study where they completed self-report questionnaires including questions on psychotic experiences (PROD-screen) (14), alcohol use, illicit substance use and additional questions on smoking habits.

MEASURES

Daily tobacco smoking in adolescence

Subjects were considered smokers, if they were smoking tobacco daily. Information on regular smoking was collected from postal questionnaires and during the field study (15). In the postal questionnaire adolescents were asked if they currently smoked cigarettes daily (at least 1 cigarette/day, no/yes), and how many filtered or unfiltered cigarettes they smoked per day (n). The information on number of smoked cigarettes for daily smokers was then divided into groups and we categorized this into three levels (no smoking (reference), 1-9 cigarettes/day and ≥10 cigarettes/day). Rationale for using this categorization was the consistent use of it in the previous prospective samples (8-10). Subjects who reported any smoking, but did not answer (yes) being daily smokers were considered as non-smokers. In the field study, the subjects were handed a self-report questionnaire where they were asked when they began to smoke daily (11 years or earlier, 12, 13, 14, 15, and 16 years of age). We categorized this variable into two groups based on the median: early initiation of daily smoking (13 years or under) and later initiation of daily smoking (14 years or older).

***insert figure 1 here**

Psychosis outcome

Information on diagnosed psychoses (ICD-10: F20, F22-F29, F30.2, F31.2, F31.5, F32.3, F33.3; schizophrenia, schizoaffective disorder, delusional disorder, bipolar disorder with psychotic features, major depressive disorder with psychotic features, brief reactive psychosis, other psychosis) was gathered from nationwide registers between the ages of 15 and 30 years: the Care Register for Health Care 2001-2015 (both inpatient and outpatient registers) and the Register of Primary Health Care Visits 2011-2015 of the National Institute for Health and Welfare, disability

pensions of the Finnish Centre for Pensions 2001-2015, and the medication reimbursement register of the Social Insurance Institution of Finland 2001-2005. The Care Register contains data on patients discharged from inpatient care, and since 1998 also data on specialized outpatient care. The Register of Primary Health Care Visits covers all outpatient primary health care delivered in Finland. For more comprehensive information about the registers see Filatova et al. supplement 1 (16). Age at the time when psychosis was first detected was estimated as the onset age of psychosis. Cumulative incidences of psychoses were calculated.

Psychotic experiences in adolescence

The PROD-screen is a validated questionnaire screening for prodromal symptoms of psychosis (14). The scale has 12 specific items: These rate, for example, feelings that something strange or inexplicable is taking place in 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, amongst other symptoms. Dichotomous responses (no/yes) to these symptoms were sought for the previous six months when the cohort members were 15-16 years old (17). Reporting 3 or more items was the cutoff for psychotic experiences in this sample which has been used for research (17-19**)** and clinical purposes in Finland**.** Subjects were included in the sample if they had answered at least 10 of the 12 items in the PROD-screen questionnaire.

Other variables

Alcohol, cannabis and other substance use

Information on substance use was collected in the self-report questionnaire that the participants received during clinical examinations in adolescence**.** Frequent drunkenness was questioned as subjective measure ‘Have you been drunk during the past year (0, 1-2, 3-5, 6-9, 10-19, 20-39 or 40 times or more)’. In analyses this variable was categorized as ‘Have been drunk during the past year

10 times or more (no/yes)‘. Cannabis use was assessed by the question ‘Have you ever used marihuana or hashish (no/yes)‘. Dichotomous responses (no/yes) were also collected on any use of other substances: prescription drug use, ecstasy use, heroin use, cocaine use, amphetamine use and use of LSD. Because of the low number of users in each group, these were combined as ‘Other substance use (no/yes)’ (15).

Family structure at birth and in adolescence

Information on family structure was gathered from self-reports that were collected from parents at birth and when the cohort member was aged 15–16. Subjects that were living with their primary family from birth to adolescence (ie. living with subject all the time) were classified as (1) “intact families” and all the others as (2) “non-intact families”.”

Socio-economic status of the family in adolescence

The socio-economic status of the family was estimated by the highest education level achieved by either parent when the child was aged 15–16. This variable was categorized as: professionals (professionals, entrepreneurs and other white-collar workers) and non-professionals (17).

Place of residence

Data were collected based on the population density of the residential area at age 15–16 years in order to account for possible confounding due place of residence. The variable was dichotomized in the analyses (urban vs. non-urban) (20).

Parental psychosis and substance abuse

Information on parental psychosis (ICD-10: F20, F22-F29, F30.2, F31.2, F31.5, F32.3, F33.3)) (no/yes) and parental substance abuse (ICD-10: F10.1, F10.2, F11.1, F11.2, F12.1, F12.2, F13.1, F13.2, F14.1, F14.2, F15.1, F15.2, F16.1, F16.2, F17.1, F17.2, F19.1, F19.2) (no/yes) were based

on parental diagnoses in the nationwide registers: 1) Care Register of Health Care (Hospital Discharge Register until 1994) 1972-2015 that also includes specialized outpatient health care visits since 1998, 2) disability pensions of Finnish Centre for Pensions (1965-2015), and 3) the Register of Primary Health Care Visits (new register only for 2011-2015).

Statistical methods

Logistic regression with odds ratios (OR; 95% confidence interval, CI) was used to study the crude associations between a) potential covariates and daily smoking (dichotomized), and b) covariates and psychosis diagnosis. Covariates were selected from a comprehensive dataset, based on previous literature (see online supplement table). Covariates were selected using two-step method: firstly based on earlier literature, and secondly on the statistical analyses of the present study sample. The literature-based covariates included family characteristics, smoking, alcohol use, and other drug use including cannabis, and parental psychosis and parental substance abuse diagnoses. Thereafter we conducted logistic regression analyses to seek whether the selected covariates were associated with psychosis risk. Logistic regression was used for covariate selection since no time-dependent data was available on tobacco smoking.

In the multivariable models (both crude and adjusted), we used Cox regression analysis (Hazard Ratio, HR; with 95% CI) to assess the effect of adolescent daily smoking (non-smokers, 1-9 cigarettes/day, ≥10 cigarettes/day) on the risk of psychosis. A subanalysis was also conducted, where we examined subjects reporting less than cutoff (< 3) in PROD-screen in a model that was similar to the one above. Subjects with missing data were not included in the multivariable analyses if they had not answered the question that was used in the model. In addition, we used Cox-regression

analyses to study whether the age at initiation of daily smoking (early; before or at 13 years of age *vs.* late; after 14 years of age) contributed to psychosis risk among daily smokers. Times at emigration and death were used as censoring points in analyses (data until December 2013). We also examined for a dose-response between cigarette smoking and psychosis risk with a trend test, using the number of smoked cigarettes as a continuous variable in the logistic regression analysis. Linear regression and multicollinearity diagnostics were used to detect correlation between multiple variables. The statistical analyses for logistic and cox-regression analyses were done using SPSS 23.0 and the inverse probability of treatment weighting analyses we carried out using R 3.3.2 with packages mice (2.25), survival (2.40-1) and boot (1.3-18).

The stability of primary Cox regression analysis results was assessed using the inverse probability of treatment weighting (IPTW) based on propensity score with Cox regression. The propensity score is the subject's conditional probability to treatment assignment, in this case to daily smoking, given the observed baseline covariates. It is used in observational studies to reduce selection bias by balancing the baseline characteristics between the treatment and control groups. IPTW based on the propensity score is then used to create a synthetic sample by weighting individual observations. The full description of the method and the demographics are presented in an online supplement.

RESULTS

Study characteristics

The demographics of the study and their relationship with daily tobacco smoking and occurrence of psychosis during the follow-up are presented in Table 1. In all, there were 745 daily smokers in the sample population. Adolescents with cannabis use, other illicit substance use and frequent alcohol use were significantly more likely to be smoking daily than those without substance use ($p<0.05$ in all, see table 1). Subjects with history of parental substance abuse and parental psychosis were also

more likely to be daily smokers compared with those without these parental histories. All of these factors were also associated with a higher incidence of psychosis during the follow up (see table 1). No significant multicollinearity was present. In total, 1883 adolescents (31% of the sample) endorsed 3 or more items in PROD-screen.

insert table 1 here

Daily smoking as risk factor for psychosis

Altogether 6081 subjects answered questions concerning the number of cigarettes smoked per day, of these 745 (12.3%) were daily smokers. 110 participants were diagnosed with incident psychosis in this sample population. Compared to non-smokers, those who smoked heavily (>10 cigarettes/day) were at increased risk of subsequent psychosis (unadjusted HR = 3.15; 95%CI 1.94-5.13), however there was no association between light smoking (1-9 cigarettes/day) and later psychosis. After adjusting for baseline psychotic experiences the association persisted (highest; HR = 2.87; 1.76-4.68). Further adjustment for cannabis use, frequent alcohol use, other illicit substance use, parental substance abuse and psychosis (see table 2) attenuated the association, but the association remained significant. Consistent with the data from our primary Cox-regressions, the IPTW – analyses further indicate that smoking daily 10 or more cigarettes is a risk factor for psychosis compared to non-smokers (adjusted HR= 3.44, 95%CI 1.61 - 7.32, see online supplement). Similarly, in the subanalysis of subjects reporting less than 3 items (cutoff) in PROD-screen, daily smokers with 10 or more cigarettes/day were at increased risk of psychosis (fully adjusted HR = 3.26; 95%CI 1.52-7.01). A dose-response was seen with the trend test (fully adjusted OR=1.05; 95%CI 1.01-1.08).

Age at initiation of daily smoking and risk of psychosis

We performed additional analyses to study whether early initiation of daily smoking was associated with greater risk for subsequent psychosis compared to the late initiation group. In all, 737 daily

smokers answered the question concerning age at initiation of daily smoking. 19/373 (5.1%) subjects who began smoking daily early (before or at 13 years of age) were diagnosed with psychosis and the respective number of subjects who began smoking later (after 14 years of age) was 8/364 (2.2%). In multivariable analyses, early onset smokers had greater risk for subsequent psychosis compared to late-onset group (HR=2.36; 1.03-5.39) and the association remained at similar level and statistically significant (HR=2.34; 1.02-5.34) even after adjustment for psychotic experiences. The association between early initiation of smoking and risk of psychosis remained significant after further adjustments for cannabis use, frequent alcohol use in adolescence and other substance use (HR=2.92; 1.15-7.36) compared to the later initiation group. Inclusion of history of parental psychosis and substance abuse to the previous model did not significantly change the strength of the association (HR=2.84; 1.12-7.18).

Insert table 2 here

Attrition

Attrition analysis from our current sample (NFBC 1986) has been presented previously (17). In this sample males were less likely to participate in the follow-up study than females (64% v. 71%; χ^2 test, $p<0.001$), as were participants living in urban areas (66% v. 71%, $p<0.001$). Non-participation in the follow-up study was associated with greater risk for psychosis (HR = 1.52, 95%CI 1.13-2.04).

DISCUSSION

Consistent with the results of the previous meta-analyses (6,7) and the prospective cohort studies (8-10), heavy tobacco smoking was an independent risk factor for psychosis even after adjustment for range of confounders. Inclusion of baseline psychotic experiences had only a minor effect on the

association suggesting the onset of tobacco smoking preceded symptoms of psychosis. Early initiation of daily smoking was also associated with greater risk of psychosis compared to later initiation.

We found a dose-response effect suggesting an increased magnitude of tobacco smoking in adolescence was associated with greater risk of psychosis. The dose-response effect has been also reported in previous studies and the effect sizes are similar to this sample. A Swedish general population based study found that heavy smoking was more strongly associated with schizophrenia than light smoking both in males and females even after adjusting for socioeconomic status and drug use (8). Also, an Israeli military sample study (n=14.000) reported that adolescents who smoked 1-9 cigarettes/day were 1.38 times (95%CI 0.48-4.00) likely to be hospitalized later for schizophrenia and adolescents who smoked 10/cigarettes day or more were 2.28 times (95%CI 1.19-4.34) as likely (9). Furthermore, a Danish study reported a linear association between number of smoked cigarettes and later hospitalization for schizophrenia spectrum disorders (10). Interestingly, light smoking seemed to have a potential protective effect for psychosis. We speculated that adolescents with sporadic smoking could be more likely to smoke because of peer-pressure and social acceptability among adolescents, and therefore be more likely to be socially active and better coping that would likely confer to a lower psychosis risk.

Heavy smoking in adolescence was a significant risk factor for psychosis even after adjusting for baseline psychotic experiences and the adjustment had only minor effect on outcome (here 8.6% decrease in HR). Based on our results it is unlikely that the association would arise from reverse causation. Therefore, the hypothesis that smoking could manifest as a part of a prodromal syndrome (2) is not supported in our study. There is other additional evidence against this hypothesis. Kendler et al. examined the smoking-schizophrenia association using buffer periods and found no declining with longer buffer periods either in male or female sample (8).

Early initiation of daily smoking was also a slightly greater risk factor for psychosis compared to late initiation of daily smoking even after adjusting for many potential confounders. This result is consistent with a previous study (19), which showed that earlier initiation of ever-smoking was associated with psychosis outcomes. It can be speculated that earlier onset of smoking could result in greater cumulative dose of nicotine or other harmful byproducts from tobacco over time. It is plausible that excess nicotine intake during vulnerable periods such as early adolescence could influence the balance of dopaminergic and cholinergic neurotransmitters in the brain (22,23) and disrupt brain maturation (24) and thus contribute to the risk of mental health outcomes. Furthermore, timing of the "hits" during neurodevelopment may lead to different outcomes whereby earlier hits may cause more widespread abnormalities compared with later exposure (25).

Adjustment for co-substance use has been lacking in previous psychosis studies (7, 26). In our study, heavy smoking exposure in adolescence remained a significant risk factor after adjustment for cannabis use, frequent alcohol use and other illicit substance use. The association attenuated significantly indicating that frequent alcohol use, cannabis use and other illicit substance use are confounders, but some of the decrease in HR is likely due high correlation between daily smoking and other target substances since 38.1% of frequent alcohol users, 49.1% of those who had used cannabis and 63.3% of those who had used other illicit substances were also daily smokers. A recent nationwide Danish study reported associations between different substance abuse diagnoses and risk of schizophrenia (cannabis, alcohol, amphetamine, hallucinogens etc.) (26) although only other substance use associated with psychosis in our adjusted analyses. However we were restricted by relatively low number of other illicit substance users and therefore might be underpowered for these analyses. Our study population might not be not entirely comparable to other samples as we focused on self-reported substance use in adolescence, adjusted for smoking and included also non-

schizophrenic psychoses.

There has been discussion as to whether the smoking-psychosis association arises from genetic or familial factors such as family history of psychosis. Gage and colleagues studied the association of initiation of smoking and schizophrenia using Mendelian randomization and found out that schizophrenia risk was not causally associated with initiation of smoking (27)**.** However, bidirectional association between smoking and schizophrenia has been proposed due to findings of common variants between nicotine dependence and schizophrenia (3-5), but the shared variants are likely to explain only a fraction of the association. A recent Swedish study found in a co-relative analysis that heavy smokers had an increased risk of non-affective psychosis compared to their nonsmoking twin and only a modest decline in HR was reported when comparing full siblings to more distant relatives or the general population (5).Therefore, it is unlikely that the association could be explained by familial/genetic factors entirely. Here parental psychosis was weakly associated with psychosis in the logistic regressions, but did not remain statistically significant in adjusted analyses. Parental substance abuse has been also linked to child mental health outcomes and substance use (28) and to further study this we included it as a potential confounder. However, parental substance abuse did not reach statistical significance for psychosis (see table 2). Confounding due to the parental factors was not present either since adjusting for these parental factors made little difference to the strength of the association (HR decline from 2.87 to 2.73, 4.9%). Although parental factors might influence offspring psychosis and smoking behavior, it is unlikely these explain the association between adolescent smoking and psychosis entirely.

Strengths and limitations

The strengths of the present study include the study sample, the NFBC 1986 is one of the largest birth cohort studies with high genetic and ethnic homogeneity; the considerable number of daily

smokers in the study allowing robust examination of the associations and the dose-response relationship and the use several nationwide registers combined with a very small proportion of cohort members deceased or emigrated during the follow-up. Therefore, the coverage of clinically significant psychosis diagnoses within this population during the 15-year-follow-up can be considered high (16). Indeed, the incidence rate in this sample was 121 per 100000 per year, which is significantly higher than in most of the previous samples (29-31). Furthermore, our extensive dataset provided information on a range of possible confounders. However, there are also limitations: Like all large longitudinal studies, there was attrition and the information on substance abuse was collected using self-reports, which may give rise to a bias of underreporting and therefore possible underestimation of the true association. Since males and subject from urban areas were less likely to participate in the follow-up study in 2001-2002, some selection might be present. The data concerning psychotic experiences was gathered when the study population was around 15-16 years old, so it is possible that some subjects might have experienced these symptoms before the onset of substance use reflective of reverse causality. Although the PROD-screen has been validated in previous studies (14), this study used it as a self-report questionnaire and therefore the specificity may have been reduced since 30% reported three or more items. However, it is well established that psychotic experiences in adolescence are common (32,33). Our conclusions are restricted to adolescent smoking at baseline only, since we are missing the time-dependent data on continuation of smoking and other confounders. Measures of confounding substance use were limited to single self-report items. We cannot rule out the concurrent use of cannabis with tobacco smoking as an explanation for part or all of the associations reported in this study as cannabis users usually smoke cannabis mixed with tobacco and heavier smoking is also associated with heavier cannabis use (34) and we adjusted only for the binary measure of use. Follow up for psychosis ended at 30 years. Some individuals will go on to develop psychosis after this age and this may attenuate the association between tobacco smoking and psychosis. Last, we were not able adjust for potential

confounding due to the childhood or familial adversity.

Heavy smoking in adolescence was independently associated with increased risk for subsequent psychosis even after adjustment for baseline psychotic experiences, substance use and parental history of psychosis and substance abuse. Earlier initiation of daily smoking resulted in a greater risk of psychosis compared to those who began smoking daily later. The data are consistent with the hypothesis that tobacco smoking is an independent risk factor for psychotic disorders. In addition to the many other health problems, the evidence is mounting that use of tobacco in adolescence may contribute to serious mental illness in young adults. This is another reason to implement effective strategies to prevent adolescents from commencing use of tobacco.

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Figure 1. Data flow from the current study in the Northern Finland Birth Cohort 1986.

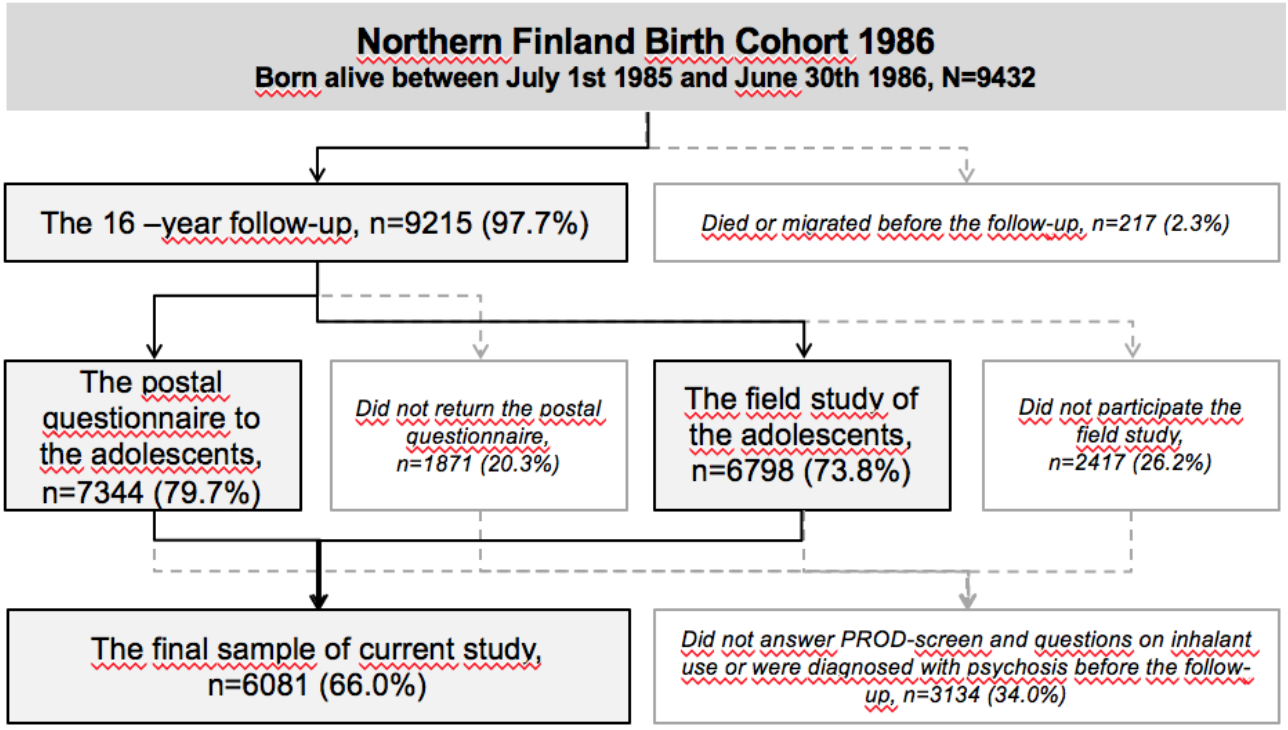

Table 1: Family characteristics and substance use by smoking categories at the ages of 15 to 16 years and cumulative incidence of psychosis in the follow-up in the Northern Finland 1986 Birth Cohort

	Do you smoke cigarettes daily?				Statistical test	Cumulative incidence of psychosis during the follow-up				Statistical test
	No		Yes			No		Yes		No vs. Yes
	n	%	n	%	OR (95% CI)[1]	n	%	n	%	OR (95% CI)[1]
Total sample (n=6081)	5336	87.7	745	12.3	-	5971	98.2	110	1.8	-
Gender										
- Boys (n=2899)	2579	89.0	320	11.0	[Reference]	2841	98.0	58	2.0	[Reference]
- Girls (n=3182)	2757	86.4	425	13.7	**1.24 (1.06-1.45)**	3130	98.4	52	1.6	0.81 (0.56-1.19)
Place of residence at age 15-16 years										
- Non-urban (n=3984)	3470	87.1	514	12.9	[Reference]	3914	98.2	70	1.8	[Reference]
- Urban (n=2097)	1866	89.0	231	11.0	**0.84 (0.71-0.99)**	2057	98.1	40	1.9	1.09 (0.74-1.61)
Family background										
Family structure										
- Intact (n=3904)	3567	91.4	337	8.6	[Reference]	3837	98.3	67	1.7	[Reference]
- Non-Intact (n=2177)	1769	81.3	408	18.7	**2.44 (2.09-2.85)**	2134	98.0	43	2.0	1.15 (0.78-1.70)
Socio-economic status of the family										
- Non-professionals (n=1149)	987	85.9	162	14.1	[Reference]	1128	98.2	21	1.8	[Reference]
- Professionals (n=4298)	3843	89.4	455	10.6	**0.72 (0.60-0.87)**	4219	98.2	79	1.8	1.01 (0.62-1.64)
Parental psychosis										
- No (n=5819)	5115	87.9	704	12.1	[Reference]	5718	98.3	101	1.7	[Reference]
- Yes (n=262)	221	84.4	41	15.6	**1.35 (0.96-1.90)**	253	96.6	9	3.4	**2.01 (1.01-4.03)**
Parental substance abuse disorder										
- No (n=5634)	4991	88.6	643	11.4	[Reference]	5537	98.3	97	1.7	[Reference]
- Yes (n=447)	345	77.2	102	22.8	**2.30 (1.81-2.91)**	434	97.1	13	2.9	**1.71 (0.95-3.08)**
Adolescent substance use										
Have been drunk 10 or more times during the past 12 months										
- No (n=4864)	4528	93.1	336	6.9	[Reference]	4790	98.5	74	1.5	[Reference]
- Yes (n=1072)	675	63.0	397	37.0	**7.93 (6.71-9.36)**	1040	97.0	32	3.0	**1.99 (1.31-3.03)**
Ever used marihuana or hashish										
- No (n=5691)	5113	89.8	578	10.2	[Reference]	5600	98.4	91	1.6	[Reference]
- Yes (n=342)	181	52.9	161	47.1	**7.87 (6.26-9.89)**	326	95.3	16	4.7	**3.02 (1.76-5.20)**
Other subtstance use										
- No (n=6009)	5286	88.0	723	12.0	[Reference]	5906	98.3	103	1.7	[Reference]
- Yes (n=30)	12	40.0	18	60.0	**10.97 (5.26-22.86)**	26	86.7	4	1.3	**8.82 (3.02-25.73)**

[1]Odds Ratio (95% Confidence Interval). Statistically significant (p<0.10) differences are in **bold**.

Table 2. The hazard ratios (HR) for risk of psychosis in Northern Finland Birth Cohort 1986 in different groups of daily smoking

	Daily tobacco smoking	**n**	**HR for risk of psychosis (95%CI)**	**P-value**
Crude (N=6081)	Non-smokers	5336	Ref.	
	1-9 cigarettes/day	345	0.72 (0.26-1.96)	0.52
	≥10 cigarettes	400	**3.15 (1.94-5.13)**	**0.000**
Model 1 (N=6081)	Non-smokers	5336	Ref.	
	1-9 cigarettes/day	345	0.66 (0.24-1.79)	0.41
	≥10 cigarettes	400	**2.87 (1.76-4.68)**	**0.000**
Model 2 (N=5872)	Non-smokers	5147	Ref.	
	1-9 cigarettes/day	332	0.42 (0.13-1.35)	0.14
	≥10 cigarettes	393	**2.06 (1.17-3.63)**	**0.012**
Model 3 (N=6081)	Non-smokers	5336	Ref.	
	1-9 cigarettes/day	345	0.64 (0.24-1.75)	0.39
	≥10 cigarettes	400	**2.73 (1.67-4.48)**	**0.000**
Model 4 (N=5872)	Non-smokers	5147	Ref.	
	1-9 cigarettes/day	332	0.42 (0.13-1.34)	0.14
	≥10 cigarettes	393	**2.00 (1.13-3.54)**	**0.017**

Statistically significant (p<0.05) differences are in **bold**. Covariates: *Model 1*: PROD-screen; *Model 2*: PROD-screen, cannabis use HR = 1.54 (0.81-2.92), frequent alcohol use HR = 1.29 (0.79-2.09), **other substance use HR = 3.02 (1.01-9.00)**; *Model 3*: PROD-screen, parental substance abuse HR = 1.33 (0.73-2.40), parental psychosis HR = 1.78 (0.89-3.57); *Model 4*: PROD-screen, cannabis use HR = 1.53 (0.81-2.90), frequent alcohol use HR = 1.26 (0.78-2.06), other substance use HR = 2.97 (0.99-8.90**)**, parental substance abuse HR = 1.28 (0.69-2.38), parental psychosis HR = 1.82 (0.90-3.67)