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Authors

Lotfipour, S
Ferguson, E
Leonard, G
et al.

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Maternal cigarette smoking during pregnancy predicts drug use via externalizing behavior in two community-based samples of adolescents

Shahrdad Lotfipour[1]*, Eamonn Ferguson[2]*, Gabriel Leonard[3], Jouko Miettunen[4,5], Michel Perron[6,7], G. Bruce Pike[8], Louis Richer[9], Jean R. Séguin[10], Suzanne Veillette[6,7], Marjo-Riitta Jarvelin[11], Irma Moilanen[5], Pirjo Mäki[4], Tanja Nordström[12], Zdenka Pausova[6,13], Juha Veijola[4] & Tomáš Paus[14]

Hatos Center for Neuropharmacology and Semel Institute for Neuroscience & Human Behavior, David Geffen School of Medicine, University of California, Los Angeles, CA, USA,[1] School of Psychology, University of Nottingham, Nottingham, UK,[2] Montreal Neurological Institute, McGill University, Montreal, QC, Canada,[3] Department of Psychiatry, University of Oulu and Oulu University Hospital, Oulu, Finland,[4] Clinic of Child Psychiatry, University of Oulu and Oulu University Hospital, Oulu, Finland,[5] Department of Medicine, University of Montreal, Montreal, QC, Canada,[6] CEGEP Jonquiere, Jonquiere, QC, Canada,[7] Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada,[8] Department of Psychology, University of Quebec in Chicoutimi, Chicoutimi, QC, Canada,[9] Department of Psychiatry and Centre de Recherche du CHU Ste-Justine, University of Montreal, Montreal, QC, Canada,[10] Department of Epidemiology and Biostatistics, Imperial College, London, UK, and the Department of Children, Young People and Families National Institute for Health and Welfare, Institute of Health Sciences, University of Oulu, Oulu, Finland,[11] Institute of Health Sciences, University of Oulu, Oulu, Finland,[12] Hospital for Sick Children, University of Toronto, Toronto, ON, Canada[13] and Rotman Research Institute, University of Toronto, Toronto, ON, Canada[14]

ABSTRACT

Background and Aims Prenatal exposure to maternal cigarette smoking (PEMCS) is associated with a higher probability of substance use in adolescence. We explore if externalizing behavior mediates this relationship, while controlling for a number of potential covariates of this mediation process. **Methods** We used data obtained in two geographically distinct community samples of adolescents. The first (cross-sectional) sample consisted of 996 adolescents (12–18 years of age) recruited from the Saguenay Youth Study (SYS) in Canada (47% with PEMCS). The second (longitudinal) sample consisted of 1141 adolescents (49% with PEMCS) from the Northern Finland Birth Cohort (NFBC1986). In both samples, externalizing behavior and substance use were assessed during adolescence. In the NFBC1986 cohort, externalizing behavior was also assessed in childhood. **Results** In both populations, PEMCS is associated with a higher likelihood of adolescent drug experimentation. In the NFBC1986 cohort, exposed (versus non-exposed) adolescents experiment with an extra 1.27 [B = 0.24, 95% confidence intervals (CI) = 0.15, 0.33 $P < 0.001$] drugs. In the SYS cohort, a clear protective effect of not being exposed is shown: non-exposed (versus exposed) adolescents are 1.5 times [B = –0.42, 95% CI = –0.75, –0.09, $P = 0.013$] less likely to take drugs. These associations between PEMCS and drug experimentation remain in the multivariate and mediational analyses. **Conclusions** Prenatal exposure to maternal cigarette smoking appears to be associated with a higher probability of experimenting with drugs during adolescence, both directly and indirectly via externalizing behavior and the number of peers reported as using drugs.

Keywords Addiction, adolescence, attention deficit hyperactivity disorder, drug experimentation, externalizing behavior, maternal smoking, tobacco exposure.

Correspondence to: Tomáš Paus, Rotman Research Institute, University of Toronto, 3560 Bathurst Street, Toronto M6A 2E1, ON, Canada. E-mail: tpaus@research.baycrest.org
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INTRODUCTION

Addiction to tobacco affects more than a billion individuals world-wide. While tobacco consumption harms primarily the user, epidemiological studies have provided evidence that *in-utero* exposure to maternal cigarette smoking is associated with certain addictive behaviors in exposed offspring (reviewed in [1]). Studies in

*These authors contributed equally to this study.

experimental animals suggest that this association is due, at least in part, to direct effects of nicotine on the developing brain (reviewed in [2]).

While nicotine-induced alterations of the offspring brain, as observed in experimental studies, provide a robust mechanistic explanation for a direct link between prenatal exposure to maternal cigarette smoking (PEMCS) and addictive behavior later in life, it is likely that there are additional routes involving variations in behaviors known to increase, in turn, probability of substance use [3]. Externalizing behavior is a prime candidate behavior to mediate the relationship between PEMCS and substance use. In humans, PEMCS is associated with higher rates of externalizing behavior in pre-schoolers [4] and adolescents [5–7], as well as brain variations in young adults similar to those observed in attention deficit hyperactivity disorder [8]. Furthermore, developmental-cascade theories suggest etiological connections between externalizing behavior and substance use [9,10]. While this mediation pathway is clearly implicated, no studies have evaluated it formally. The main aim of this paper is to test this mediation hypothesis and examine if it replicates across two culturally distinct cohorts in both cross-sectional and longitudinal analyses.

Such a mediation process should not be viewed in isolation of its social and environmental context. As such, we explore how five potential covariates influence this mediation process. These covariates are selected on theoretical grounds to identify an optimal set that will reduce the possibility of 'backdoor' causality [11]. To do this, we examine three classes of covariates that may influence all aspects of the mediation process, namely: (i) distal exposure (maternal *in-utero* alcohol use), (ii) concurrent exposure (the number of peers reported to be taking drugs) and (iii) salient background risks (sex, family income and mother's education). The rationale for each of these and how they influence the mediation process is given below.

Maternal alcohol use during pregnancy has been reported as a significant predictor of adolescent substance use [12] and externalizing behavior [7,13]. It is possible that mothers who smoke during pregnancy also drink [14]. As such, maternal alcohol use during pregnancy may confound the whole mediation process. The number of peers reported as taking drugs is associated with adolescent substance use [3] and can also be predicted by childhood delinquency [3]. As such, the number of peers reported as taking drugs may act as an additional route through which externalizing behavior may influence adolescent experimentation with drugs. Sex of the offspring is known to influence associations between PEMCS and the brain [15–17]. Family income is associated with the prevalence of smoking during pregnancy [3] and drug taking in adolescents [18,19], as well as externalizing behavior [20]. Thus, both sex and family income can also confound the mediation process. Finally, mother's education is known to influence externalizing behavior [21]. As such, mother's education should be a simple covariate for externalizing behavior.

MATERIALS AND METHODS

The data presented in the current report originate from continuing work on the cross-sectional Saguenay Youth Study (SYS) in Canada and the prospective Northern Finland Birth Cohort 1986 (NFBC 1986) in Finland. Ethical approval for the SYS study protocol was obtained from the Research Ethics Committee of the Chicoutimi Hospital. The NFBC 1986 study protocol has been approved by the ethics committee of Northern Ostrobothnia Hospital District, Finland. Written informed consent and assent were acquired from parents and adolescents, respectively.

The Saguenay Youth Study (SYS) in Canada

Participants

The procedures for recruitment have been described previously [22]. Recruitment and all assessments took place in the Saguenay-Lac-Saint-Jean region of Quebec, Canada between 2003 and 2012. Adolescents and their maternal and paternal grandparents were of white Caucasian French-Canadian ancestry born within the region. Adolescents had to be between 12 and 18 years of age and have at least one sibling of the same age group. Mothers who reported having drunk more than 210 ml/week of pure alcohol (14 bottles of beer, or nine glasses of wine, or seven glasses of hard liquor) during pregnancy were excluded from the study.

From an initial sample of 1028 participants, 996 were entered into these analyses. Participants who had missing data on drug taking (answered three or fewer questions) or externalizing behavior were excluded. For the remaining participants, there were 32 with one ($n = 28$), two ($n = 3$) or three ($n = 1$) missing values on drug taking and these were imputed with the modal value. There were 526 (53%) non-exposed and 470 (47%) exposed adolescents. These two groups did not differ on age ($t_{(994)} = -0.48$, $P = 0.63$), but did on sex ($\chi^2_{(d.f. = 1)} = 3.88$, $P = 0.049$), there being slightly more females in the exposed group. These individuals had complete data on PEMCS, externalizing behavior and drug use; there were some missing data on the covariates and exact *n*s are detailed in all the analyses.

PEMCS. Prenatal exposure to maternal cigarette smoking was classified as having had a history of exposure of more than one cigarette per day during the second trimester of pregnancy, as ascertained in a structured

interview with the mother. We showed good agreement of this retrospective assessment and medical reports attained from a subset of the mothers during the time of pregnancy [22]. The non-exposed adolescents must have had a negative history of cigarette exposure during pregnancy and the year preceding. At recruitment, we matched adolescents with and without *in-utero* cigarette exposure by maternal education and the school they attended.

Symptoms of externalizing behavior. The symptoms of externalizing behavior were assessed as the sum of 14 questions relating to the symptoms of inattention, hyperactivity and conduct disorder, assessed using the Diagnostic Interview Schedule for Children (DISC) predictive scales developed and validated by Lucas and colleagues [23]. This overall index of externalizing behavior was reliable ($\alpha = 0.70$).

Substance use. Substance use was assessed using a questionnaire that asked whether or not the adolescent has ever experimented with any or all of a list of 14 drugs, as reported previously [24,25]. All answers were dichotomized to never (coded 0) versus at least once (coded 1).

The Northern Finland Birth Cohort 1986 (NFBC 1986) in Finland

Participants

The sample comprised a prospective mother–child birth cohort collected in the two northernmost provinces in Finland [26]. The general population-based Northern Finland Birth Cohort 1986 (NFBC 1986) originally included 9432 children (4865 males) born alive whose expected date of birth fell between 1 July 1985 and 30 June 1986. The cohort covers 99% of the deliveries taking place in the target period of the cohort. Data collection started prospectively before the birth and has continued in field studies at ages 7–8 and 15–16 years [27]. A total of 9340 adolescents (4806 males) were alive at the time of the 16-year follow-up. Of these, 6441 consented and completed the questionnaires described below.

For an initial matched sample of 1646 participants (see details below of matching protocol), a final sample of 1141 participants were included in the analyses, based on the availability of complete data on externalizing behavior and substance use. There were 560 (49%) in the exposed group and 581 (51%) in the non-exposed group. There was no significant difference between the groups on sex ($\chi^2 = 0.26$, $P = 0.60$).

General protocol for matching

We adopted a two-step matching procedure to ensure that the SYS and NFBC samples were as similar as possible. First, we selected a sample from the NFBC that were matched to the SYS sample in terms of the exclusion criteria used in the latter cohort. This was to ensure that key variables such as exposure to maternal cigarette smoking were assessed in the same way in both samples. Once we had a matched NFBC sample, the second stage of matching focused on replicating the procedure used to match exposed and non-exposed mothers in the SYS sample. In the SYS sample, mothers who smoked and those who did not during pregnancy were matched on educational level and their offspring were matched on the high school they attended. Thus, the exposed and non-exposed samples within the NFBC sample were similarly matched on these variables. Therefore, the SYS and NFBC samples were similar as far as possible on (i) exclusion criteria and (ii) on how the samples were matched based on developmental exposure to maternal cigarette smoking (see Supporting information, Table S1).

Measures

PEMCS. Maternal cigarette smoking was determined prospectively during visits to the antenatal clinic [28]. The PEMCS status was defined as having a history of exposure of one or more cigarette per day during the second trimester of pregnancy. In contrast, non-exposed adolescents must have had a negative history of cigarette exposure during pregnancy. Data on maternal smoking during the year preceding the pregnancy were not available.

Externalizing symptoms at 7–8 years of age. Information on early emotional and behavioral problems was collected from teachers' and parents' reports using Children's Behavior Questionnaires (Rutter B2 for teachers and Rutter A2 for parents [29]) at ages of 7–8 years [27]. When the children were 8 years old, their teachers rated their behavior during the previous year using the Rutter B scale. The parents had rated the behavior of the offspring at the age of 7 years. The scales consisted of brief statements scored from 0 to 2 (0 = does not apply, 1 = applies somewhat, 2 = certainly applies). The symptoms of externalizing behavior were assessed as the sum of 15 questions relating to the symptoms of inattention, hyperactivity and conduct disorder, as assessed by these questionnaires ($\alpha = 0.86$).

Externalizing symptoms at 15–16 years of age. At 15–16 years of age, participants were asked to complete a postal questionnaire concerning their life habits (e.g. smoking) and social background; this questionnaire also included the Youth Self-Report (YSR) to assess externalizing behavior [30,31]. Adolescents rated themselves for how true each item was during the past 6 months. The scores

for each item ranged from 0 to 2 (0 = not true, 1 = sometimes true, 2 = very true or often true). The items were classified to the subscales based on the 2001 version of the YSR scale [31], which included seven items for attention and hyperactivity problems [32] and 12 items for rule-breaking behavior. The aggressive behavior items were not used for comparability with the SYS measure. In 65 (0.9%) participants, YSR subscales were excluded because more than three answers were missing in the subscales. If there were at most three missing values in the subscale, those were replaced by the mean value of items in that particular subscale for that person. The sum of 18 items constituted the total externalizing behavior index and was reliable ($\alpha = 0.96$).

Substance use. Information on substance use was collected in two phases in the 15–16-year follow-up: (i) information on regular smoking was ascertained in postal questionnaires and (ii) data on substance use were collected in the questionnaire that the participants received during a clinical examination. Information on life-time experimentation with eight drugs covered tobacco use, alcohol, medicines, marijuana [33] and hard drugs (e.g. heroin). All answers were dichotomized to never (coded 0) versus at least once (coded 1).

Covariates. In both samples, we examined five potential covariates (mother's alcohol consumption during pregnancy, family income, mother's education, number of peers reported to be taking drugs and sex). Questions, scaling for the covariates and descriptive statistics are presented in Table 1.

STATISTICAL ANALYSES

Initial univariate regression models were conducted to examine the simple associations between drug-taking behavior, PEMCS, externalizing behavior and the covariates. When the outcome is a count variable (i.e. the number of drugs tried), these data are modeled using Poisson regression. In cases where the counts contain a high proportion of zeros, we estimated zero-inflated Poisson (ZIP) regression models [34–36]. These models provide two components. The first component examines predictors of the zeros (binary component: never used drugs versus those who have used drugs). The second component provides an estimate of the number of drugs tried (referred to in the analyses as the count variable). These models thus allow for the differentiation between predictors of never using drugs and—for those who have used drugs—the number of drugs used. The statistical regression models were conducted using Stata version 12.

Univariate analyses were used to identify significant effects among the theoretical covariates of the main mediation model. Significant covariates were included in the mediation models specified as path models in Mplus version 7.1. The basic mediation model was specified to determine whether exposure (i.e. PEMCS) directly and/or indirectly predicts adolescent substance use via externalizing behavior in the two populations of adolescents studied in the absence of any covariates.

In the NFBC sample, the sampling procedure was stratified within four geographical regions defined by crossing Oulu or Lapland province with city or urban region. As such, panel models were used to specify region in the regression models and the complex survey procedure in Mplus version 7.1 to control for region in the path models.

In the SYS sample, participants are nested within families, with two covariates assessed at the family level (level 2; family income and mother's education), with the remaining variables assessed at the individual level (level 1). As such, multi-level path models were specified to explore the mediation models. The family-level variables and externalizing behavior were grand mean centered. Externalizing behavior was grand mean centered to reflect its status as a trait at the population level. The number of peers reported to be taking drugs (level 1) was group mean centered. The level 1 variables of sex, PEMCS and mothers alcohol use during pregnancy were specified as fixed effects. All other effects were specified as random effects. For the univariate regression models, the standard errors in the regression models were specified to control for within family clustering (see notes to Table 2).

The possibility of interactions between predictors/covariates

For the NFBC we ran 15 separate regressions (one regression for each of the five covariates combined with each of the three predictors), the outcome being the number of drugs tried. All continuous variables were mean centered prior to estimating the cross-product term. Given the exploratory nature of these regressions, we applied a Bonferroni correction to the *P*-value. For the SYS data, we ran a series of two-level random intercepts model to examine the level 1 interactions and random coefficients models to examine the cross-level interactions (all zero-inflated Poisson models).

RESULTS

Univariate and multivariate analyses and covariates

Table 2 provides the univariate associations in both samples. The results demonstrate consistent associations across variables. Most importantly, in both samples, PEMCS predicted externalizing behavior and substance

Table 1 Assessment of covariates across the Saguenay Youth Study (SYS) and Northern Finland Birth Cohort (NFBC) samples.

	SYS		*NFBC*	
Variable	*Question*	n, *mean (SD) median (range)*	*Question*	*Mean/median (SD/range)*
Family income	Household income measured on a 9-point scale 1 = 15 K or less; 9 = 85 K or more (Canadian dollars)	*n* = 988, median = 6 (1, 9)	Household income (Finnish markka)	*n* = 816 (free response), mean = 241 612.7 (SD 276 705), range = 1000–6 500 000
Mother's alcohol use during pregnancy	Scale = yes (1) or no (0)	*n* = 993, mean = 0.23 (0.42) 76.4% never drank	'Have you had alcoholic drinks during this pregnancy?' Scale = yes (2) or no (1)	*n* = 1123, mean = 1.1 (SD = 0.37), median = 1 84% = no
Number of peers estimated to be using drugs	The sum of three questions asking if friends (1) smoke, (2) drink alcohol (3) use illicit drugs Scored on a 4-point scale 1 = All my friends 2 = Majority of my friends 3 = Some of my friends 4 = None of my friends (scoring is reversed so that high scores equate to having more friends try drugs)	*n* = 990, mean = 8.66 (2.3) median = 9 (3, 12)	Do you know anybody who would have experimented with drugs during the past 12 months (including hashish, thinners or other things to sniff, intoxicating medicines, etc.)?' Scored on a 4-point scale 1–4, with high scores indicating knowing more	*n* = 1134, mean = 1.6 (SD = 0.93), median = 1 (1, 4)
Mother's education	1 = primary not completed to 9 = master or doctorate	*n* = 977, median = 4 (1, 9)	1 = less than 8 years to 5 = University level	*n* = 1141, median = 3 (1, 5)
Sex	Male = 0, female = 1	52% female	Male = 1, female = 2	54% female

SD = standard deviation.

Table 2 Univariate analysis for predictors and covariates from Northern Finland Birth Cohort (NFBC) and Saguenay Youth Study (SYS).

	NFBC				*SYS*		
	Logistic *Exposure* *OR (95% CI)*	*OLS* *Externalizing at 7–8* *B (95% CI)*	*OLS* *Externalizing at 15–16* *B (95% CI)*	*Poisson* *Total drugs (see note)* *B (95% CI)*	*Logistic* *Exposure* *OR (95% CI)*	*OLS* *Externalizing at 16* *B (95% CI)*	*ZI Poisson* *Total drugs (see note)* *B (95% CI)*
Mediation model variables							
Exposure to maternal cigarette smoke		0.65 (0.20, 1.1)	1.1 (0.60, 1.63)	0.24 (0.15, 0.33)		0.37 (0.10, 0.64)	Count: 0.11 (–0.06, 0.29) *P* = 0.19 Binary: –0.42 (–0.75, –0.09)
		P = 0.004	*P* < 0.001	*P* < 0.001		*P* = 0.007	*P* = 0.013
Externalizing at 7–8			0.12 (0.05, 0.18) *P* < 0.0001	0.01 (0.001, 0.023) *P* = 0.023			
Externalizing at 15–16				0.06 (0.05, 0.07)			Count: 0.11 (0.08, 0.15) *P* < 0.001 Binary: –0.16 (–0.24, –0.08
				P < 0.0001			*P* < 0.001
Covariates							
Sex[a]	1.06 (0.844, 1.34)	–1.9 (–2.4, –1.50)	1.38 (0.87, 1.89)	0.14 (0.05, 0.23)	1.2 (0.99, 1.65)	–0.09 (–0.36, 0.18)	Count = 0.05 (–0.12, 0.22) *P* = 0.57 Binary = –0.32 (0.65, –0.02)
	P = 0.59	*P* < 0.0001	*P* < 0.0001	*P* = 0.002	*P* = 0.051	*P* = 0.51	*P* = 0.039
Family income	0.99 (0.99, 1.0)	0.0000002 (–0.0000007, 0.000001)	0.000001 (0.00000003, 0.000002)	0.000001 (0.000000007, 0.0000003)	0.93 (0.76, 1.00)	–0.10 (–0.16, –0.05)	Count = –0.05 (–0.09, –0.02) *P* = 0.003 Binary = 0.01 (–0.05, –0.07)
	P = 0.23	*P* = 0.65	*P* = 0.045	*P* = 0.06	*P* = 0.06	*P* < 0.001	*P* = 0.75
Mother's alcohol use during pregnancy	2.5 (1.8, 3.5)	0.13 (–0.49, 0.75)	0.40 (–0.31, 1.11)	0.15 (0.04, 0.27)	2.0 (1.34, 3.09)	0.08 (–0.23, 0.39)	Count = –0.15 (–0.36, 0.06) *P* = 0.16 Binary = –0.30 (–0.73, 0.13)
	P < 0.0001	*P* = 0.67	*P* = 0.27	*P* = 0.01	*P* = 0.001	*P* = 0.61	*P* = 0.18

Table 2 *Cont.*

	NFBC				*SYS*		
	Logistic *Exposure* *OR (95% CI)*	*OLS* *Externalizing at 7–8* *B (95% CI)*	*OLS* *Externalizing at 15–16* *B (95% CI)*	*Poisson* *Total drugs (see note)* *B (95% CI)*	*Logistic* *Exposure* *OR (95% CI)*	*OLS* *Externalizing at 16* *B (95% CI)*	*ZI Poisson* *Total drugs (see note)* *B (95% CI)*
Number of peers reported to be taking drugs[b]	0.20 (0.09, 0.31)	0.009 (–0.004, 0.024)	0.08 (0.066, 0.088)	0.24 (0.19, 0.28)	0.49 (0.17, 0.80)	0.26 (0.18, 0.34)	Count = 0.23 (0.16, 0.29) $P < 0.001$ Binary = –1.1 (–1.3, –0.92)
	$P < 0.001$	$P = 0.17$	$P < 0.0001$	$P < 0.0001$	$P = 0.003$	$P < 0.001$	$P < 0.001$
Mother's education	1.0 (0.91, 1.09)	–0.18 (–0.35, –0.005)	–0.13 (–0.33, 0.07)	–0.02 (–0.06, 0.01)	0.90 (0.81, 1.006)	–0.14 (–0.22, –0.06)	Count = –0.05 (–0.11, 0.002) $P = 0.06$ Binary = 0.09 (–0.006, 0.20)
	$P = 0.96$	$P = 0.044$	$P = 0.21$	$P = 0.181$	$P = 0.065$	$P = 0.001$	$P = 0.07$

NFBC = exposure to maternal cigarette smoke (0 = not smoked during pregnancy; 1 = smoked during pregnancy). Sex [1 = male; 2 = female (except when sex is treated as an outcome then 0 = male; 1 = female)]. Mother's alcohol use during pregnancy (0 = no; 1 = yes). Dependent variables are listed across the table on the top row, except for (1) 'sex' with respect to 'exposure to maternal cigarette smoke', (2) 'number of peers reported to be taking drugs' with respect to 'exposure to maternal cigarette smoke' and (3) 'number of peers reported to be taking drugs' with respect to 'externalizing behavior'. [a]For results pertaining to the covariate 'sex' with respect to 'exposure to maternal cigarette smoke,' sex is treated as the outcome. This is to avoid reverse causation, as sex of the adolescent could potentially be predicted by exposure and not the other way around. The coefficient reported is an odds ratio (OR). [b]Results pertaining to the covariate 'number of peers reported to be taking drugs' the likely casual order is that 'number of peer's taking drugs' is predicted by 'exposure to maternal cigarette smoke' and 'externalizing behavior'. Therefore, for these analyses 'number of peers reported to be taking drugs' is treated as the outcome using ordinary least squares (OLS) panel regression with reported coefficient being unstandardized. For all models, panel regressions are specified with region as the panel identifier. For logistic regression ORs are reported. For OLS regression, random-effects models with unstandardized coefficients are reported. For total drugs, the coefficients reported are for panel Poisson models. The same results were obtained with standard Poisson regressions. For the standard Poisson models for total drugs, the models were underdispersed and standard errors are corrected by scaling with Pearson coefficient for dispersion. Based on the standard Poisson regression the following standardized effects are reported. Exposed versus non-exposed adolescents resulted in 1.27 more drugs having been tried; for externalizing behavior at 7–8 years a 1 standard deviation (SD) increase in externalizing behavior equates to a 1.05 increase in the number of drugs tried; externalizing behavior at 15–16 years, a 1 SD increase in externalizing behavior equates to a 1.3 increase in the number of drugs tried; for sex being female is associated with trying 1.15 more drugs; for family income, a 1 SD increase is linked to taking 1.03 more drugs having been tried; if the mother took alcohol during pregnancy, the adolescent will try 1.1 more drugs; for the number of peers taking drugs, a 1 SD increase is associated with taking 1.24 more drugs tried); for mother's education, a 1 SD decrease is linked to 0.98 more drugs tried. Sex $n = 1141$, family income $n = 816$, mother's alcohol $n = 1123$, number of peers reported to be taking drugs $n = 1134$, mother's education $n = 1141$. SYS: 'exposure to maternal cigarette smoke' (0 = not smoked during pregnancy; 1 = smoked during pregnancy). Sex (0 = male; 1 = female). Mother's alcohol use during pregnancy (0 = no; 1 = yes). Dependent variables are listed across the table on the top row, except for (1) 'sex' with respect to 'exposure to maternal cigarette smoke', (2) 'number of peers reported to be taking drugs' with respect to 'exposure to maternal cigarette smoke' and (3) 'number of peers reported to be taking drugs' with respect to 'externalizing behavior'. [a]For results pertaining to the covariate 'sex' with respect to 'exposure to maternal cigarette smoke', sex is treated as the outcome. This is to avoid reverse causation, as sex of the adolescent could potentially be predicted by exposure and not the other way around. The coefficient reported is an OR. [b]Results pertaining to the covariate 'number of peers reported to be taking drugs' the likely casual order is that 'number of peer's taking drugs' is predicted by 'exposure to maternal cigarette smoke' and 'externalizing behavior'. Therefore, for these analyses 'number of peers reported to be taking drugs' is treated as the outcome using OLS panel regression with reported coefficient being unstandardized. All standard errors are corrected for within family clustering. For logistic regressions ORs are reported. For OLS regression unstandardized coefficients are reported. For total drug taking, there were 428 subjects of 996 with zero drug taking and, as such, a zero-inflated Poisson (ZIP) model was conducted. Pearson inflation factors were all greater than 2. Please note that for the binary component of the ZIP model the outcome this is scored in the direction of predicting the zeros (having never taken drugs). For the ZIP model for exposure, the binary function is significant and equates to an OR of 0.65, indicating that the non-exposed group are 1.5 times more likely to have never taken drugs. For externalizing behavior, both the count and binary values are significant. The count effect indicates that for those who take drugs, for every SD change in externalizing behavior, an extra 1.25 drugs are tried; the binary effect indicates that for every SD decrease in externalizing behavior the odds ratio for never taking drugs is 1.37. For sex, only the binary function is significant. This indicates that being male is associated with an OR of 1.4 for never taking drugs. For family income only the count function is significant; this indicates that for each unit increase in income, the OR for taking drugs is 0.95 (higher family income is linked to lower drug taking). For mother's alcohol intake during pregnancy there are no significant effects. For the number of peers reported to be taking drugs, both effects are significant. The count function indicates that every SD increase in the number of peers reported to be taking drugs is associated with adolescents taking an extra 1.27 drugs. The binary function indicates that for every SD decrease in the number of peers reported to be taking drugs, the odds of never taking drugs is 14.3. Finally, for mother's education, neither effect is significant. Standardization for Poisson models were run using the *listcoef* function developed by Long & Freese [36]. For sex $n = 996$, peers taking drugs $n = 990$, family income $n = 988$, mother's education $n = 977$ and mother's alcohol use during pregnancy = 993. For both mother's education and family income, these values reflect level 2 between-subject factors. The results pertaining to these were confirmed using a multi-level model in MPlus 7.

use of the offspring; it was also associated with mother's alcohol use during pregnancy and the number of peers reported as taking drugs. Lower family income was associated with greater externalizing behavior in SYS and lower externalizing behavior in the NFBC.

For the NFBC sample, multivariate regressions (regressing drug taking on predictors and covariates) showed that current drug-taking behavior was associated (positive correlations) with externalizing behavior at 15–16 years, the number of peers reported to be taking drugs, mother's alcohol use during pregnancy and PEMCS. For the SYS sample, the binary component of the analyses (i.e. an adolescent never started to take drugs) indicates that adolescents were more likely to have never taken drugs if (i) they had not been exposed to maternal cigarette smoking during pregnancy, (ii) reported a smaller number of peers as taking drugs, (iii) had lower externalizing behavior and (iv) were male. For adolescents experimenting with drugs, the count component of the analyses indicates that higher experimentation with drugs is associated with lower family income, greater externalizing and the greater the number of peers reported as taking drugs. Full details of these analyses can be found in Supporting information, Table S2.

The possibility of interactions between predictors/covariates

In the NFBC sample, three interactions were significant by conventional standards, namely PEMCS by mother's alcohol use during pregnancy, family income by externalizing behavior at 7–8 and number of peers reported to be taking drugs by externalizing behavior at 15–16; however, none of these interactions was significant after the Bonferroni correction.

For the SYS sample, there were two significant interactions by traditional standards, namely between externalizing behavior and number of peers reported to be taking drugs on drug use using the count component, and between PEMCS and number of peers reported to be taking drugs on drug use using the binary component. The first interaction did not pass our Bonferroni-corrected *P*-value of 0.0025, while the latter did, but adding the latter component to our two-level model caused it to fail to converge. For this reason, and given that this interaction was not predicted *a priori*, we dropped it from the final model.

Predicting substance use

The basic mediation models—without the covariates—are reported in Supporting information, Fig 1a,b and show that the basic mediation prediction is supported.

Figure 1 shows the path model predicting substance use in the NFBC cohort including covariates identified from the univariate analyses. The results demonstrate that PEMCS and alcohol use during pregnancy predicted directly a higher number of drugs tried by adolescent offspring. In addition to these direct effects for PEMCS, indirect effects were observed via: (i) externalizing behavior at 7–8 and 15–16 years of age; and (ii) the number of peers reported to be using drugs. In these cases, the greater the number of peers reported to experiment with drugs and the greater the externalizing behavior at 15–16 associates with a higher number of drugs tried by the adolescent. Female adolescents had higher externalizing behavior at 15–16 years of age, but males were more likely to have higher externalizing behavior at 7–8 years of age.

Figure 2 shows the path model for the SYS sample; it replicates the main findings observed in the NFBC sample. Most importantly, PEMCS predicted adolescent substance directly and indirectly via externalizing behavior and the number of peers reported as using drugs.

DISCUSSION

In two community-based samples of adolescents recruited in geographically distinct populations, we demonstrate that PEMCS was associated with a higher probability of experimenting with drugs during adolescence directly and indirectly via externalizing behavior and the number of peers reported as using drugs.

In the prospective longitudinal NFBC 1986 sample, we demonstrate that PEMCS predicted higher likelihood for externalizing behavior both in childhood (7–8 years of age) and mid-adolescence (16 years of age), with externalizing behavior at the age of 7–8 predicting externalizing behavior at ages 15–16. Both PEMCS and externalizing behavior at age 16 related to higher total drug use during mid-adolescence. These results are in line with a series of previous reports associating PEMCS with short and long-term psychological and behavioral deficits [3,4,24,25,37–42]. The above relationship was replicated in the SYS, suggesting that the association is independent of culturally specific confounders.

We also observed a number of novel associations between the number of peers the adolescents report are experimenting with drugs and a number of relevant phenomena. In particular, we show that—in both samples—children whose mothers smoked during pregnancy reported more peers experimenting with drugs. Reporting more peers experimenting with drugs was predicted by higher externalizing behavior and predicted greater drug experimentation. Thus, the number of peers reported to be experimenting with drugs also acts as an additional indirect path from PEMCS to drug experimentation and as an indirect path linking externalizing behavior and drug experimentation. Targeting

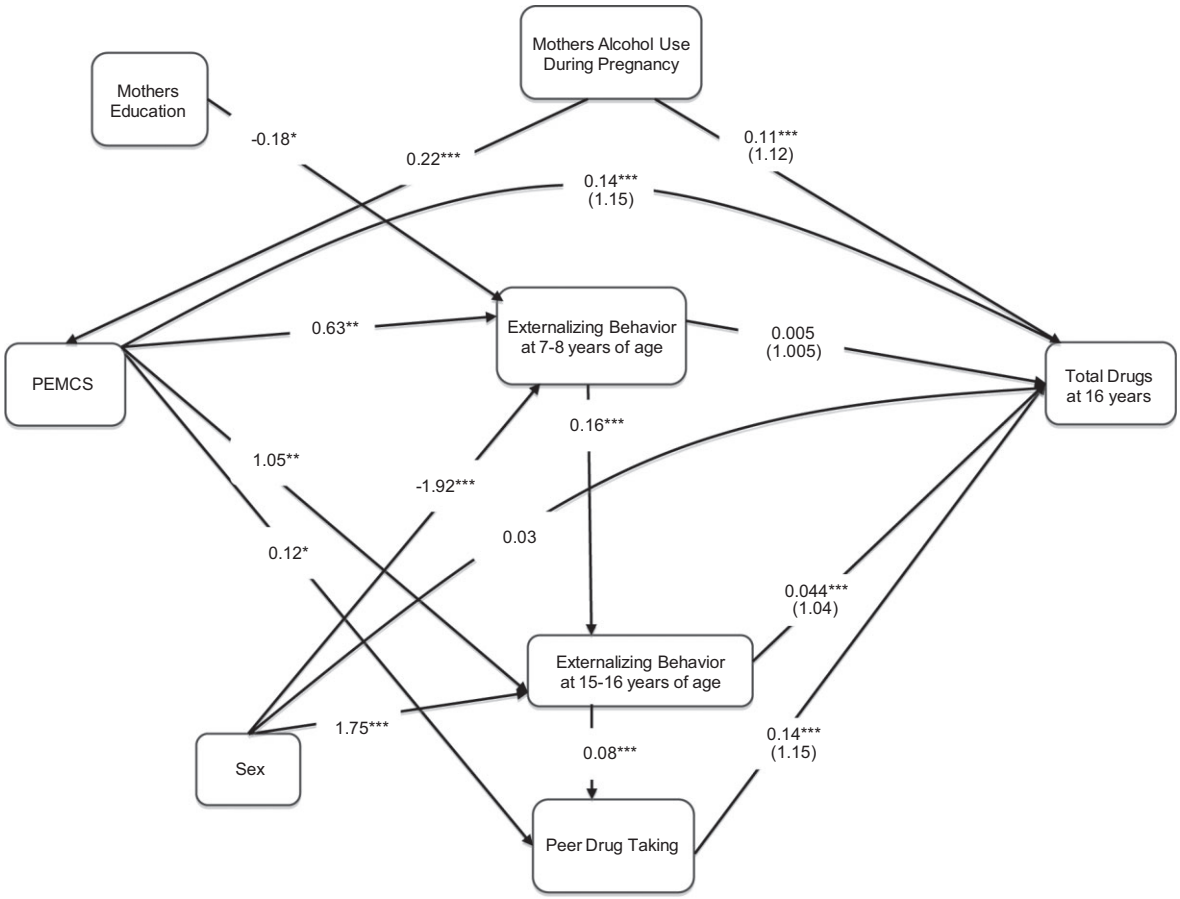

Figure 1 Longitudinal analysis of the Northern Finland Birth Cohort (NFBC) data for total drugs (Poisson path model). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Unstandardized coefficients. Estimator is robust maximum likelihood. Family income is not in the model due to 325 missing cases. Full information maximum likelihood (FIML) is used to deal with missing data ($n = 1141$). Stratification for geographical region. Exposure (0 = not smoked during pregnancy, 1 = smoked during pregnancy). Sex (1 = male, 2 = female). Mother's alcohol use during pregnancy (0 = no, 1 = yes). Figures in parentheses on the paths predicting total drugs at 16 years represent the exponentiated coefficients to ease interpretation. For example, a person exposed to maternal smoking is expected to try, on average, 1.15 times more drugs than a person not exposed. For every increment in externalizing behavior at 16, a person tries, on average, 1.04 more drugs. The path between mother's alcohol use during pregnancy and adolescent drug use is not shown, as the association is not significant in the univariate analyses for covariate selection. PEMCS = prenatal exposure to maternal cigarette smoking.

and reducing exposure to such peers may offer an important means to disrupt part of the link between drug experimentation and both PEMCS and externalizing behavior. We did not predict this link between PEMCS and reported peer drug experimentation, but it did emerge in both samples. Therefore, we feel it is a robust finding. At this point, we can only offer a few possible avenues to pursue in future studies to explain this phenomenon. At least three possibilities could be considered. First, mother's (or mother's partner) smoking may influence their child's smoking behavior ('imitation'), which then influences their autonomous decision to affiliate with peers who also smoke and use substances. Secondly, the mother's smoking behavior may influence the type of environmental exposure their children have with other families where parents and adolescents smoke, thus influencing the probability of affiliation with peers who also smoke and use substances. Thirdly, geographical proximity of families with a particular rate of smoking behavior may, again, influence the probability of interacting with peers sharing similar exposures. The latter two scenarios are consistent with the known role of social networks in the person-to-person spread of smoking behavior [43]. At this point, these are only theoretical speculations that need to be tested in future studies.

Overall, the results suggest that maternal cigarette smoking is a significant predictor of adolescent substance use directly and indirectly via externalizing and reported peer drug use. Possible interventions and reducing externalizing behavior at 7–8 years of age may assist in reducing substance use behaviors during the peak of adolescence [10] or interventions targeted at reducing exposure in other adolescent drug users. We note that

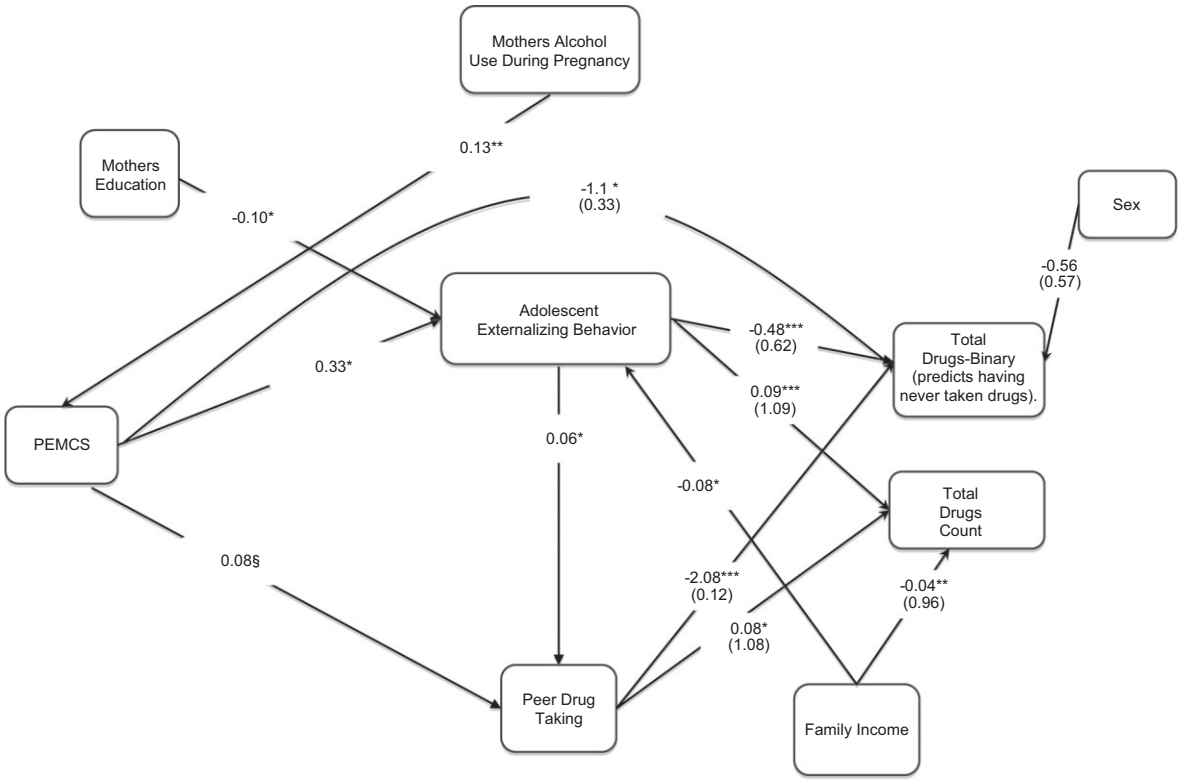

Figure 2 Cross-sectional analysis of the Saguenay Youth Study (SYS) data for total drugs (zero-inflated multi-level Poisson path model with random effects and fixed effects). §$P = 0.051$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$. Unstandardized coefficients. Estimator is robust maximum likelihood ($n = 969$). Full information maximum likelihood (FIML) is used for missing data at level 1, but due to level 2 missing data some participants were lost in the analysis. The estimate of the number of peers taking drugs is group mean centered, with family income, mother's education and externalizing grand mean centered. Effects for sex, exposure and mother's alcohol use are fixed effects with random intercepts, all other level 1 effects are specified random effects. Exposure (0 = not smoked during pregnancy, 1 = smoked during pregnancy). Sex (0 = male, 1 = female). Mother's alcohol use during pregnancy (0 = no, 1 = yes). Please note that for the binary component of the zero-inflated Poisson model the outcome this is scored in the direction of predicting the zeros (having never taken drugs). The same pattern of effects is observed when the model is specified as a fully fixed-effect random intercepts model. Figures in parentheses represent the exponentiated coefficients. For example, the effect of adolescent externalizing behavior on not taking drugs (total drugs–binary) indicates that for every point decrease from the grand mean in externalizing is associated with a 1.61 (1/0.62) times increase in the odds of having never taken drugs. The effect of exposure on never taking drugs (total drugs–binary) indicates that the effect of not being exposed to smoking is associated with a three times increase in the odds of having never taken drugs. A one-unit decrease from the mean in the scale assessing the estimated number of peers taking drugs is associated with an eightfold increase in the odds of having never taken drugs. Every increase in externalizing behavior from the mean is associated with trying 1.09 times more drugs. PEMCS = prenatal exposure to maternal cigarette smoking.

other factors could mediate adolescent substance use including, for example, internalizing behavior (anxiety and depression) of the parents and adolescents, as well as current maternal smoking/drug use [1,3].

In summary, this report makes a number of contributions to the existing literature on the relationship between PEMCS and substance use during adolescence. First, we have used a mediation model and tested formally the role of externalizing behavior in mediating the relationship between PEMCS and substance use. Secondly, we have explored the role of theory-driven covariates targeting specific components of the mediation process. Thirdly, we contribute a new observation to the literature, namely that the number of peers who are reported to take drugs act as an additional mediator of the relationships between both PEMCS and substance use and externalizing behavior and substance use. Finally, the strength of this report also rests in the fact that we replicate these relationships in two geographically and culturally distinct cohorts, thus supporting the generalizability of the findings.

Declaration of interests

None.

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References

1. Lotfipour S., Paus T. Association between prenatal exposure to maternal cigarette smoking and the brain and behaviour of adolescent offspring. Wakschlag L. S., topic editor. In: Tremblay R. E., Boivin M., Peters R. De V., editors. *Encyclopedia on Early Childhood Development*. Montreal, Quebec: Center of Excellence for Early Childhood Development; 2011, pp. 1–8.
2. Dwyer J. B., McQuown S. C., Leslie F. M. The dynamic effects of nicotine on the developing brain. *Pharmacol Ther* 2009; **122**: 125–39.
3. Cornelius M. D., Leech S. L., Goldschmidt L., Day N. L. Prenatal tobacco exposure: is it a risk factor for early tobacco experimentation? *Nicotine Tob Res* 2000; **2**: 45–52.
4. Huijbregts S. C., Seguin J. R., Zoccolillo M., Boivin M., Tremblay R. E. Associations of maternal prenatal smoking with early childhood physical aggression, hyperactivity-impulsivity, and their co-occurrence. *J Abnorm Child Psychol* 2007; **35**: 203–15.
5. Linnet K. M., Dalsgaard S., Obel C., Wisborg K., Henriksen T. B., Rodriguez A. *et al*. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry* 2003; **160**: 1028–40.
6. Fergusson D. M., Woodward L. J., Horwood L. J. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry* 1998; **55**: 721–7.
7. Hill S. Y., Lowers L., Locke-Wellman J., Shen S. A. Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. *J Stud Alcohol* 2000; **61**: 661–8.
8. Holz N. E., Boecker R., Baumeister S., Hohm E., Zohsel K., Buchmann A.F. *et al*. Effect of prenatal exposure to tobacco smoke and inhibitory control: neuroimaing results from a 25-year prospective study. *JAMA Psychiatry* 2014; **343**: 786–96.
9. Krueger R. F., Hicks B. M., Patrick C. J., Carlson S. R., Iacono W. G., McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J Abnorm Psychol* 2002; **111**: 411–24.
10. Castellanos-Ryan N., Seguin J. R., Vitaro F., Parent S., Tremblay R. E. Impact of a 2-year multimodal intervention for disruptive 6-year-olds on substance use in adolescence: randomised controlled trial. *Br J Psychiatry* 2013; **203**: 188–95.
11. Pearl J. Causal inference in statistics: an overview. *Stat Surv* 2009; **3**: 96–146.
12. Baer J. S., Barr H. M., Bookstein F. L., Sampson P. D., Streissguth A. P. Prenatal alcohol exposure and family history of alcoholism in the etiology of adolescent alcohol problems. *J Stud Alcohol* 1998; **59**: 533–43.
13. Hayatbakhsh M. R., McGee T. R., Bor W., Najman J. M., Jamrozik K., Mamun A. A. Child and adolescent externalizing behavior and cannabis use disorders in early adulthood: an Australian prospective birth cohort study. *Addict Behav* 2008; **33**: 422–38.
14. Haste F. M., Anderson H. R., Brooke O. G., Bland J. M., Peacock J. L. The effects of smoking and drinking on the anthropometric measurements of neonates. *Paediatr Perinat Epidemiol* 1991; **5**: 83–92.
15. Toro R., Leonard G., Lerner J. V., Lerner R. M., Perron M., Pike G. B. *et al*. Prenatal exposure to maternal cigarette smoking and the adolescent cerebral cortex. *Neuropsychopharmacology* 2008; **33**: 1019–27.
16. Paus T., Nawazkhan I., Leonard G., Perron M., Pike G. B., Pitiot A. *et al*. Corpus callosum in adolescent offspring exposed prenatally to maternal cigarette smoking. *Neuroimage* 2008; **40**: 435–41.
17. Paus T., Bernard M., Chakravarty M. M., Davey Smith G., Gillis J., Lourdusamy A. *et al*. KCTD8 gene and brain growth in adverse intrauterine environment: a genome-wide association study. *Cereb Cortex* 2012; **22**: 2634–42.
18. Patrick M. E., Wightman P., Schoeni R. F., Schulenberg J. E. Socioeconomic status and substance use among young adults: a comparison across constructs and drugs. *J Stud Alcohol Drugs* 2012; **73**: 772–82.
19. Goodman E., Huang B. Socioeconomic status, depressive symptoms, and adolescent substance use. *Arch Pediatr Adolesc Med* 2002; **156**: 448–53.
20. Stone S. L., Speltz M. L., Collett B., Werler M. M. Socioeconomic factors in relation to discrepancy in parent versus teacher ratings of child behavior. *J Psychopathol Behav Assess* 2013; **35**: 314–20.
21. Andersson H. W., Sommerfelt K. The relationship between cognitive abilities and maternal ratings of externalizing behaviors in preschool children. *Scand J Psychol* 2001; **42**: 437–44.
22. Pausova Z., Paus T., Abrahamowicz M., Almerigi J., Arbour N., Bernard M. *et al*. Genes, maternal smoking, and the offspring brain and body during adolescence: design of the saguenay youth study. *Hum Brain Mapp* 2007; **28**: 502–18.
23. Lucas C. P., Zhang H., Fisher P. W., Shaffer D., Regier D. A., Narrow W. E. *et al*. The DISC Predictive Scales (DPS):

efficiently screening for diagnoses. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 443–9.
24. Lotfipour S., Ferguson E., Leonard G., Perron M., Pike B., Richer L. *et al*. Orbitofrontal cortex and drug use during adolescence: role of prenatal exposure to maternal smoking and BDNF genotype. *Arch Gen Psychiatry* 2009; **66**: 1244–52.
25. Lotfipour S., Leonard G., Perron M., Pike B., Richer L., Seguin J. R. *et al*. Prenatal exposure to maternal cigarette smoking interacts with a polymorphism in the alpha6 nicotinic acetylcholine receptor gene to influence drug use and striatum volume in adolescence. *Mol Psychiatry* 2010; **15**: 6–8.
26. Jarvelin M. R., Hartikainen-Sorri A. L., Rantakallio P. Labour induction policy in hospitals of different levels of specialisation. *Br J Obstet Gynaecol* 1993; **100**: 310–5.
27. Taanila A., Ebeling H., Kotimaa A., Moilanen I., Jarvelin M. R. Is a large family a protective factor against behavioural and emotional problems at the age of 8 years? *Acta Paediatr* 2004; **93**: 508–17.
28. Kotimaa A. J., Moilanen I., Taanila A., Ebeling H., Smalley S. L., McGough J. J. *et al*. Maternal smoking and hyperactivity in 8-year-old children. *J Am Acad Child Adolesc Psychiatry* 2003; **42**: 826–33.
29. Rutter M. A children's behaviour questionnaire for completion by teachers: preliminary findings. *J Child Psychol Psychiatry* 1967; **8**: 1–11.
30. Achenbach T. M. Manual for the ASEBA school-age forms and profiles, in Vermont. Burlington, VT: Research Center for Children, Youth and Families; 1991.
31. Achenbach T. M., Rescorla L. A. Manual for the ASEBA school-age forms and profiles, in Vermont. Burlington, VT: Research Center for Children, Youth and Families); 2001.
32. Hurtig T. M., Taanila A., Veijola J., Ebeling H., Maki P., Miettunen J. *et al*. Associations between psychotic-like symptoms and inattention/hyperactivity symptoms. *Soc Psychiatry Psychiatr Epidemiol* 2011; **46**: 17–27.
33. Miettunen J., Tormanen S., Murray G. K., Jones P. B., Maki P., Ebeling H. *et al*. Association of cannabis use with prodromal symptoms of psychosis in adolescence. *Br J Psychiatry* 2008; **192**: 470–1.
34. Long J. S. *Regression Models for Categorical and Limited Dependent Variables*. Cary, NC: SAS Publishing; 1997.
35. Atkins D. C., Gallop R. J. Rethinking how family researchers model infrequent outcomes: a tutorial on count regression and zero-inflated models. *J Fam Psychol* 2007; **21**: 726–35.
36. Hilbe J. M. *Negative Binomial Regression*. New York: Cambridge University Press; 2011.
37. Buka S. L., Shenassa E. D., Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry* 2003; **160**: 1978–84.
38. Porath A. J., Fried P. A. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicol Teratol* 2005; **27**: 267–77.
39. Thapar A., Fowler T., Rice F., Scourfield J., van den Bree M., Thomas H. *et al*. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *Am J Psychiatry* 2003; **160**: 1985–9.
40. Weissman M. M., Warner V., Wickramaratne P. J., Kandel D. B. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *J Am Acad Child Adolesc Psychiatry* 1999; **38**: 892–9.
41. Toledo-Rodriguez M., Lotfipour S., Leonard G., Perron M., Richer L., Veillette S. *et al*. Maternal smoking during pregnancy is associated with epigenetic modifications of the brain-derived neurotrophic factor-6 exon in adolescent offspring. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 1350–4.
42. Cornelius M. D., Day N. L. The effects of tobacco use during and after pregnancy on exposed children. *Alcohol Res Health* 2000; **24**: 242–9.
43. Christakis N. A., Fowler J. H. The collective dynamics of smoking in a large social network. *N Engl J Med* 2008; **358**: 2249–58.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Simple mediation models. (a) Poisson path model: longitudinal analysis of the Northern Finland Birth Cohort (NFBC) data for the total drugs basic mediation model. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Unstandardized coefficients. Estimator is robust maximum likelihood. Full information maximum likelihood (FIML) used to deal with missing data $n = 1141$. Stratification for region controlled. Figures in parentheses on the paths predicting total drugs at 16 years represent the exponentiated coefficients. For example, a person exposed to maternal smoking is expected to try, on average, 1.2 times as many drugs as a person not exposed. For every increment in externalizing behavior at 16 a person is, on average, likely to try 1.06 more drugs. (b) Zero-inflated multi-level mixed random and fixed effects Poisson path model—basic mediation model. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. Unstandardized coefficients. Estimator is robust maximum likelihood (= 996). Paths from exposure represent random intercepts and paths from externalizing are specified as random slopes. Adolescent externalizing behavior is grand mean centered. Please note that for the binary component of the zero-inflated Poisson model the outcome of this is scored in the direction of predicting the zeros (having never taken drugs). Figures in parentheses on the paths predicting total drugs at 16 years represent the exponentiated coefficients. For example, the effect of adolescent externalizing behavior on not taking drugs (total drugs–binary) indicates that for every point decrease from the grand mean in externalizing is associated with a 1.25 increase in the odds of never starting to take drugs. The effect of exposure on whether or not an adolescent starts taking drugs (total drugs–binary) indicates that those not exposed to maternal cigarette smoking are 1.6 times more likely never to use drugs

Table S1 Exclusion criteria in the Saguenay Youth Study (SYS) and in the Northern Finland Birth Cohort 1986 (NFBC 1986).

Table S2 Multivariate linear regression models predicting total drug taking. PEMCS = prenatal exposure to maternal cigarette smoking.