



Published in final edited form as:

Twin Res Hum Genet. 2010 December ; 13(6): 550–558. doi:10.1375/twin.13.6.550.

Externalizing Behaviors and Cigarette Smoking as Predictors for Use of Illicit Drugs: A Longitudinal Study Among Finnish Adolescent Twins

Tellervo Korhonen^{1,2}, Esko Levälahti², Danielle M. Dick³, Lea Pulkkinen⁴, Richard J. Rose⁵, Jaakko Kaprio^{1,2,6}, and Anja C. Huizink^{7,8}

¹Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Finland ²Department of Public Health, University of Helsinki, Finland ³Virginia Institute for Psychiatric and Behavioral Genetics and Department of Psychiatry, Virginia Commonwealth University, United States ⁴Department of Psychology, University of Jyväskylä, Finland ⁵Department of Psychological and Brain Sciences, Indiana University, United States ⁶Institute for Molecular Medicine, University of Helsinki, Finland ⁷Department of Child and Adolescent Psychiatry, Erasmus Medical Center and Research Institute of Child Development and Education, University of Amsterdam, the Netherlands ⁸IVO, Addiction Research Institute, Rotterdam, the Netherlands

Abstract

We examined whether externalizing problem behaviors (hyperactivity–impulsivity, aggressiveness, and inattention) predict illicit drug use independently, or whether their associations with drug use are mediated through cigarette smoking. We used a prospective longitudinal design within the *FinnTwin12-17* study among Finnish adolescents with baseline at age 12 and follow-up surveys at ages 14 and 17. Path models were conducted with *Mplus* and included 1992 boys and 2123 girls. The outcome was self-reported ever use of cannabis or other illicit drugs at age 17. The predictors were: externalizing behaviors (hyperactivity–impulsivity, aggressiveness, and inattention) assessed by teachers and parents (age 12) and self-reported cigarette smoking (age 14). The findings differed across behavior studied. The association of hyperactivity–impulsivity with drug use was mostly mediated through earlier cigarette smoking. Concerning aggressiveness and inattention, the results were different among girls than boys. Among girls no significant mediation occurred, whereas among boys more consistent evidence on mediation was seen. Consistently in all models, the direct association of early cigarette smoking on drug use was strong and highly significant. We conclude that the associations of externalizing problem behaviors with illicit drug use are partially mediated through cigarette smoking. Although interventions targeting externalizing problem behaviors may protect adolescents from early onset smoking and subsequently experimenting with drugs, interventions to prevent cigarette smoking initiation are also important in reducing risk of later drug use.

Keywords

externalizing behavior; hyperactivity-impulsivity; aggressiveness; inattention; cigarette smoking; tobacco; cannabis; illicit drugs; adolescents

Address for correspondence: Tellervo Korhonen, University of Helsinki, Department of Public Health, P.O. Box 41, 00014 Helsinki, Finland. tellervo.korhonen@helsinki.fi.

Declarations of Interest

None.

Use of illicit drugs such as cannabis has important health and social consequences (World Health Organization, 2004). The search for determinants predicting illicit drug use has led researchers to examine behavioral problems, such as externalizing behaviors (Kreek et al., 2005; White et al., 2001). Different dimensions of externalizing behavior may have specific mechanisms explaining vulnerability for substance use. Hyperactivity and impulsivity are correlated with novelty seeking (Zuckerman, 1993) which could lead to experimenting with a range of substances in adolescence. Hyperactivity-impulsivity problems were indeed associated with progression from non-smoking in adolescence to regular cigarette smoking in young adulthood (Fuemmeler et al., 2007) but not among college students (Stoltenberg et al., 2008). Hyperactivity-impulsivity problems are associated also with cannabis abuse (Elkins et al., 2007). Aggressiveness is more correlated with affiliation to delinquent and substance using peers (Fite et al., 2008), increasing access to drugs and offering substance using role models. The association of aggressiveness with tobacco and cannabis use has remained strong and independent in adjusted analyses (Ernst et al., 2006).

Inattention problems may have their own specific mechanisms explaining substance use. Adolescents with inattention problems might initiate stimulant use to improve their ability to concentrate (Tercyak et al., 2002). Here, cigarette smoking could be motivated by nicotine's cognitive-enhancing effects (Potter & Newhouse, 2004), as supported by Finnish data showing that inattentiveness in childhood predicted experimental and regular smoking in adolescence (Barman et al., 2004) and by an American study reporting that earlier onset of cigarette smoking among adolescents was associated with ADHD (Molina & Pelham, 2003). Moreover, interventions to reduce ADHD symptoms protected children from early cigarette smoking onset (Huizink et al., 2009) and prevented the development of substance use disorders (SUD) (Wilson & Levin, 2005). However, Molina and Pelham (2003) did not observe a significant ADHD association on cannabis use onset. Thus, in contrast to associations of inattention with cigarette smoking, those associations with cannabis use are not clear (Elkins et al., 2007; Korhonen et al., 2008). This leads to hypothesize that inattention as a risk for cigarette smoking could be explained by self-medication but this would not be true for the association between inattention and cannabis use. Finally, early onset cigarette smoking is an established risk factor for illicit drug use (Gilvarry, 2000; Kandel & Yamaguchi, 1993; Korhonen et al., 2008; Vega & Gil, 2005).

In summary, the associations of externalizing problem behaviors and cigarette smoking on drug use initiation as such are well documented. In order to further explore complex associations of externalizing problem behaviors and cigarette smoking on drug use initiation, we recognize several conceptual approaches. First, the gateway hypothesis suggests a causal link from use of licit (tobacco) to illicit (drugs) substances (Kandel & Yamaguchi, 2002). In this context, there is new evidence from animal studies, indicating that earlier exposure to nicotine may sensitize dopaminergic systems to other stronger drugs (Vihavainen et al., 2008). An alternative view postulates that early onset cigarette smoking is perhaps the first expression of vulnerability to substance use. By inhalation of nicotine, the step towards other drug use may be enhanced. Here, the shared route of administration may play an important role and this may represent a physiological adaptation of the aerorepiratory system (Agrawal & Lynskey, 2009).

Only a few earlier studies have longitudinally explored interplay between behavioral problems and cigarette smoking in influencing illicit drug use. Hayatbakhsh and co-authors (2008) investigated the association between externalizing behavior and cannabis use disorders (CUDs). The CUDs were assessed at age 21 and externalizing behavior at ages 5 and 14. Children with 'childhood-onset-persistent' or 'adolescent-onset' externalizing behavior had a 2.5-fold risk of CUD as young adults. However, cigarette smoking at 14

years partially mediated that link between externalizing behavior and CUD. A case-control family study (Biederman et al., 2006) demonstrated moderation, where the association of cigarette smoking with drug use was particularly robust in the youth with ADHD.

Our central study question was whether externalizing behavior and cigarette smoking are independent predictors of illicit drug use, studied in a population where cannabis is the main illicit drug used during adolescence. The specific objective was to investigate prospectively whether the associations of hyperactivity-impulsivity, aggressiveness, and inattention with illicit drug use are mediated through cigarette smoking. Further, studies are lacking that describe whether different dimensions of externalizing behavior have a similar role in the process of transition from cigarette smoking to use of illicit drugs. Based on earlier literature, we hypothesized that hyperactivity-impulsivity leads to an increased risk of experimenting with several substances in adolescence, and therefore, cigarette smoking could mediate its association with drug use. In contrast, aggression is hypothesized to lead to deviant behaviors in general. Thus, we expect it to show a more independent association with drug use. The role of inattention motivating cigarette smoking could be explained via stimulation self-medication, which however may not be that mechanism for cannabis use. Finally, because boys usually score higher in externalizing behaviors than girls, we utilized our data to conduct sex-specific analyses.

Method

Sample

This investigation was based on longitudinal data of the *FinnTwin12-17* study, started in 1994 to examine genetic and environmental determinants of precursors of health-related behaviors in initially 10- to 11-year-old twins (born 1983–1987). The study targeted five consecutive and complete birth cohorts of about 5600 Finnish twins including questionnaire assessments of both twins and about 5000 parents at baseline in the year before the twins reach age 12 (87% participation rate). The following spring the twins' parents and classroom teachers rated the behavior of the twins, as described elsewhere in detail (Kaprio et al., 2002; Pulkkinen et al., 1999). There was follow-up of all twins at ages 14 (1997–2001) and 17.5 (2000–2005). The study protocol was approved by the IRB of the Indiana University and the Ethical Committee of the University of Helsinki. The parents provided written informed consent for participation (Kaprio et al., 2002; Kaprio, 2006).

At first follow-up mean age was 14.1 years. The response rate was 88% (4740 questionnaires returned out of 5362 mailed). Information on cigarette smoking initiation was used from this survey. At second follow-up at age 17.5, a questionnaire provided information on illicit drug use, as well as concomitant behavioral assessments. In all, 4236 questionnaires were returned out of 4594 mailed (response rate 92.2% for those participating in earlier questionnaires).

Among those 4138 adolescents participating in all three surveys, data on illicit drugs use at age 17.5 were available from 4129 individuals (1997 male and 2132 female). Although number of individuals with complete data on behavioral assessment scales varied 1755–1914 in boys and 1864–2023 in girls, some missing data were allowed in the path models, which included total of 4115 subjects (1992 boys and 2123 girls). Thus, the final sample of these analyses represented 99% of the sample participating three surveys of the *FinnTwin12-17* study.

Measures

Drug Use—Self-reported ever use of cannabis or other illicit drugs at age 17.5 was assessed with the item ‘Have you ever tried or used drugs, such as hashish, something to sniff, or other drugs or substances that would make you feel “intoxicated”?’ The options were: 1 = *I Have never tried or used*; 2 = *1–3 times*; 3 = *4–9*; 4 = *10–19*, and 5 = *20 times or more*. For the analyses of this study the outcome was re-coded to be a dichotomous variable, that is, 1 = *Never used* and 2 = *Ever used* (all categories with any use).

Externalizing Problem Behaviors—Among behavioral problems we considered *externalizing behavior*, such as *aggressiveness* and symptoms of Attention Deficit Hyperactivity Disorder (ADHD), that is, *hyperactivity—impulsivity and inattention* (White et al., 2001). The Multidimensional Peer Nomination Inventory (MPNI) Teacher and Parental Forms were used to collect data on teacher and parental ratings on the child’s behavior at age 12. Based on factor analysis conducted in these adolescent data, validity and reliability being reported in detail elsewhere (Pulkkinen et al., 1999), three main factors were extracted and the scales were formed, covering a wide spectrum of externalizing and internalizing behaviors, accordingly. Three scales, that is, those for aggression, hyperactivity–impulsivity, and inattention formed a factor for externalizing problem behaviors. Scale reliability studied using coefficients alpha varied for teacher scales 0.80–0.90 in girls and 0.84–0.94 in boys, whereas for parental scales 0.62–0.75 and 0.66–0.82, respectively (Pulkkinen et al., 1999). The teacher and parental ratings had moderate correlations for hyperactivity–impulsivity ($r = 0.42$ for boys, $r = 0.34$ for girls) and inattention ($r = 0.47$, $r = 0.41$). However the correlations for aggression were clearly smaller ($r = 0.27$, $r = 0.21$), leading us to use those teacher and parental ratings as separate variables (mean scores) in the path models.

Cigarette Smoking—Cigarette smoking was assessed at the age 14 survey. This was based on the question: ‘Have you ever smoked cigarettes or tried cigarette smoking (no/yes)’. Ever smoking in the present analyses was defined as a dichotomy, separating those who had ever smoked at least one cigarette by the age of 14 from those who had not smoked cigarettes at all.

Statistical Analyses

Preliminary Analyses—As preliminary analysis we conducted logistic regressions using the Stata statistical package, version 9.2 (StataCorp., 2005) to test the assumptions of mediation model. We considered twins as individuals but accounted statistically for twinship. We used robust estimators of variance and the cluster option when estimating standard errors (Williams, 2000). We adjusted all analyses for exact age at the time of outcome measurement. According to these preliminary analyses, all problem behaviors as such were initially associated both with cigarette smoking and with illicit drug use, while smoking initiation, in turn, was associated with drug use (data not shown). However, these associations were tested formally with path modeling where all paths were simultaneously included in the model.

Path Modeling—Mediation models for initiation of illicit drugs, cigarette smoking and ratings for problem behaviors were performed using robust maximum likelihood estimation method with Monte Carlo-integration and assuming logit link (Muthén & Muthén, 1998–2007). The model shown in Figure 1 tested whether cigarette smoking at age 14 mediates the association of each problem behavior assessed separately by teachers and parents at age 12 with drug use at age 17.5. To establish mediation, the following conditions were considered: First, the independent variable (externalizing behavior) must affect the mediator (cigarette smoking). Second, that independent variable must affect the dependent variable

(illicit drug use). Third, the mediator must affect the dependent variable when the independent variable is taken into account (MacKinnon et al., 2007). Thus, we considered significant mediation if the direct path coefficient became non-significant — even if the parameter value was not zero. Further, if the direct path coefficient dropped but remained statistically significant, there would be evidence for partial mediation if the indirect path would be significant at the same time. Considering statistical significance, the 95% confidence intervals (CI) for each point estimate and the p values for two-tailed tests are given. Path modeling was conducted using the *Mplus* software (version 5) (Muthén & Muthén, 1998–2007). We adjusted all analyses for exact age at the time of outcome measurement and accounted for nesting of twins.

Results

Descriptive Results

The mean scores and standard deviations for the age 12 externalizing problem behaviors among boys and girls are shown in Table 1. By 14 years of age, 41.8% of boys and 41.5% of girls had ever smoked at least one cigarette. By age 17.5, 12.1% of boys while 14.5% of girls had used cannabis or other illicit drugs at least once. Among boys 7.8% had used 1–3 times, 1.5% 4–9, 1.0% 10–19 and 1.8% 20 times or more, whereas the rates for girls were 9.2%, 2.7%, 1.3% and 1.3%, respectively ($p=0.036$; adjusted for correlated twinship).

Results of the Path Models

Path model analyses were applied to test formally how the data support mediation among the predictors of illicit drugs use. According to Figure 1, four paths have been estimated in each model; the associations of behavioral problems with cigarette smoking (β_{st}/β_{sp}), the associations of cigarette smoking with drugs (β_{ds}), as well as the direct (β_{dt}/β_{dp}) and indirect ($\beta_{st}/\beta_{sp} * \beta_{ds}$) associations of behavioral problems with drugs. These estimates are simultaneously controlled for each other. The regression coefficients (β) and odds ratios (OR) based on those mediation models conducted separately among boys and girls are shown in Tables 2–4.

Hyperactivity–Impulsivity—Among boys cigarette smoking mediated the relationship between hyperactivity-impulsivity and drug use. The direct independent association of parent rated hyperactivity-impulsivity with drugs did not remain significant ($\beta_{dp} = 0.17$; 95% CI $-0.11, 0.46$; $p = .222$), when the association of cigarette smoking was simultaneously taken into account. However, no full mediation occurred if teacher ratings were considered, as there was still direct association left ($\beta_{dt} = 0.25$; 95% CI $0.04, 0.46$; $p = .018$). Among girls the teacher-rated hyperactivity-impulsivity was mediated by cigarette smoking ($\beta_{dt} = 0.18$; 95% CI $-0.06, 0.42$; $p = .149$), while no full mediation occurred if parental ratings were considered, as there was still direct association left ($\beta_{dp} = 0.28$; 95% CI $0.01, 0.56$; $p = .042$) (Table 2).

Aggressiveness—Among boys cigarette smoking mediated the relationship between aggressiveness and drug use. The direct independent association of parent rated aggression with drugs did not remain significant ($\beta_{dp} = 0.28$; 95% CI $-0.09, 0.64$; $p = .135$), when the association of cigarette smoking was simultaneously taken into account. However, such mediation was not complete if teacher ratings were considered, because the direct association remained significant ($\beta_{dt} = 0.30$; 95% CI $0.08, 0.53$; $p = .008$). Among girls neither the teacher-rated nor the parent rated aggressiveness was mediated by cigarette smoking, as there was still significant direct association for both ratings ($\beta_{dt} = 0.29$; 95% CI $0.05, 0.30$; $p = .017$; $\beta_{dp} = 0.57$; 95% CI $0.24, 0.90$; $p = .001$) (Table 3).

Inattentiveness—Among boys cigarette smoking mediated the relationship between inattention and drug use, no matter if the teacher or parent ratings were considered. The direct independent association of teacher rated inattention with drugs did not remain significant ($\beta_{dt} = 0.17$; 95% CI $-0.08, 0.41$; $p = .177$), nor did the association of respective parental rated behavior ($\beta_{dp} = 0.21$; 95% CI $-0.07, 0.49$; $p = .139$), when the association of cigarette smoking was simultaneously taken into account. Among girls no full mediation was seen, the direct associations remaining significant for both teacher ($\beta_{dt} = 0.39$; 95% CI $0.16, 0.62$; $p = .001$) and parental ratings ($\beta_{dp} = 0.46$; 95% CI $0.18, 0.74$; $p = .001$) (Table 4).

Discussion

This longitudinal study explored whether early onset cigarette smoking mediates the association between externalizing behaviors and illicit drugs use. To summarize the results of the mediation models where all paths were simultaneously estimated, the association of hyperactivity–impulsivity was mostly mediated through cigarette smoking. Concerning aggressiveness and inattention, the results differed by sex. Among girls no significant mediation occurred, whereas among boys more consistent evidence on mediation was seen. Concerning all behavioral problems and both sexes, one assumption of a mediation model existed; i.e. that the path from behavioral problem to cigarette smoking (β_{st}/β_{sp}) was significant. In all models the direct association of cigarette smoking with drugs (β_{ds}) was strong and significant. Also consistently, the indirect associations of behavioral problems, i.e. the paths from behaviors to drug use via cigarette smoking ($\beta_{st}/\beta_{sp} * \beta_{ds}$) were very significant, even if no significant mediation existed.

Many of our findings support the hypothesis that children with externalizing behavior in early adolescence initiate use of tobacco first, and then progress to illicit drugs use (King et al., 2004). According to this hypothesis, externalizing behavior in childhood is a root cause while cigarette smoking is seen as intermediate consequence that lead on to drug use. This has been previously shown in a sample of male and female adolescents, using different instruments to assess externalizing behaviors (Hayatbakhsh et al., 2008). Similarly to our findings, a recent population-based cohort study among Dutch adolescents suggested that the association of DSM-IV externalizing behavior problems with cannabis use were inconsistent across informants and sexes being mediated by earlier cigarette smoking in many cases (Korhonen et al., 2010). Despite methodological differences in behavior assessments between our study and these studies, we replicated here several of those earlier findings.

Based on our findings, we suggest that behavioral dimensions may have their specific relationships with substance use. For example, in line with our study, Ernst and colleagues (2006) reported that impulsivity was associated with a licit substance, alcohol, rather than with illicit drugs. Compared to our study, examining tobacco instead of alcohol, those results seem to be consistent, because we observed hyperactivity-impulsivity as a highly significant predictor of cigarette smoking, but the independent associations with illicit drugs were inconsistent and clearly weaker. Impulsivity might interfere with adolescent's understanding of the long-term consequences of the substances they are about to experiment with (Wilson & Levin, 2005). Thus, because tobacco as licit substance is more easily available and awareness of the addictive power of nicotine (DiFranza et al., 2007) is still limited, adolescents with high levels of hyperactivity-impulsivity are especially vulnerable first to cigarette smoking and subsequently to experimenting with illicit drugs. A further question is which neurobiological mechanisms could explain our findings that cigarette smoking mediated the associations of hyperactivity-impulsivity with drugs. There is evidence that the dopamine receptor system is associated with many behavioral outcomes, that is, novelty-seeking and compulsive behaviors, as well as with use of psychoactive

substances, such as nicotine and cannabinoids (World Health Organization, 2004). Another neurobiological explanation might be a synapse mediation model involving various specific genes interacting with nicotine exposure in the association with ADHD (Todd & Neuman, 2007).

Weakest evidence on mediation through tobacco was seen with aggressiveness, because in three out of four models the direct associations between aggressiveness and illicit drugs remained significant after cigarette smoking was taken into account. Aggressiveness may be related to several antisocial and conduct behaviors. Aggressiveness places adolescents at risk for drug use initiation because such behavior alienates them from normative youth groups while fostering affiliation with more deviant teenagers (Fite et al., 2008). In line with our finding, relatively independent associations of aggressiveness with cannabis use but also with severity of multi-drug use even after multiple adjustments have been reported earlier (Ernst et al., 2006). Here the motivators of illicit drug use may not be so clearly mediated through use of licit substances — be it tobacco or alcohol — but rather through various illegal behaviors and delinquent peers (Fite et al., 2008).

Finally, the role of inattention as a predictor of drug use seems to be different among boys than among girls. While self-medication as a mechanism could be either stimulation or relaxation, different substances may have different roles in this play. Adolescents with inattention problems may perceive need to try substances which stimulate (nicotine) or relax (cannabinoids) them. Among boys, where mediation through cigarette smoking occurred, tobacco may be the first substance more easily available at an early age to provide such self-medication. Among girls, however, there was no mediation through tobacco. Thus, the mechanism may be different. It is possible, that especially among girls the influence of inattention is reflecting early anxiety symptoms which in turn, may motivate cannabis use via relaxing expectations. However, whether this mechanism is actually different for girls than boys needs further investigation.

In all, it seems that the potential mechanisms explaining our results are very complicated and beyond this study. The mechanisms vary depending on the type of behavioral problem and on the type of substance studied — for example, nicotine as a stimulator or cannabis as a relaxant. Here, we could refer to frontal networks in adolescents because in that age there is relative imbalance between the networks seen as appetitive and those seen as inhibitory (Chambers et al., 2003; Schepis et al., 2008).

Strengths

This large, prospective study used a longitudinal design including a timely order of assessments on problem behaviors, cigarette smoking, and use of illicit drugs. The methodological strengths include the use of a well-designed longitudinal study with high retention over follow-up and tests of mediation taking into account the developmental emergence of specific problem behaviors. We assessed externalizing behavior at age 12 by using multiple informants — that is, teachers and parents — as a source of information, which is another strength. Concerning externalizing behaviors, the teacher assessments may be more accurate than the parental ones, because teachers have more experience of observing a wide range of behaviors. Cigarette smoking was assessed at age 14 by asking whether the subject had ever smoked or tried cigarettes. Finnish twin data suggest that most individuals who initiate smoking in adolescence have done it before age 16 (Rose et al., 2008). Similarly, the Finnish national data showed that most experimental smoking is initiated in ages 11–15 (Rimpelä et al., 2006). In our study sample 42% had ever smoked by age 14, suggesting that our time point was appropriate.

Limitations

We recognize that our cigarette smoking measure used a low threshold — whether one ever tried. This is a limitation to consider in interpreting the findings because it does not permit an examination of whether experimentation, repeated use, or both account for such mediation. This might be an important distinction for future research. Concerning the outcome measure, the question included, in addition to cannabis, ‘something to sniff, or other drugs or substances that would make you feel intoxicated’. Recent statistics in Finland (Virtanen & Sjöberg, 2006) indicate that the most common illicit drug used in Finland is actually cannabis. Nevertheless, we could not disentangle what proportion was cannabis use only and what proportion was mixed use of cannabis and other illicit drugs. Ideally a multi-item measure about use of specific substances; for example, cannabis, cocaine, ecstasy, and so on would allow a more detailed and comprehensive assessment of the relationship between problem behaviors and use of specific illicit substances, and how cigarette smoking impacts these relations. Further, we did not assess use of illicit drugs at age 14. However, based on the intensively studied subsample we know from the interview at age 14 that about 1% had experimented with illicit drugs at that age (unpublished result). Thus, all cases from 14 to 17 are virtually all new. Finally, we recognize as a limitation that both cigarette and drug use was based on self-reports that were not biochemically verified.

Conclusions

There may be specific mechanisms in the interplay between the dimensions of problem behaviors and cigarette smoking in predicting illicit drug use. The associations of externalizing problem behaviors with drugs seem to be at least partially mediated through cigarette smoking. Although interventions targeting externalizing problem behaviors may protect adolescents from early onset smoking and then later experimenting with drugs, interventions to prevent or delay smoking initiation are also important in reducing risk of later drug use.

Acknowledgments

This work was supported in part by the Academy of Finland Research Program on Substance Use and Addictions (118555 to J.K.), the Academy of Finland (100499; 205585 to J.K.), the Academy of Finland Center of Excellence in Complex Disease Genetics (to J.K.), and by The National Institutes of Alcohol Abuse & Alcoholism (NIAAA), USA (AA-12502; AA-09203; AA-00145 to R.J.R.; AA015416, to D.M.D.). Work for the current paper was funded by the NWO — Vidi scheme, Netherlands (452–06–004 to A.C.H., T.K. and E.L).

References

- Agrawal A, Lynskey MT. Tobacco and cannabis co-occurrence: Does route of administration matter? *Drug and Alcohol Dependence*. 2009; 99:240–247. [PubMed: 18926646]
- Barman SK, Pulkkinen L, Kaprio J, Rose RJ. Inattentiveness, parental smoking and adolescent smoking initiation. *Addiction*. 2004; 99:1049–1061. [PubMed: 15265102]
- Biederman J, Monuteaux MC, Mick E, Wilens TE, Fontanella JA, Poetzl KM, Kirk T, Masse J, Faraone SV. Is cigarette smoking a gateway to alcohol and illicit drug use disorders? A study of youths with and without attention deficit hyperactivity disorder. *Biological Psychiatry*. 2006; 59:258–264. [PubMed: 16154546]
- Chambers MS, Atack JR, Broughton HB, Collinson N, Cook S, Dawson GR, Hobbs SC, Marshall G, Maubach KA, Pillai GV, Reeve AJ, MacLeod AM. Identification of a novel, selective GABA(A) alpha5 receptor inverse agonist which enhances cognition. *Journal of Medicinal Chemistry*. 2003; 46:2227–2240. [PubMed: 12747794]
- DiFranza JR, Savageau JA, Fletcher K, O’Loughlin J, Pbert L, Ockene JK, McNeill AD, Hazelton J, Friedman K, Dussault G, Wood C, Wellman RJ. Symptoms of tobacco dependence after brief intermittent use: The development and assessment of nicotine dependence in youth-2 study. *Archives of Pediatrics & Adolescent Medicine*. 2007; 161:704–710. [PubMed: 17606835]

- Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Archives of General Psychiatry*. 2007; 64:1145–1152. [PubMed: 17909126]
- Ernst M, Luckenbaugh DA, Moolchan ET, Leff MK, Allen R, Eshel N, London ED, Kimes A. Behavioral predictors of substance-use initiation in adolescents with and without attention-deficit/hyperactivity disorder. *Pediatrics*. 2006; 117:2030–2039. [PubMed: 16740845]
- Fite PJ, Colder CR, Lochman JE, Wells KC. The relation between childhood proactive and reactive aggression and substance use initiation. *Journal of Abnormal Child Psychology*. 2008; 36(2):261–271. [PubMed: 17823863]
- Fuemmeler BF, Kollins SH, McClernon FJ. Attention deficit hyperactivity disorder symptoms predict nicotine dependence and progression to regular smoking from adolescence to young adulthood. *Journal of Pediatric Psychology*. 2007; 32:1203–1213. [PubMed: 17602186]
- Gilvarry E. Substance abuse in young people. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. 2000; 41:55–80.
- Hayatbakhsh MR, McGee TR, Bor W, Najman JM, Jamrozik K, Mamun AA. Child and adolescent externalizing behavior and cannabis use disorders in early adulthood: An Australian prospective birth cohort study. *Addictive Behaviors*. 2008; 33:422–438. [PubMed: 17996381]
- Huizink AC, van Lier PA, Crijnen AA. Attention deficit hyperactivity disorder symptoms mediate early-onset smoking. *European Addiction Research*. 2009; 15:1–9. [PubMed: 19052457]
- Kandel D, Yamaguchi K. From beer to crack: Developmental patterns of drug involvement. *American Journal of Public Health*. 1993; 83:851–855. [PubMed: 8498623]
- Kandel, DB.; Yamaguchi, K. Stages of drug involvement in the U.S. population. In: Kandel, DB., editor. *Stages and pathways of drug involvement: Examining the gateway hypothesis*. New York: Cambridge University Press; 2002. p. 65–89.
- Kaprio J. Twin studies in Finland 2006. *Twin Research and Human Genetics*. 2006; 9:772–777. [PubMed: 17254406]
- Kaprio J, Pulkkinen L, Rose RJ. Genetic and environmental factors in health-related behaviors: Studies on Finnish twins and twin families. *Twin Research*. 2002; 5:366–371. [PubMed: 12537860]
- King SM, Iacono WG, McGue M. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction*. 2004; 99:1548–1559. [PubMed: 15585046]
- Korhonen T, Prince van Leeuwen A, Reijneveld SA, Ormel J, Verhulst FC, Huizink AC. Externalizing behavior problems and cigarette smoking as predictors of cannabis use: The TRAILS study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:61–69. [PubMed: 20215927]
- Korhonen T, Huizink AC, Dick DM, Pulkkinen L, Rose RJ, Kaprio J. Role of individual, peer and family factors in the use of cannabis and other illicit drugs: A longitudinal analysis among Finnish adolescent twins. *Drug and Alcohol Dependence*. 2008; 97:33–43. [PubMed: 18455885]
- Kreek MJ, Nielsen DA, Butelman ER, LaForge KS. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscience*. 2005; 8:1450–1457.
- MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. *Annual Review of Psychology*. 2007; 58:593–614.
- Molina BS, Pelham WE Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *Journal of Abnormal Psychology*. 2003; 112:497–507. [PubMed: 12943028]
- Muthén, LK.; Muthén, BO. *Mplus user's guide*. 5. Los Angeles, CA: Muthén & Muthén; 1998–2007.
- Potter AS, Newhouse PA. Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology*. 2004; 176:182–194. [PubMed: 15083253]
- Pulkkinen L, Kaprio J, Rose RJ. Peers, teachers and parents as assessors of the behavioral and emotional problems of twins and their adjustment: The multidimensional peer nomination inventory. *Twin Research*. 1999; 2:274–285. [PubMed: 10723806]
- Rimpelä, A.; Rainio, S.; Pere, L.; Lintonen, TP. *Use of tobacco products, alcohol use and exposure to drugs in 1977–2005*. Helsinki, Finland: Ministry of Social Affairs and Health; 2006.

- Rose, RJ.; Boms, U.; Korhonen, T.; Dick, DM.; Kaprio, J. Genetics of smoking behavior. In: Kim, YK., editor. Handbook of behavior genetics. New York: Springer; 2008. p. 411-432.
- Schepis TS, Adinoff B, Rao U. Neurobiological processes in adolescent addictive disorders. The American Journal on Addictions/American Academy of Psychiatrists in Alcoholism and Addictions. 2008; 17:6–23. [PubMed: 18214718]
- StataCorp. Stata statistical software. College Station, TX: Author; 2005.
- Stoltenberg SF, Batien BD, Birgenheir DG. Does gender moderate associations among impulsivity and health-risk behaviors? Addictive Behaviors. 2008; 33:252–265. [PubMed: 17913380]
- Tercyak KP, Lerman C, Audrain J. Association of attention-deficit/hyperactivity disorder symptoms with levels of cigarette smoking in a community sample of adolescents. Journal of the American Academy of Child and Adolescent Psychiatry. 2002; 41:799–805. [PubMed: 12108804]
- Todd RD, Neuman RJ. Gene-environment interactions in the development of combined type ADHD: Evidence for a synapse-based model. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics. 2007; 144B:971–975.
- Vega WA, Gil AG. Revisiting drug progression: Long-range effects of early tobacco use. Addiction. 2005; 100:1358–1369. [PubMed: 16128725]
- Vihavainen T, Relander TR, Leiviska R, Airavaara M, Tuominen RK, Ahtee L, Piepponen TP. Chronic nicotine modifies the effects of morphine on extracellular striatal dopamine and ventral tegmental GABA. Journal of Neurochemistry. 2008; 107:844–854. [PubMed: 18786163]
- Virtanen, A.; Sjöberg, S. 2005 national report to the EMCDDA by the Finnish national focal point. Helsinki: STAKES; 2006. Finland — drug situation 2005.
- White HR, Xie M, Thompson W, Loeber R, Stouthamer-Loeber M. Psychopathology as a predictor of adolescent drug use trajectories. Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors. 2001; 15:210–218. [PubMed: 11563798]
- Williams RL. A note on robust variance estimation for cluster-correlated data. Biometrics. 2000; 56:645–646. [PubMed: 10877330]
- Wilson JJ, Levin FR. Attention-deficit/hyperactivity disorder and early-onset substance use disorders. Journal of Child and Adolescent Psychopharmacology. 2005; 15:751–763. [PubMed: 16262592]
- World Health Organization. Neuroscience of psychoactive substance use and dependence. Geneva: World Health Organization; 2004.
- Zuckerman M. *P*-impulsive sensation seeking and its behavioral, psychophysiological and biochemical correlates. Neuropsychobiology. 1993; 28:30–36. [PubMed: 8255407]

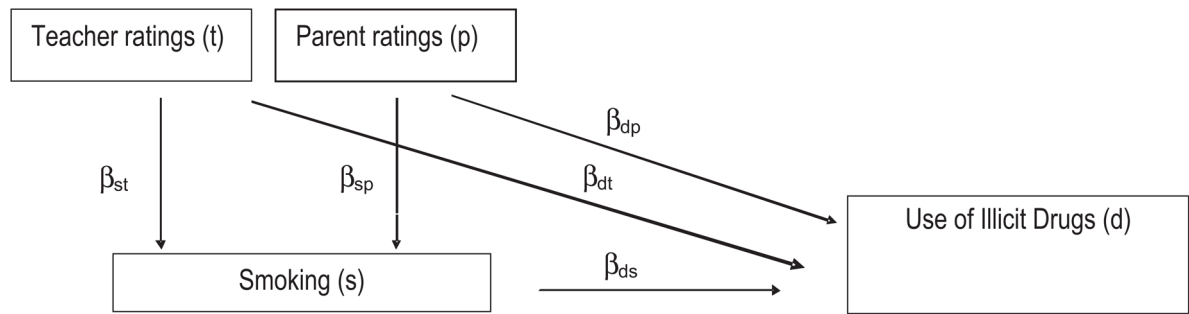


Figure 1.

Mediation model. Testing of mediation effect of ever smoking at age of 14 (s) on the association between externalizing behavioral problems at age of 12 (t = teacher ratings, p = parental ratings) and use of illicit drugs at age of 17 (d) (β = path coefficient).

Table 1

The Mean Symptom Scores (Standard Deviations) of Problem Behaviors Among Boys and Girls^a: Teacher and Parental Ratings at Age 12

	Teacher ratings		Parental ratings	
	M	SD	M	SD
Boys	n = 1755		n = 1914	
Hyperactivity-impulsivity	0.89	0.78	0.81	0.55
Aggressiveness	0.71	0.66	0.62	0.42
Inattention	0.89	0.72	0.80	0.52
Girls	n = 1864		n = 2023	
Hyperactivity-impulsivity	0.45	0.55	0.64	0.55
Aggressiveness	0.49	0.55	0.54	0.39
Inattention	0.48	0.55	0.57	0.46

Note:

^a *p* value of gender difference < .001 for all scores (based on t test adjusted for correlated twinship)

M: mean; SD: standard deviation

Table 2

Mediation Models for Hyperactivity-Impulsivity: Regression Coefficients (β) and Odds Ratios (OR) with 95% Confidence Intervals in Parentheses

	Hyperactivity-Impulsivity		Direct effect: Hyperactivity-Impulsivity \rightarrow Drug use		Hyperactivity-Impulsivity \rightarrow Smoking		Smoking \rightarrow Drug use		Indirect effect: Hyperactivity-Impulsivity \rightarrow Drug use	
	β_{ur}/β_{dp}	OR	β_{sr}/β_{sp}	OR	β_{ds}	OR	$\beta_{sr}/\beta_{sp} * \beta_{ds}$	OR	$\beta_{sr}/\beta_{sp} * \beta_{ds}$	OR
Boys ($n = 1992$)										
Teacher ratings	0.25 (0.04, 0.46)	1.28 (1.04, 1.58)	0.54 (0.39, 0.68)	1.71 (1.48, 1.97)	1.73 (1.38, 2.08)	5.67 (3.99, 8.04)	0.93 (0.62, 1.24)	2.53 (1.74, 3.32)		
	($p = .018$)		($p < .001$)		($p < .001$)		($p < .001$)		($p < .001$)	
Parental ratings	0.17 (-0.11, 0.46)	1.19 (0.90, 1.58)	0.52 (0.34, 0.70)	1.68 (1.40, 2.02)	1.78 (1.44, 2.12)	5.95 (4.23, 8.36)	0.93 (0.56, 1.29)	2.52 (1.60, 3.45)		
	($p = .222$)		($p < .001$)		($p < .001$)		($p < .001$)		($p < .001$)	
Girls ($n = 2123$)										
Teacher ratings	0.18 (-0.06, 0.42)	1.20 (0.94, 1.53)	0.83 (0.61, 1.04)	2.29 (1.84, 2.84)	1.82 (1.49, 2.14)	6.15 (4.44, 8.51)	1.50 (1.02, 1.98)	4.50 (2.34, 6.66)		
	($p = .149$)		($p < .001$)		($p < .001$)		($p < .001$)		($p < .001$)	
Parental ratings	0.28 (0.01, 0.56)	1.33 (1.01, 1.75)	0.70 (0.49, 0.91)	2.02 (1.63, 2.40)	1.82 (1.50, 2.13)	6.15 (4.47, 8.46)	1.27 (0.83, 1.72)	3.58 (1.99, 5.17)		
	($p = .042$)		($p < .001$)		($p < .001$)		($p < .001$)		($p < .001$)	

Table 3

Mediation Models for Aggressiveness: Regression Coefficients (β) and Odds Ratios (OR) with 95% Confidence Intervals in Parentheses

Aggressiveness	Direct effect: Aggressiveness → Drug use		Aggressiveness → Smoking		Smoking → Drug use		Indirect effect: Aggressiveness → Drug use	
	β_{dir}/β_{dp}	OR	β_{dir}/β_{sp}	OR	β_{ds}	OR	$\beta_{dir}/\beta_{sp} * \beta_{ds}$	OR
Boys (n = 1992)								
Teacher ratings	0.30 (0.08, 0.53)	1.35 (1.08, 1.69)	0.61 (0.44, 0.79)	1.85 (1.56, 2.19)	1.73 (1.38, 2.08)	5.65 (3.99, 8.00)	1.06 (0.70, 1.43)	2.90 (1.83, 3.97)
	(<i>p</i> = .008)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	
Parental ratings	0.28 (-0.09, 0.64)	1.32 (0.92, 1.90)	0.74 (0.49, 0.99)	2.09 (1.63, 2.68)	1.78 (1.43, 2.12)	5.91 (4.20, 8.32)	1.31 (0.79, 1.83)	3.71 (1.77, 5.64)
	(<i>p</i> = .135)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	
Girls (n = 2123)								
Teacher ratings	0.29 (0.05, 0.30)	1.35 (1.05, 1.72)	0.98 (0.75, 1.21)	2.65 (2.11, 3.34)	1.78 (1.45, 2.11)	5.92 (4.27, 8.21)	1.74 (1.22, 2.53)	5.67 (2.73, 8.61)
	(<i>p</i> = .017)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	
Parental ratings	0.57 (0.24, 0.90)	1.72 (1.27, 2.47)	0.84 (0.57, 0.84)	2.32 (1.74, 3.04)	1.80 (1.47, 2.12)	6.02 (4.37, 8.30)	1.51 (0.96, 2.07)	4.55 (2.01, 7.71)
	(<i>p</i> = .001)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	

Table 4

Mediation Models for Inattentiveness: Regression Coefficients (β) and Odds Ratios (OR) with 95% Confidence Intervals in Parentheses

Inattentiveness	Direct effect: Inattentiveness → Drug use		Inattentiveness → Smoking		Smoking → Drug use		Indirect effect: Inattentiveness → Drug use	
	β_{dir}/β_{dp}	OR	β_{dir}/β_{sp}	OR	β_{ds}	OR	$\beta_{dir}/\beta_{sp} * \beta_{ds}$	OR
Boys (<i>n</i> = 1992)								
Teacher ratings	0.17 (-0.08, 0.41)	1.18 (0.93, 1.51)	0.52 0.37, 0.67	1.68 (1.44, 1.96)	1.77 (1.42, 2.11)	5.86 (4.14, 8.28)	0.92 (0.60, 1.24)	2.51 (1.70, 3.31)
Parental ratings	0.21 (-0.07, 0.49)	1.24 (0.93, 1.64)	0.60 (0.40, 0.79)	1.82 (1.50, 2.21)	1.78 (1.44, 2.12)	5.93 (4.21, 8.34)	1.07 (0.67, 1.46)	2.91 (1.75, 4.06)
	(<i>p</i> = .177)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	
	(<i>p</i> = .139)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	
Girls (<i>n</i> = 2123)								
Teacher ratings	0.39 (0.16, 0.62)	1.47 (1.17, 1.86)	0.73 (0.52, 0.93)	2.07 (1.69, 2.54)	1.78 (1.46, 2.11)	5.95 (4.32, 8.20)	1.30 (0.87, 1.73)	3.66 (2.08, 5.33)
Parental ratings	0.46 (0.18, 0.74)	1.57 (1.20, 2.10)	0.69 (0.47, 0.91)	1.99 (1.59, 2.48)	1.80 (1.48, 2.12)	6.05 (4.40, 8.32)	1.24 (0.79, 1.69)	3.50 (1.90, 5.00)
	(<i>p</i> = .001)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	
	(<i>p</i> = .001)		(<i>p</i> < .001)		(<i>p</i> < .001)		(<i>p</i> < .001)	