Article

Early Smoking Onset and Risk for Subsequent Nicotine Dependence: A Monozygotic Co-Twin Control Study

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Objective: Early onset of regular smoking is associated with an elevated risk for later nicotine dependence. Whether or not this association is causal is unknown and has substantial public policy implications.

Method: The authors used a monozygotic co-twin control study design. Pairs were selected from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders for discordance in age at onset of regular smoking. Nicotine dependence was measured by the Fagerström Test for Nicotine Dependence and level of craving.

Results: The authors identified 175 male-male and 69 female-female monozygotic twin pairs who differed by at least 2 years in age at onset of regular smoking. During their period of heaviest smoking, the twin who began smoking earlier had significantly higher Fagerström Test scores in both the male-male (Cohen's d=0.20) and female-female twin pairs (d=0.26). Craving for cigarettes when unable to smoke was also higher in the early-onset member in both groups (male pairs, d=0.38; female pairs, d=0.25). The early-onset smoking twin did not differ from the later-onset twin in symptoms of alcohol or cannabis abuse or dependence, current alcohol use, or maximal level of cannabis, sedative, stimulant, or cocaine use.

Conclusions: Controlling for genetic and familial-environmental effects, age at onset of regular smoking predicted level of nicotine dependence. Consistent with the animal literature, these findings suggest that in humans, early nicotine exposure directly increases level of later nicotine dependence. These results should be interpreted in the context of the methodological strengths and limitations of the monozygotic co-twin design.

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Compared with those who start smoking later in life, individuals who begin smoking at a young age are at substantially higher risk for subsequent nicotine dependence (1, 2). This association could arise in two different ways that would have different implications for efforts to prevent nicotine dependence. Early exposure to nicotine could directly increase the risk for later nicotine dependence through the effects of nicotine on the developing human brain. If this is true, then reducing early exposure at a population level should reduce risk for subsequent nicotine dependence and all the disorders to which it predisposes. Alternatively, the association between nicotine dependence and early onset of smoking could arise because both are influenced by the same set of risk factors, which could range from features of the home environment to personality traits. If this is the case, then intervening to reduce early exposure to smoking would have little effect on population rates of nicotine dependence.

The animal literature supports a direct causal effect of early nicotine exposure on subsequent risk for dependence-associated behaviors. Compared with adult rodents, adolescent rodents are more sensitive to the rewarding properties of nicotine and less sensitive to its withdrawal and aversive effects (3–7). This combination may lead to a more rapid acceleration of nicotine intake in adolescence. Furthermore, nicotine exposure in adolescence in rodents has long-lasting effects, increasing both the intake of (8) and tolerance to (7) nicotine in adulthood.

However, other findings suggest that a noncausal association between age at onset of smoking and nicotine dependence is plausible. Both smoking initiation and subsequent nicotine dependence are predicted by low levels of education and high levels of certain personality traits (9). While early onset of alcohol consumption is strongly correlated with later heavy drinking and alcohol dependence (10), several studies have suggested that some or all of that association is not causal (11–13) but rather due to genetic and environmental confounders that have an impact on both age at drinking initiation and subsequent alcohol misuse.

While it would never be ethical to conduct a controlled trial in humans for early-onset compared with late-onset smoking initiation, the question can be addressed in a co-twin control study, one of the human "natural experiments" that can aid in the clarification of causal processes (14, 15). In this study, we examined a sample of male-male monozygotic twin pairs and a sample of female-female monozygotic twin pairs who differed from each other by at least 2 years in the age at which they report first smoking regularly.

We evaluated two hypotheses about the association between adult levels of nicotine dependence and age at onset of smoking, which we term "noncausal" and "causal." If the correlation between onset age for smoking and subsequent levels of nicotine dependence is not causal but rather results from social or temperamental factors acting on both variables, the noncausal hypothesis would predict little association between age at onset of smoking and later nicotine dependence within our monozygotic twin pairs. This is because both members of each pair will be quite similar in their social background and temperament. However, if the observed correlation between age at onset of smoking and later nicotine dependence is causal, then we would predict, even within our closely matched monozygotic pairs, a strong association between age at smoking onset and levels of subsequent nicotine dependence.

We also wished to test for the specificity of this effect. If within our monozygotic twin pairs the early-onset smoking member does have an elevated risk for nicotine dependence, would that be specific to nicotine dependence, or might we also see an elevated risk for use and abuse of, and dependence on, alcohol and level of use of a range of illicit substances?

Method

Participants in this study derived from two interrelated studies of Caucasian same-sex twin pairs who participated in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (16). All subjects were ascertained from the population-based Virginia Twin Registry, which was formed from a systematic review of birth certificates in the Commonwealth of Virginia. Female-female twin pairs born between 1934 and 1974 were eligible if both members responded to a mailed questionnaire in the period 1987–1988. For this study, data were obtained from the third (1992–1995) and fourth (1995–1997) interview waves. Cooperation at the first two waves was in the range of 92%–93% (16); for the third and fourth waves, we succeeded in interviewing 88% and 85%, respectively, of eligible twins. Data on the male-male pairs came from a sample (birth years 1940–1974) initially ascertained directly from registry records containing all twin births; the cooperation rate was 72%. The first interview was completed largely by telephone between 1993 and 1996. The second wave of interviews was conducted between 1994 and 1998, with a response rate of 83%. All the data for these analyses come from the wave 2 data. After an explanation of the research protocol was given, signed informed consent was obtained for face-to-face interviews and verbal consent for telephone interviews. This project was approved by the Office of Research Subjects Protection at Virginia Commonwealth University. Members of a twin pair were always interviewed by different interviewers.

Zygosity was determined by discriminate function analyses using standard twin questions validated against DNA genotyping in 496 pairs (17). The twins' mean age and years of education were 36.3 years (SD=8.2) and 14.3 years (SD=2.2), respectively, at the wave 4 interview of female-female pairs, and 37.0 years (SD=9.1) and 13.6 years (SD=2.6), respectively, at the wave 2 interview of male-male pairs.

Age at onset of regular smoking was assessed by the interview question "How old were you when you began to use tobacco regularly?" Nicotine dependence was assessed by the Fagerström Test for Nicotine Dependence and by an assessment of intensity of craving for the time in participants' lives when they reported smoking most heavily (18). The wording of the item assessing craving was as follows: "During this time when you smoked most heavily, if you didn't smoke for a period of time, how strong would your craving get for another? Would you say very strong, strong, moderate, or hardly any craving?"

Our main statistical analysis was conducted by paired t tests for continuous measures and McNemar chi-square tests for dichotomous variables. We used one-tailed p values, as we had a clear directional hypothesis that the early-onset smoker in each pair would have greater levels of nicotine dependence and other drug use and misuse than his or her later-onset co-twin. For our analyses of maximal illicit substance use, if the twin denied ever trying the substance, they received a score of zero. Effect sizes were estimated using Cohen's d statistic, for which values of 0.2, 0.5, and 0.9 are considered small, medium, and large effects, respectively (19).

A priori, we decided to analyze these pairs separately and consider as positive results that broadly replicated across both samples. The female-female sample was considerably smaller and had less statistical power. Therefore, we analyzed the male-male sample first and then considered a result replicated if the effect size (rather than the p value) was similar in the female-female pairs.

Results

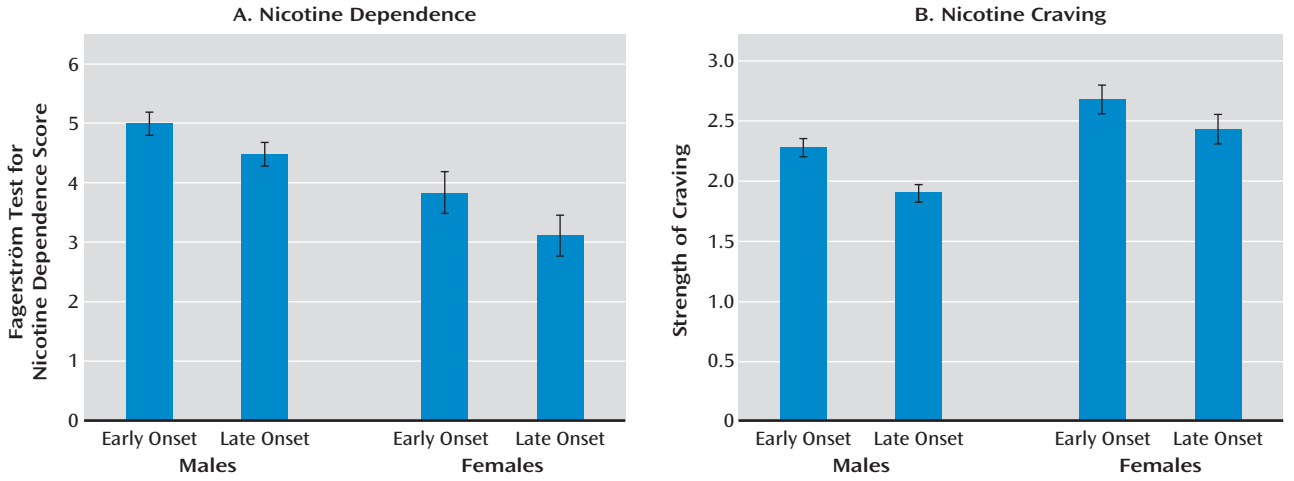
Onset of Regular Smoking and Subsequent Symptoms of Nicotine Dependence

We identified 175 male-male monozygotic twin pairs and 69 monozygotic female-female twin pairs in which the reported age at first regular smoking in the two members differed by at least 2 years. For the male-male pairs, the early-onset smoking member had a mean current age of 36.1 years (SD=8.6). Parallel results for the later-onset smoking member were 36.3 years (SD=8.5). The mean age at onset of regular smoking was 14.8 years (SD=3.1) for the early-onset member and 19.1 years (SD=3.7) for the late-onset member.

For the female-female pairs, the mean age at interview was 36.1 years (SD=7.8) for the early-onset member and 35.9 years (SD=7.8) for the late-onset member. The mean age at onset of regular smoking was 16.3 years (SD=2.6) for the early-onset member and 21.1 years (SD=5.3) for the late-onset member.

The early-onset member reported an earlier age at heaviest smoking than the late-onset member both in males (by a mean of 2.4 years; p=0.0009) and in females (by a mean of 1.5 years; p=0.07). As shown in Figure 1A, during this period of heaviest smoking, the early-onset member had a significantly higher score on the Fagerström Test for Nicotine Dependence than the late-onset member in both the male-male pairs (by a mean of 0.53 points; p=0.004; Cohen's d=0.20) and the female-female pairs (by a mean of 0.67 points; p=0.04; d=0.27). We also assessed the intensity of craving for cigarettes when participants were unable to smoke for a period of time. As shown in Figure 1B, the early-onset members in the male pairs were on average

FIGURE 1. Levels of Nicotine Dependence and Craving in Male-Male and Female-Female Monozygotic Twin Pairs Discordant for Age at Onset of Regular Smoking[a]



[a] The graphs depict levels of nicotine dependence and craving during the period of heaviest lifetime smoking. Craving was assessed by the question "During this time when you smoked most heavily, if you didn't smoke for a period of time, how strong would your craving get for another? Would you say very strong, strong, moderate, or hardly any craving?" Scores of 0, 1, 2, and 3 indicate craving that was described as hardly any, moderate, strong, and very strong, respectively.

0.37 points higher on a 4-point scale than the late-onset member, a highly significant difference (t=4.26, $p<0.0001$; d=0.38). In the female pairs, the difference was in the same direction but more modest (0.25 points higher; t=1.56, p=0.06; d=0.26).

Onset of Regular Smoking and Subsequent Other Substance Use

We then sought to determine whether the early-onset members in our pairs were at higher risk than the late-onset members for other forms of substance use or misuse. As outlined in Table 1, we found no evidence in our male-male twin pairs that the early-onset member met more DSM-IV criteria (20) for alcohol or cannabis abuse or dependence than did the later-onset member of that pair. We found no evidence that the two members of these pairs differed significantly in their drinking frequency or quantity in the year prior to their last interview. The twins did not differ at the time of maximal use in their consumption of cannabis, sedatives, stimulants, or cocaine. We also examined lifetime diagnosis of DSM-IV alcohol abuse or dependence and found that it was equally common in the early-onset and late-onset members in both the male-male and female-female pairs.

Discussion

We sought to evaluate two hypotheses about the nature of the correlation between age at onset of smoking and subsequent nicotine dependence. To do this, we selected, from a large population-based twin sample, monozygotic twin pairs in which both members had a lifetime history of regular smoking and one twin (the early-onset member) reported the onset of regular smoking at least 2 years prior to his or her co-twin (the late-onset member). We identified 175 male-male and 69 female-female pairs who met this definition. On average, the early-onset members reported starting to smoke 4–5 years before the later-onset co-twin.

Our noncausal hypothesis predicted that within these monozygotic twin pairs, we would see no systematic differences in levels of nicotine dependence in the early-onset member compared with the late-onset member. By contrast, the causal hypothesis predicted that the association would still be observed in these pairs despite the fact that the early-onset member and the late-onset member were matched for genotype and social background.

Our results supported the causal hypothesis. Compared with the late-onset members, the early-onset members reported significantly higher levels of nicotine dependence as assessed both by the Fagerström Test for Nicotine Dependence and by levels of craving. The results were consistent across the male-male and female-female twin pairs, supporting the validity of our findings.

We then examined in these pairs whether early-onset smoking predisposed to the heavy use and misuse of other commonly used psychoactive substances. In neither the male nor the female twin pairs was there any consistent evidence that the early-onset member drank more alcohol, had more symptoms of alcohol abuse or dependence, or consumed more illicit substances than the late-onset member.

These results suggest but do not prove that the association between early exposure to nicotine and later symptoms of nicotine dependence is a causal one. The power of the monozygotic co-twin control design is that it controls for any genetic or familial-environmental confounding effects—both those that we could measure and

TABLE 1. Maximal Lifetime Drinking Behaviors and Use of Illicit Psychoactive Substances in Monozygotic Twin Pairs Discordant for Age at Onset of Regular Smoking

	Male Twin Pairs			Female Twin Pairs		
Variable	Mean Change	Paired t Test	p	Mean Change	Paired t Test	p
Number of endorsed alcohol abuse or dependence criteria	0.11	0.60	0.27	0.09	0.32	0.38
Number of endorsed cannabis abuse or dependence criteria	–0.10	1.12	0.13	0.21	1.23	0.11
Days out of 30 drinking[a]	–0.13	0.14	0.44	–0.80	0.57	0.29
Drinks per day[a]	0.27	0.41	0.34	0.24	0.77	0.22
Maximum cannabis use	–3.69	0.96	0.17	1.23	0.63	0.27
Maximum sedative use	–0.45	1.27	0.11	0.73	1.33	0.13
Maximum stimulant use	0.42	0.40	0.34	–0.63	0.63	0.27
Maximum cocaine use	–0.14	0.26	0.40	–0.11	0.18	0.43

[a] During the period in their lives when participants were drinking most heavily.

those of which we could not even conceive. Our results rule out the possibility that the association we are seeing between age at first smoking and subsequent levels of nicotine dependence results from the effects of genetically influenced temperamental variables that have an impact both on age at onset of smoking and on risk for nicotine dependence, as has been seen for early-onset drinking and subsequent levels of alcohol consumption (9, 11). This is critical because in general population samples, we and others have shown that there are shared genetic risk factors between smoking initiation and subsequent levels of nicotine dependence (9, 21) and smoking persistence (22). Furthermore, Korhonen et al. (23) found in a longitudinal study that the effects of hyperactive-impulsive traits (known to be substantially heritable [24, 25]) on illicit drug use were mediated through early smoking. But such genetic effects cannot be operating within our monozygotic twin pairs. Furthermore, low socioeconomic status influences both age at regular smoking and risk for nicotine dependence, as well as related constructs, such as heavy or persistent smoking (9, 26, 27). Such effects, however, could not have an influence on the association between age at onset of smoking and nicotine dependence in our pairs because they all grew up together.

Despite its methodological strengths, however, this study is purely observational, and the confidence in causal inference can never approach what is possible with randomized trials. In particular, we cannot rule out the possibility that the risk factor and the outcome (here, early-onset smoking and nicotine dependence) are associated because both resulted from environmental experiences occurring to one member of the twin pair and not the other. We were able, at least partly, to address the plausibility of this explanation and found that the early-onset members were at increased risk only for nicotine dependence and not for the use or misuse of other psychoactive substances. It is difficult to imagine an exogenous environmental experience unique to one twin of a pair that could be so specific in its effect—that would increase risk for nicotine dependence and for no other form of substance use or misuse.

Our data set also contained information about the experiences of childhood physical and sexual abuse, in both the male-male and female-female twin pairs (28, 29), which are associated with an elevated risk for a range of adverse psychiatric outcomes, including heavy smoking and nicotine dependence (30–32). This gave us the opportunity to evaluate empirically the possibility that our findings resulted from these severe environmental exposures. In a fixed-effects (conditional) linear regression implemented in PROC GLM in SAS (SAS Institute, Cary, N.C.), the associations between onset of smoking and nicotine dependence were effectively unchanged in both male-male and female-female pairs when controlling for childhood physical and sexual abuse. Of course these results do not address the possibility that our study results emerged from the impact of other environmental exposures unique to one member of these monozygotic pairs.

The other key potential limitation of this study is its reliance on long-term recall. Could some correlated memory bias cause one twin in each pair to both move back in time their age at onset of smoking and exaggerate their subsequent levels of nicotine dependence? We did assess, over a mean of approximately 50 months, the test-retest reliability both for age at onset of regular smoking (N=962) and for total score on the Fagerström Test for Nicotine Dependence (N=846) in our male-male twin pairs. Both were high (r values, 0.79 and 0.76, respectively). While we cannot rule out the possibility that our findings result from correlated errors of recall, in the light of the highly reliable nature of memory for our key exposure and outcome variables, this seems unlikely.

Our results in humans are consistent with animal studies, which show that exposure to nicotine earlier in life renders experimental subjects at higher risk for nicotine dependence later in life. Exposure of female and male rats and mice to nicotine in early adolescence, but not in adulthood, is associated with greater nicotine self-

administration and conditioned reward and preference as manifested in adulthood (5, 8, 33).

Furthermore, studies in rodents have suggested possible biological mechanisms for the results of the present study. For example, gene expression profiling analyses in rats comparing nicotine exposures during adolescence and adulthood found that many genes, in particular those that influence neuroplasticity, showed persistent changes in brain regions involved in nicotine's reinforcing and rewarding, such as the ventral tegmental area, only when nicotine was administered during adolescence (34, 35). In addition, these studies suggest that these effects could be mediated through the regulation of brain $\alpha_4\beta_2$ nicotinic receptors. These receptor subtypes play a crucial role in nicotine dependence and are the primary target for varenicline, a smoking cessation drug. Higher levels and functioning of these nicotinic receptor subtypes were observed in the midbrain and striatum of rats and mice exposed to nicotine during adolescence than those exposed only in adulthood (5, 33). Overall, animal studies show that nicotine exposure during adolescence induces long-lasting biochemical, anatomical, molecular, and behavioral changes that differ substantially from those seen with adult exposure.

If correct, our findings have implications for public policy. It has already been established that nicotine dependence is the primary cause of chronic cigarette consumption, which in turn is responsible for a wide range of health problems and premature mortality. It therefore follows that if early age at first smoking is causally related to subsequent levels of nicotine dependence, then reducing access to tobacco products for adolescents will reduce the total population burden of nicotine dependence and the substantial associated morbidity and mortality. This problem has an added urgency with the increasing rates of smoking worldwide in what has been termed the globalization of the tobacco epidemic, which is driven in part by youth exposure to tobacco-friendly messages in a variety of public media (36). While our findings suggest that delaying onset of smoking by 2 or more years will produce only a modest reduction in levels of maximal nicotine dependence in adulthood at the individual level (Cohen's d between ~0.2 and 0.4, a small to medium effect size), such effects when extrapolated to a population level would result in a substantial total reduction in nicotine dependence and smoking-related disease burden. Our findings reinforce the importance of efforts already under way (37, 38) to try to ensure that the developing brains of adolescents are protected, in so far as possible, from exposure to the nicotine in tobacco products.

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