Archival Report

Smoking During Adolescence as a Risk Factor for Attention Problems

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ABSTRACT

BACKGROUND: Cigarette smoking and attention-deficit/hyperactivity disorder (ADHD) are highly comorbid. One explanation is that individuals with ADHD use cigarettes as "self-medication" to alleviate their attention problems. However, animal studies reported that exposure to nicotine during adolescence influences the developing brain and negatively affects attention. This is the first human study exploring the effects of smoking during adolescence on attention problems.

METHODS: Longitudinal data on smoking and attention problems were available for 1987 adult and 648 adolescent monozygotic twin pairs from the Netherlands Twin Register. Twin pairs were classified as concordant/discordant for smoking and compared on attention problems. Within adult discordant pairs, the difference in attention problems between the smoking and never-smoking twins was first assessed cross-sectionally. In longitudinal analyses, the increase in attention problems from adolescence, when neither twin smoked, to adulthood was compared within discordant pairs. In subgroups with longitudinal data from childhood and adolescence, changes in smoking concordance and subsequent changes in attention problems were explored.

RESULTS: Adult twins who ever smoked reported significantly more attention problems than their never-smoking co-twin. Longitudinal analyses showed a larger increase in attention problems from adolescence to adulthood in smoking twins than their never-smoking co-twin ($p < .05$). In childhood and adolescence, smoking twins had more attention problems than their never-smoking co-twin, whereas scores were similar before smoking was initiated or after both twins started smoking (not significant in all groups).

CONCLUSIONS: Results from this genetically informative study suggest smoking during adolescence leads to higher attention problem scores, lasting into adulthood.

Keywords: Adolescence, Attention problems, Causality, Discordant twin design, Longitudinal, Smoking

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Attention-deficit/hyperactivity disorder (ADHD) is highly comorbid with smoking. Adolescents and young adults diagnosed with ADHD show significantly higher smoking rates compared with individuals without the disorder (1–6). Approximately 40% of adults with ADHD smoke compared with 26% of the general population (5). A common disorder, ADHD has an estimated prevalence of ~5%–6% in children (7,8). In adults, the prevalence was 4.4% in a nationally representative household survey in the United States, based on diagnostic interviews (9); 6%–7.4% of a Dutch population met the criteria for adult ADHD based on the ADHD index (10).

Several mechanisms may explain why smoking and ADHD are related. One hypothesis is that individuals with ADHD use cigarettes as "self-medication" to alleviate their attention problems (11,12). A 10-year follow-up study of young adolescents with and without ADHD demonstrated that ADHD is a significant risk factor for the development of substance use disorders and smoking (2). Kollins *et al*. (4) showed that each additional ADHD symptom increases the likelihood of being a regular smoker.

Animal research has drawn attention to an alternative hypothesis: the direction of causality in the association between smoking and ADHD symptoms may also go from smoking to ADHD. In rats, nicotine exposure during adolescence causes diminished attentional performance, lasting into adulthood (13,14). Although smoking can have an immediate positive effect on attention in adults with ADHD (15–17), exposure to nicotine may have detrimental long-term effects on the brain when it is still developing (18), especially on the prefrontal cortex (PFC). The PFC is involved in attention and impulse control (impulsivity), and it continues to develop into late adolescence and early adulthood. During this critical period, nicotine inhaled through tobacco smoke can affect the developing PFC, causing long-lasting changes in brain function (19). Epidemiologic studies in humans have also suggested a negative effect of smoking on attention (20–22). A functional magnetic resonance imaging study showed that prefrontal attentional network function was significantly reduced in young adult smokers ($n = 15$) compared with

nonsmokers (n = 12) and that the extent of this reduction was related to the number of years smoked (23). These results support an effect of smoking on attentional performance but cannot establish causality because of the cross-sectional design of the study. To date, there are no longitudinal human studies concerning the long-term effects of smoking during adolescence on attention problems.

The present study explores the effect of smoking on attention problems by employing the discordant monozygotic (MZ) co-twin design. This genetically informative design tests whether smoking causally leads to more attention problems by comparing the attention problem score of the twin who has smoked with that of his or her co-twin who has never smoked. Because MZ twins are genetically almost identical and grow up in the same family, the design corrects for confounding of genetic factors and shared family environment (24–27). If the association between smoking and attention problems is due only to genetic or shared environmental factors, one would expect the smoking and the never-smoking twin of a discordant MZ twin pair to score the same on attention. In contrast, if the association is causal, we expect that within-pair differences in smoking are associated with within-pair differences in attention problem score. In other words, the smoking twin should score significantly higher on attention problems compared with the never-smoking co-twin in MZ pairs discordant for smoking. We analyze data from different subsets of MZ twin pairs who took part in surveys spanning from childhood to adulthood. The attention problem scores were first compared cross-sectionally within adult MZ twin pairs discordant for smoking initiation. For a subsample of the discordant adult twin pairs with longitudinal data, the increase in attention problems from adolescence, when neither smoked, to adulthood (average follow-up 10 years) was compared. In adolescent MZ twin pairs with data at two ages, changes in smoking concordance and subsequent changes in attention problems were explored. If smoking

causally increases attention problem scores, it is predicted that twins of a MZ twin pair will not differ in attention problems when both do not initiate smoking, whereas attention problems will be higher in the smoking twin than in the never-smoking twin when the twin pair becomes discordant for smoking.

METHODS AND MATERIALS

Subjects

All participants are registered with the Netherlands Twin Register (NTR) (28,29). The Young NTR consists of participants who were recruited as newborn twins from 1987 onward and their siblings who were included later on. At 3, 5, 7, 10, and 12 years of age, parents completed surveys about the development of the twins. At approximately 14, 16, and 18 years of age, the twins and their siblings completed surveys themselves. The Adult NTR comprises adolescent and adult twins and their family members who were recruited since 1990. From 1991 onward, surveys were sent out to all participants of the Adult NTR approximately every 2–3 years.

Data on attention problems and smoking were available for 20,824 adults (mean age, 42 years [SD 15.6]; range, 18–97 years) and 11,386 adolescents (mean age, 15 years [SD 1.2]; range, 8–18 years). Subgroups of MZ twin pairs were selected to measure the effects of smoking on attention problem scores (Figure 1).

For 1987 adult MZ twin pairs (mean age, 34 years [SD 13.8]), information on attention problems and smoking in adulthood was available from surveys sent in 2004–2005 or in 2009 (group I) (Table S1 in Supplement 1). Mean sum scores on attention problems were calculated for concordant pairs (731 pairs concordant ever smokers and 721 pairs concordant never smokers) and for 454 discordant pairs (one twin had smoked, whereas the other had never smoked). For a
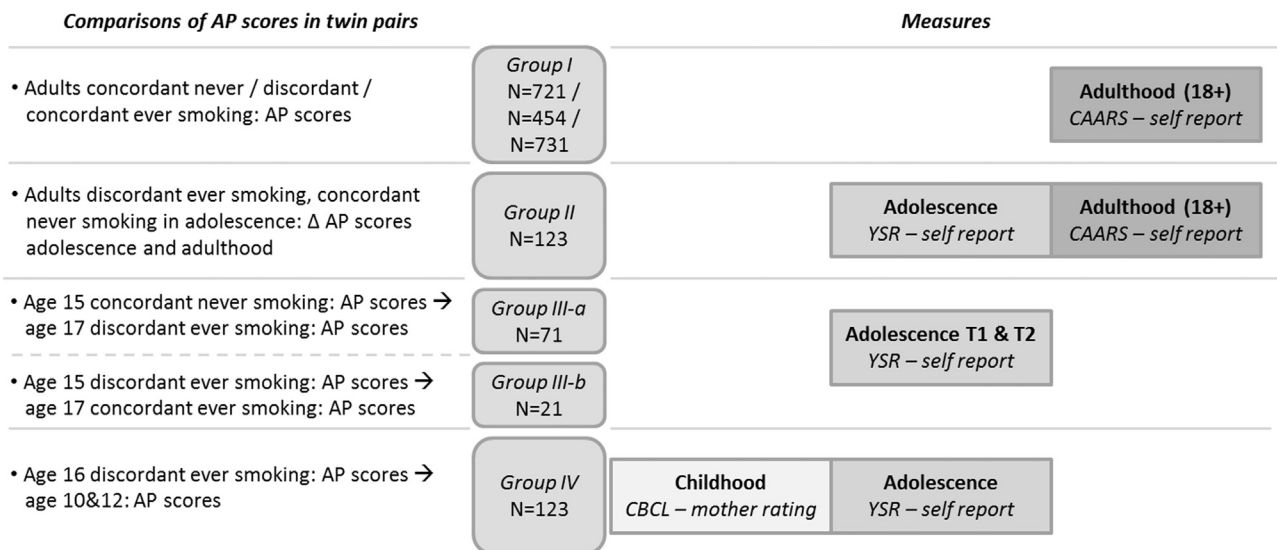
Figure 1. Overview of the four groups of subjects and their corresponding analyses and measurements. AP, attention problem; CAARS, Conners' Adult ADHD Rating Scales, attention-deficit/hyperactivity disorder index; YSR, Youth Self Report, rating scale on attention problems; CBCL, Child Behavior Checklist, rating scale on attention problems; T1, time-point 1; T2, time-point 2.

subgroup of the 454 adult discordant twin pairs, information on attention problems was also available at an age when the smoking twin had not yet started smoking (group II; $n = 123$ pairs).

In adolescents, information on attention problems and smoking at two ages was available for 648 MZ twin pairs. Their mean age was 15 years (SD .9) at the first observation and 17 years (SD .6) at the second observation (group III) (Table S1 in Supplement 1). Two trajectories were explored: First, we looked at 71 pairs concordant for never smoking at age 15 years that became discordant at age 17 years because one of the twins started smoking (group III-a). Next, we studied 21 pairs who were discordant for smoking at age 15 years but became concordant at age 17 years because the never-smoking co-twin had started smoking (group III-b). Finally, we selected all discordant MZ twin pairs who completed at least one survey during adolescence (mean age, 16 years [SD 1.1]) and who had information on childhood attention problem scores reported by the mother at ages 10 and 12 years (group IV; $n = 123$).

Measures

Adult ADHD symptoms were measured by the ADHD index, taken from the Conners' Adult ADHD Rating Scales. The Conners' Adult ADHD Rating Scales are self-report scales for adults consisting of 30 items that reflect DSM-IV ADHD symptom measures. A sum score of 12 core items makes up the ADHD index. Participants were asked to respond with "never" (score = 0), "once in a while" (score = 1), "often" (score = 2), or "very frequently" (score = 3) to statements such as "I am always on the go as if driven by a motor" and "I am easily distracted from what I am doing by things I hear or see" (30). Childhood and adolescent ADHD symptoms were measured by empirically based rating scales on attention problems from the Child Behavior Checklist, completed by mothers, and the Youth Self Report, completed by twins. Both the Child Behavior Checklist and the Youth Self Report are part of the Achenbach System of Empirically Based Assessment (31–33) and consist of nine statements such as "I have trouble sitting still" and "I have trouble concentrating or paying attention for long." Answers on a 3-point scale—"not true" (score = 0), "somewhat or sometimes true" (score = 1), or "very true or often true" (score = 2)—were summed. Childhood ADHD symptoms (at 10 and 12 years of age) were rated by mothers on the nine items mentioned before plus two additional age-specific items (34). For Conners' Adult ADHD Rating Scales, Child Behavior Checklist, and Youth Self Report, the total distributions of sum scores on attention problems and hyperactivity were analyzed. Throughout this article, these sum scores are referred to as "attention problem scores."

A dichotomous variable with the categories "ever smoked" and "never smoked" reflected smoking initiation. This variable was assessed by asking participants the following questions: "Have you ever smoked?" (answer categories "no," "a few times just to try," and "yes") and "How often do you smoke now?" (answer categories "I don't smoke regularly," "I've quit smoking," "once a week or less," "a few times a week," and "once a day or more"). Participants were classified as "never smoked" when they answered "no" to the question "Have you ever smoked?" When participants answered they had smoked before (answer categories "a few times just to try" and "yes"), they were classified as "ever smoked." When the answer to the first question was missing but participants answered they had quit smoking or said they currently smoke ("once a week or less," "a few times a week," and "once a day or more"), they were also classified as "ever smoked."

Data on methylphenidate (Ritalin) use collected by the NTR showed that 2.8% of twins had used methylphenidate (from 2000–2012). When looking only at the data collected in 2011, the prevalence was 3.9%, which is close to the 4.6% prevalence reported in Dutch children and youth 11–20 years old (35). Given these low numbers, methylphenidate use was not corrected for in the analyses.

Statistical Analysis

The association between attention problems and smoking was separately determined in the overall population of 20,824 adults and 11,386 adolescents. Because there is ample evidence that sex and age are associated with attention problems (36), linear regression analysis was performed with a correction for sex (0 = male, 1 = female) and age (continuous) as follows: $Y = \beta_0 + \beta_1 X_{smoking} + \beta_2 X_{age} + \beta_3 X_{sex} + \varepsilon$, where Y is the attention problem score; β_0 is the intercept (i.e., the value of Y when all independent variables are 0); independent variables are $X_{smoking}$ (regression coefficient for smoking initiation; never vs. ever smoked), X_{age} (regression coefficient for age), and X_{sex} (regression coefficient for sex); and ε is the error term. Regression analyses were corrected for family relatedness by using the robust cluster option in Stata (version 9.0; StataCorp LP, College Station, Texas).

In the discordant MZ co-twin design, paired t tests were performed to determine whether attention problem scores differed significantly within twin pairs discordant for smoking. Analyses were carried out in IBM SPSS Statistics for Windows, Version 20 (IBM Corp, Armonk, New York). All analyses and the corresponding measures are depicted in Figure 1 and described subsequently.

The within–twin pair difference was tested for discordant adult twin pairs (group I) both in the total group and for different ages at first cigarette in smokers (≤14 years old, 15–17 years old, or ≥18 years old). In the case of concordant twin pairs, a mean attention problem score was calculated for each pair (score twin 1 + score twin 2/2). The difference between the mean score in concordant twin pairs was tested with a t test for independent samples.

Longitudinal difference scores were calculated as the difference between attention problem scores at an adult age and at an adolescent age when the exposed twin had not yet smoked his or her first cigarette (group II). The mean difference between those two measurements was 10 years. We compared the difference score of the smoking twin and the never-smoking co-twin with a paired t test.

The difference in attention problem score between both twins of a twin pair (within–twin pair difference) was tested with a paired t test at 15 years old and 17 years old for twin pairs going from concordant never smoking at age 15 years to discordant at age 17 years and from discordant at age 15 years to concordant ever smoking at age 17 years (group III-a

and group III-b). Finally, the within–twin pair difference in attention problem score was tested in adolescence (16 years old) and in childhood (10 years old and 12 years old) with a paired t test (group IV).

RESULTS

Within the total sample of 20,824 adults, attention problem scores were significantly higher in ever smokers compared with never smokers (β = .636, 95% confidence intervals [CI] = .521–.751, p < .001). In 11,386 adolescents, the cross-sectional association between smoking and attention problem scores was even stronger (β = 1.127, CI = 1.018–1.237, p < .001).

In adult MZ twin pairs, the mean attention problem score was higher for 731 concordant ever-smoking pairs (8.3) than for 721 concordant never-smoking pairs (7.7), with a difference of .60 (CI = .20–.91, p < .01). In concordant ever-smoking twin pairs, attention problem scores were lower when the age at which the twins smoked their first cigarette was higher, being 8.4, 8.1, and 8.0 when age at first cigarette was ≤14 years old (n = 146), 15–17 years old (n = 126), and ≥18 years old (n = 39). Figure 2 shows mean attention problem scores for the adult MZ twin pairs discordant for smoking. In the total sample (N = 454), the smoking twins scored .50 points higher than the co-twins who never smoked (CI = .06–.88, p < .05). In subgroups based on age at first cigarette, there was a similar pattern, with higher attention problem scores for the twins who initiated smoking compared with their never-smoking co-twins. When age at first cigarette for the smoking

twins from discordant pairs was ≤14 years old, the mean attention problem score was higher than when the twins initiated smoking at 15–17 years old (difference of 1.28, CI = .22–2.35, p < .05) and ≥18 years old (1.04, CI = −.13 to 2.20, p = .08). A similar pattern was seen when comparing the never-smoking twins from discordant pairs, although here both differences were not significant (smoking initiated at ≤14 years old vs. 15–17 years old showed a difference of .54, CI = −.50 to 1.58, p = .31, and smoking initiated at ≤14 years old vs. ≥18 years old showed a difference of 1.07, CI = −.05 to 2.19, p = .06).

For 123 adult MZ twin pairs discordant for smoking with longitudinal data, difference scores were calculated between adult age and the age at which the smoking twin had not yet smoked a first cigarette. When the smoking twin had not yet smoked a first cigarette, attention problem scores of both twins did not differ significantly. The attention problem score of the twin who started smoking increased more (increase of 4.4 points) compared with the co-twin who did not start smoking (increase of 3.5 points) (CI = .07–1.75, p < .05).

In adolescent twin pairs going from concordant never smokers at age 15 years to being discordant for smoking at age 17 years, both twins scored similar on attention problems when neither smoked (Figure 3). At age 17 years, the twins who had started smoking tended to score .59 points higher (CI = −.07 to 1.25) on attention problems than the co-twins who did not smoke, but the difference was not significant (p = .08). Within 21 twin pairs discordant at age 15 years and concordant ever smoking at age 17 years, the smoking twins scored on average 1.05 points higher (CI = −.40 to 2.50) than
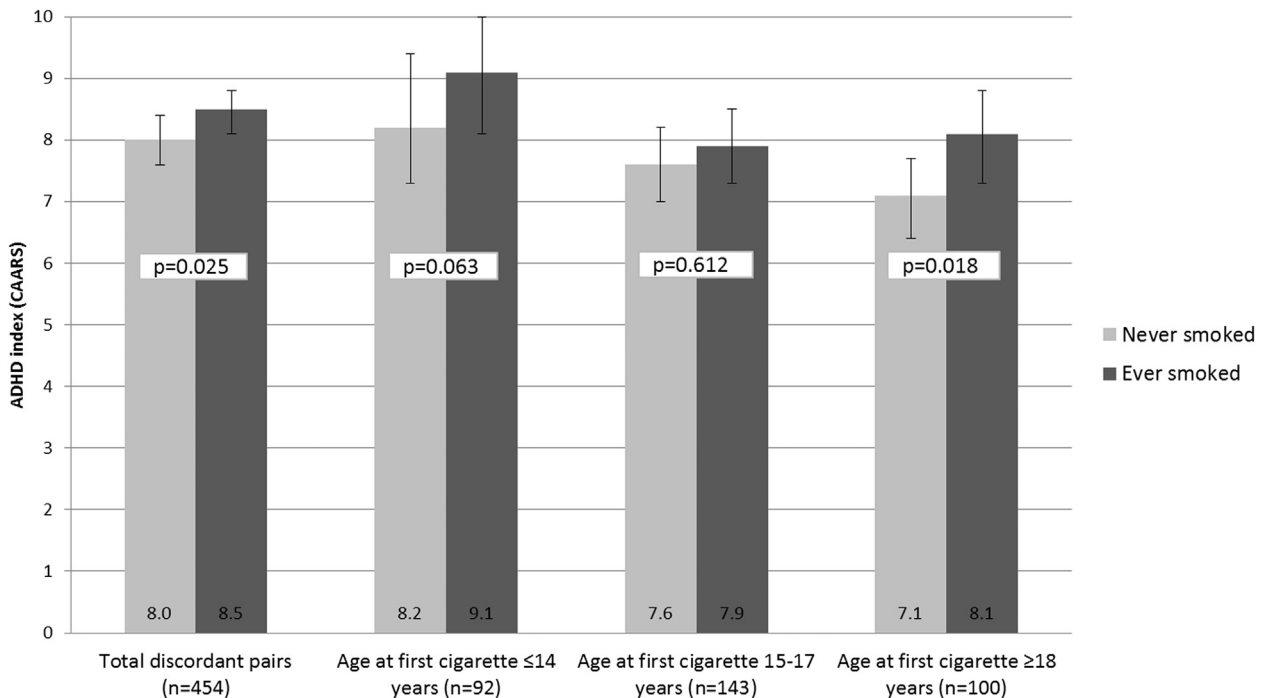
Figure 2. Mean attention problem scores (attention-deficit/hyperactivity disorder [ADHD] index) with 95% confidence interval error bars for adult monozygotic twin pairs discordant for smoking (group I). Data are shown for the total group and for different age groups, defined by the age at which the smoking twin from discordant monozygotic pairs smoked the first cigarette. p value for paired t test within monozygotic twin pairs.
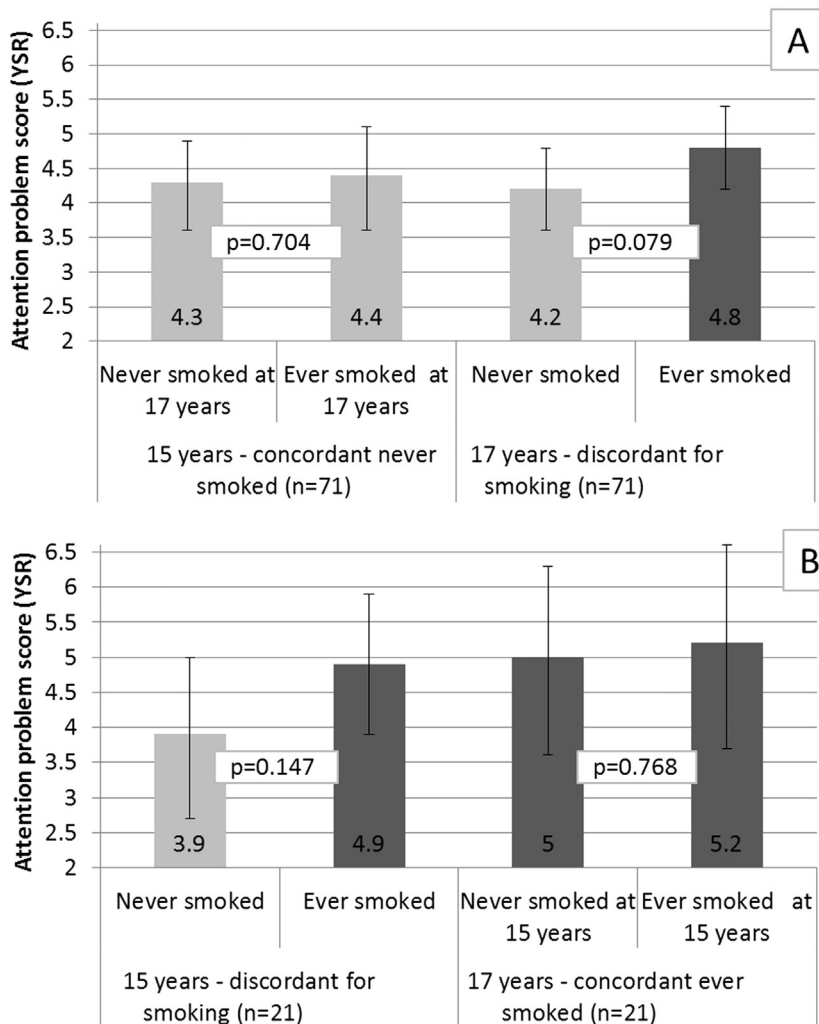
Figure 3. Mean attention problem scores (Youth Self Report [YSR]) with 95% confidence interval error bars for adolescent monozygotic twin pairs changing in concordance. **(A)** Going from concordant never smoking at 15 years to discordant for smoking at 17 years (group III-a). **(B)** Going from discordant at 15 years to concordant ever smoking at 17 years (group III-b). *p* value for paired *t* test within monozygotic twin pairs.

the never-smoking co-twins at age 15 years, but significance was not reached ($p = .15$). Twins scored equally high at age 17 years when both twins smoked. Of the 123 twin pairs discordant for smoking at age 16, the smoking twins scored on average .55 points higher (CI = .05–1.06) on attention problems than the never-smoking co-twin ($p < .05$), whereas their attention problem score did not differ at ages 12 and 10 years when both twins were nonsmoking (Figure 4).

DISCUSSION

The present study implies that adolescent smoking leads to higher attention problem scores, with the effects lasting into adulthood. This is the first time that this finding has been reported in humans based on longitudinal data spanning from childhood to adulthood. Our results provide further support for the hypothesis that smoking affects the brain and increases attention problems, as suggested in animal studies (13,14).

As shown by earlier work of the NTR, the ADHD phenotype seems to be less heritable in adults than in children (36). The

effect of nicotine use on cognitive functioning is possibly one of the factors involved in the individual differences in ADHD symptoms observed in adults. Family members are more similar in their smoking behavior because of genetic and shared environmental factors, but unique environmental factors can cause them (in particular MZ twins) to differ with regard to the initiation of smoking (37–39). Individual differences in the initiation of smoking could lead to higher attention problem scores for individuals who start smoking compared with nonsmokers.

Although cigarette smoke contains many harmful components (40), animal research suggests nicotine is the causal agent in the relationship between smoking and attention problems (13,14,19,41). Regarding the biological mechanism behind the negative effect of nicotine on attention, Counotte *et al.* (14) point to the role of metabotropic glutamate levels. It is suggested that the exposure to nicotine during adolescence affects synaptic signaling mechanisms involving metabotropic glutamate signaling in the PFC. These specific mechanisms are important for plasticity and synaptic maturation, explaining the effect on
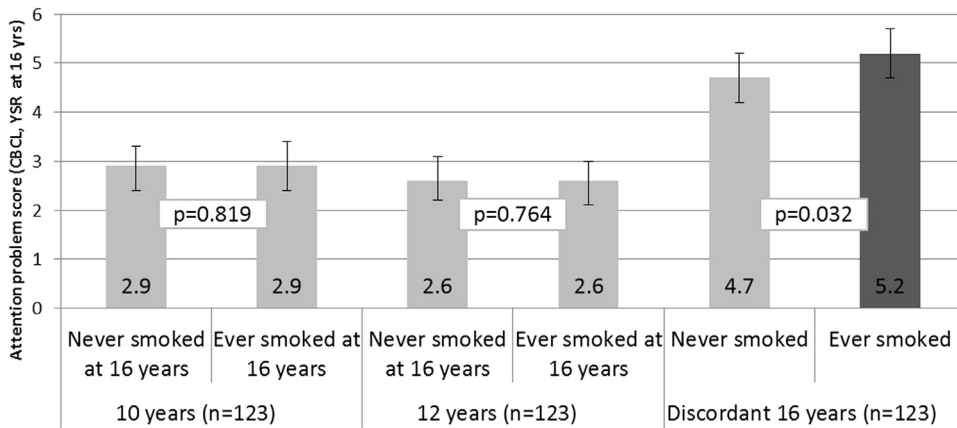
Figure 4. Mean attention problem scores with 95% confidence interval error bars for adolescent monozygotic twin pairs when they were discordant for smoking at 16 years (Youth Self Report [YSR]) and when they were 12 and 10 years old (Child Behavior Checklist [CBCL]) (group IV). Scores at age 16 are from self-ratings, and scores at ages 10 and 12 are rated by the mother of the twins. p value for paired t test within monozygotic twin pairs.

cognitive functioning (41). When Counotte et al. (14) exposed rats to nicotine during adulthood instead of during adolescence, there were no long-term consequences for attentional performance. In the present study, the smoking twins of the discordant adult twin pairs scored higher on attention problems than the never-smoking co-twins, even when smoking was initiated at ≥18 years old. This finding could be explained by the fact that development of the PFC is delayed during adolescence compared with other cortical areas and development continues into young adulthood (19,42,43). In our own data, adult smoking twins scored on average .98 points higher (CI = .02–1.93) than their never-smoking co-twins when smoking was initiated at 18–20 years old ($p < .05$, $n = 80$), whereas the within–twin pair difference was .79 points (CI = −1.27–2.84) when smoking was initiated at 21–22 years old ($p = .42$, $n = 14$) and only .17 points (CI = −2.22–2.56) when smoking was initiated at ≥23 years old ($p = .88$, $n = 12$). Given the small sample sizes, these results need to be interpreted with caution. Further research should determine whether smoking has an effect on attention problems only when occurring while the brain is still developing or also when smoking is initiated later on in life. The minimum legal age to smoke or purchase cigarettes varies worldwide from 15–21 years (44). In the Netherlands, the legal age for smoking has been raised from 16 to 18 years since January 1, 2014, in accordance with recommendations by the European Union (45). Of the 28 European Union states, 5 still have a minimum age limit of 16 years (46). Given the results of the present study, it seems important that the legal age for smoking be raised to 18 years and preferably higher. In the city of New York, a new law was adopted raising the minimum age to smoke to 21 years (47).

When smoking was initiated at ≤14 years old (compared with 15–17 years old or ≥18 years old), both the smoking and the never-smoking twin of adult MZ twin pairs discordant for smoking scored higher on attention problems. Adolescents with ADHD are not only more likely to initiate smoking (2) but also are more likely to do so at a younger age (3,48). Because MZ twins are genetically almost identical and ADHD symptoms are heritable (36), genetic factors causing the smoking twin to score higher on attention problems are also present in the never-smoking co-twin, causing him or her to score higher as well. Because the smoking twins score even higher on

attention problems than their never-smoking co-twin, an additional causal effect of cigarette smoking is suggested on top of a possible genetic vulnerability.

The brain is also vulnerable to tobacco smoke during childhood. Max et al. (49) reported that exposure to secondhand smoke (measured by self-report and cotinine level) was significantly associated with a higher chance of ADHD in children 4–15 years old, after controlling for sociodemographics, maternal smoking during pregnancy, and preschool attendance. Exposure to nicotine can occur through maternal smoking during prenatal development (in utero). Genetically informative studies demonstrated that prenatal nicotine exposure significantly increased the risk of ADHD and conduct problems in young children (50,51). The above-described studies indicate that exposure to tobacco smoke can result in more attention problems, even when it is through secondhand smoking or prenatal exposure. In the case of secondhand exposure to tobacco smoke, exposure levels are usually a lot lower than when a person smokes himself or herself [.03–.18 nmol/mL vs. 7.92–39.99 nmol/mL total cotinine, respectively (52)], suggesting that even a low exposure can have an effect on ADHD scores. In the present study, exposure to nicotine through smoking was assessed by asking participants if they ever smoked before. Attention problem scores for individuals who replied with "No," "A few times just to try," and "Yes" when asked "Have you ever smoked before?" were 7.76, 8.40, and 8.08 in 20,824 adults and 4.45, 5.25, and 5.90 in 11,386 adolescents. As shown by these scores, individuals who stated they had smoked a few times already had elevated attention problem scores. Further work needs to establish at what quantity nicotine negatively affects cognitive functioning in humans. To determine whether the effect is restricted to attention, the association of smoking with the separate dimensions of the ADHD phenotype should also be investigated.

Despite the strong design, the present study has some limitations. Some subgroups of adolescent MZ twins were small with 71 and 21 complete twin pairs. Not many of the 1987 adult and 648 adolescent MZ twin pairs were discordant for smoking. This finding is to be expected because smoking initiation and nicotine dependence are moderately to largely heritable (37–39), making it more likely that both twins of a MZ twin pair are similar in their smoking status. Although these

particular groups were small, we still observed a trend. This trend was in line with the finding that in a larger group of 123 twin pairs discordant for smoking at age 16, attention problem scores were significantly higher for the smoking twin.

Twins who smoke may also differ from their never-smoking co-twin when it comes to the use of other substances and sociodemographics (53,54). Educational achievement did not differ within twin pairs discordant for smoking in adults ($p = .98$) and adolescents ($p = .49$). Smoking twins more often drank alcohol at least two to four times a month compared with their never-smoking co-twin (75.5% vs. 67.8% in adults [$p < .05$] and 58.5% vs. 46.8% in adolescents [$p < .001$]) and more often initiated cannabis use (30.1% vs. 16.1% in adults [$p < .01$] and 16.2% vs. 3.4% in adolescents [$p < .01$]). When correcting for frequency of alcohol consumption, smoking twins still scored higher on attention problems than their never-smoking co-twin in 433 adult discordant pairs (difference of .43 points, CI = .01–.84, $p < .05$) and 94 adolescent discordant pairs (.64, CI = .06–1.21, $p < .05$). After correcting for cannabis initiation (yes/no), adolescent smoking twins continued to score higher on attention problems than their never-smoking co-twin in 118 pairs (.54, CI = .03–1.05, $p < .05$); for adults there were too few data on cannabis use. Although the smoking and never-smoking twins differed in alcohol and cannabis use, it appears this did not affect the results.

In conclusion, our analyses provide evidence for a negative effect of smoking on ADHD-related symptoms. This knowledge is important because smoking is highly prevalent worldwide (55), and it is usually initiated during adolescence or young adulthood (56). Both smoking and ADHD are influenced by genetic factors. We have now shown that, besides existing individual differences owing to genetic background, a person's score on attention problems can increase by smoking. Previous studies have reported that adolescents with ADHD are more likely to initiate smoking (2,4,11,12), making adolescents with preexisting ADHD an important target group for smoking prevention programs. When these adolescents initiate smoking, this could have an additional negative effect on their attention problems. Ongoing efforts toward preventing smoking are recommended, particularly in adolescents or young adults with ADHD.

ARTICLE INFORMATION

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