Contribution of Parental Psychopathology to Offspring Smoking and Nicotine Dependence in a Genetically Informative Design*

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ABSTRACT. Objective: It is not known if parental psychiatric disorders have an independent effect on offspring smoking after controlling for genetic and environmental vulnerability to nicotine dependence. We tested if parental alcohol, drug, or conduct disorders; antisocial personality disorder; depression; and anxiety disorders remained significant predictors of offspring smoking initiation, regular smoking, and nicotine dependence before and after adjusting for genetic and environmental risk for nicotine dependence. **Method:** Data were obtained via semi-structured interviews with 1,107 twin fathers, 1,919 offspring between the ages of 12 and 32, and 1,023 mothers. Genetic and environmental liability for smoking outcomes was defined by paternal and maternal nicotine dependence. Multinomial logistic regression models were computed to estimate the risk for offspring trying cigarettes, regular smoking, and the Fagerström Test for Nicotine Dependence (FTND) as a function of parental psychopathology and sociodemographics before and after adjusting for genetic and environmental vulnerability to nicotine dependence. **Results:** Before adjusting for genetic and environmental risk for nicotine dependence, ever trying cigarettes was associated with maternal depression, regular smoking was associated with maternal alcohol dependence and maternal conduct disorder, and FTND was associated with paternal and maternal conduct disorder and antisocial personality disorder. No parental psychopathology remained significantly associated with regular smoking and FTND after adjusting for genetic and environmental vulnerability to nicotine dependence in a multivariate model. **Conclusions:** The association between parental psychopathology and offspring smoking outcomes is partly explained by genetic and environmental risk for nicotine dependence. Point estimates suggest a trend for an association between parental antisocial personality disorder and offspring regular smoking and nicotine dependence after adjusting for genetic and environmental vulnerability. Studies in larger samples are warranted. (*J. Stud. Alcohol Drugs, 71,* 664-673, 2010)

FAMILY, ADOPTION, AND TWIN STUDIES have demonstrated that substance-use disorders—including smoking and nicotine dependence—"run" in families along with non-substance-use psychiatric disorders (Cadoret, 1978; Fu et al., 2002; Herndon and Iacono, 2005; Hicks et al., 2004; Kendler et al., 1993; Lyons et al., 2008; Rutter and Quinton, 1984; Stewart et al., 1980). Much of the evidence for co-occurrence of disorders in families comes from twin literature. These studies have established evidence of common genetic vulnerability to numerous psychiatric disorders and nicotine dependence (Fu et al., 2002, 2007; Lyons et al., 2008; Reichborn-Kjennerud et al., 2004; Scherrer et al., 2008b; True et al., 1999). In the Vietnam Era Twin Registry, the source of fathers in the present study, approximately 26% of the genetic risk for alcohol dependence was common with nicotine dependence (True et al., 1999). Recently we found a majority of genetic variance in risk for lifetime co-occurrence of nicotine dependence, alcohol dependence, and cannabis dependence is the result of overlapping genetic vulnerability (Xian et al., 2008). Previous analysis suggests the genetic contribution to conduct disorder overlaps with alcohol dependence and nicotine dependence (Fu et al., 2007). Depression and co-occurring nicotine dependence can also be accounted for by common familial factors (Lyons et al., 2001, 2008), yet this may be the result of common genetic

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variance to conduct disorder and antisocial personality disorder (Fu et al., 2007). The lifetime co-occurrence of anxiety and nicotine dependence can be partly explained by common genetic vulnerability in the case of posttraumatic stress disorder (Scherrer et al., 2008b) and shared environmental factors in smoking and panic attack (Reichborn-Kjennerud et al., 2004). Overall, the majority of behavioral genetic evidence suggests risks for smoking and nicotine dependence share a common heritability with a range of psychiatric disorders.

Although findings from twin studies suggest genetic contributions to nicotine dependence are shared with genetic vulnerability for substance-use disorders and non-substance-use psychiatric disorders, the classical twin design does not test cross-generation transmission. Classical twin designs do not help determine if vulnerability for smoking in offspring is completely explained by smoking or nicotine dependence in the parent generation or if there are independent effects of parental phenotypes that influence offspring smoking, even after controlling for correlated genetic vulnerability (e.g., genetic factors for nicotine dependence correlated with conduct disorder). D'Onofrio et al. (2003) demonstrated that the offspring-of-twins design can be used to quantify processes underlying intergenerational transmission of phenotypes. In addition to using structural equation modeling to estimate the variance resulting from genetic and environmental factors and covariates (Eaves et al., 2005), the offspring-of-twins design can also be used to estimate the familial and nonfamilial environmental contributions to smoking outcomes while accounting for genetic influences. The latter approach is undertaken in the present article. The offspring-of-twins design permits examination of the degree of genetic and environmental influence transmitted from parents to their children by evaluating the offspring of identical and fraternal twins concordant and discordant for a familial risk factor associated with multiple outcomes, in the present case, smoking and nicotine dependence.

Using a uniquely constructed male–male twin registry, we utilized the offspring-of-twins design to test if parental psychopathology remained significantly associated with offspring smoking initiation, regular smoking, and nicotine dependence after controlling for familial risk. Because genetic correlations between nicotine dependence and other psychiatric disorders are not 100%, we hypothesized that parental psychopathology would significantly contribute to offspring smoking outcomes, even after adjusting for genetic and environmental vulnerability associated with nicotine dependence in the parent generation.

Method

Subjects

Participants were offspring of members of the Vietnam Era Twin Registry, which is a national registry of male same-sex twin pairs in which both twins served in the military during the Vietnam Era (1965-1975). Construction of the registry and the method of determining zygosity have been previously reported (Eisen et al., 1987, 1989; Henderson et al., 1990).

The present study involved analyses of data from twin fathers and from diagnostic telephone interviews with biological mothers and their offspring in two complementary offspring-of-twins projects conducted from 2001 to 2004. All offspring were born to twin fathers from the Vietnam Era Twin Registry. Data from a 1992 interview with the twin fathers (Tsuang et al., 1996) permitted classifying twin fathers as alcohol dependent, drug dependent, or both. From these data, families in the offspring-of-twins projects were selected if the twin fathers were concordant or discordant for alcohol dependence (Offspring-of-Twins Project 1); in Offspring-of-Twins Project 2, families were selected if twin fathers were concordant or discordant for illicit drug dependence. Both studies included unaffected twin pairs and their families as controls. Parents provided written consent for their minor-age offspring to be interviewed. We combined data from both offspring-of-twins projects to increase our total sample size. This was possible because both studies used similar survey instruments, with the alcohol-dependence study having more questions on alcohol use and the drug-dependence study having more questions on illicit drug use. If subjects participated in the alcohol-dependence study, they were not asked duplicate questions in the drug-dependence study. Project data were merged by taking all data from all subjects in the drug-dependence study (the more recent data source) and adding subjects from the alcohol-dependence study who did not participate in the drug-dependence study.

Experienced staff from the Institute for Survey Research at Temple University (Philadelphia, PA) conducted data collection. Interviewers were blind to the substance-use history of respondents and gave equal effort to recruitment of all respondents. All participants gave verbal consent before being interviewed, as approved by the institutional review board at the participating institutions.

Analyses of nonresponse indicated no evidence for differences in participation for fathers with and without a substance-use disorder (alcoholism or drug dependence) and their offspring (Duncan et al., 2008; Scherrer et al., 2004). Descriptions of survey contents and response rates have been previously published (Duncan et al., 2008; Jacob et al., 2003; Scherrer et al., 2004, 2008a). Project 1 resulted in the following response rates: Of the 1,464 targeted twin fathers, 1,213 (83%) participated in the study, and 862 mothers (67% of 1,282 eligible) and 1,270 offspring 12-25 years of age (85.4% of 1,487 eligible) participated in the 2001 survey. In Project 2, of eligible twin fathers, 725 (81% of the 895 eligible) were interviewed, and 427 (72.8% of the 601 eligible) mothers were interviewed along with 839 offspring ages 12-32 (88% of the 950 eligible). The combined data-

base included 1,107 fathers, 1,919 offspring ages 12-32, and 1,023 biological mothers (2.9% nonbiological/rearing only).

Offspring smoking variables

Ever smoking cigarettes was defined by a positive response to the question, "Did you ever try smoking cigarettes?" Regular smoking was defined as having smoked 21 or more cigarettes over the lifetime and smoking three or more times per week for a minimum of 3 weeks. This intensity of smoking is associated with loss of control over cigarettes, nicotine dependence, and withdrawal in young smokers (DiFranza et al., 2007) and was appropriate in this young cohort, where 22% were younger than age 18. Nicotine dependence was defined according to the Fagerström Test for Nicotine Dependence (FTND; Fagerström, 1978, Heatherton et al., 1991) for all offspring who were regular smokers. Offspring with a value of 4 or greater on the FTND were defined as nicotine dependent (Breslau and Johnson, 2000). Using these smoking outcomes, we created a four-level categorical variable with the following categories: never tried smoking a cigarette, ever tried smoking a cigarette, regular smoking, and FTND-criteria nicotine dependence.

Nicotine dependence four-group design

A four-group design variable was created to reflect the genetic and environmental risk for offspring smoking outcomes based on the father's and father's co-twin Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R; American Psychiatric Association, 1987), nicotine-dependence status and whether paternal twins were monozygotic or dizygotic. Group 1 comprised offspring who had a father with a lifetime diagnosis of DSM-III-R nicotine dependence regardless of the nicotine-dependence status of the co-twin and zygosity (high-genetic, high-environment risk group). These offspring were at high genetic risk because of their father's history of nicotine dependence and at high environmental risk by virtue of being reared by a nicotine-dependent father. Group 2 comprised offspring whose father did not have nicotine dependence but the fathers' monozygotic co-twin (i.e., the offspring's uncle) met nicotine-dependence criteria (high-genetic, low-environment risk group). Group 3 comprised offspring whose father did not have nicotine dependence but his dizygotic co-twin (i.e., offspring's uncle) met nicotine-dependence criteria (medium-genetic, low-environment risk group). Offspring in the high-genetic, low-environment risk group (Group 2) are posited to have been at high genetic risk because their father shared 100% of his genes with his nicotine-dependent co-twin, whereas those in the medium-genetic, low-environment risk group (Group 3) are at medium genetic risk because the father shared, on average, 50% of his genetic material with his nicotine-dependent dizygotic co-twin. Both Group 2 and Group 3 offspring are posited to be at low environmental risk because they were reared by an unaffected father. Finally, Group 4 comprised offspring whose father and co-twin (monozygotic and dizygotic) did not meet criteria for nicotine dependence and are theorized to be at low-genetic, low-environment risk.

Maternal nicotine dependence

Maternal contribution to the familial risk for smoking was modeled using the Heaviness of Smoking Index, defined by the time to first cigarette on waking and the number of cigarettes smoked per day when smoking the most (Heatherton et al., 1989). Based on evidence that Heaviness of Smoking Index scores of 4 or greater indicate high nicotine dependence (Diaz et al., 2005; Heatherton et al., 1989) and considering the distribution of Heaviness of Smoking Index scores, we created a dichotomized Heaviness of Smoking Index score so that values of 1-2 defined low and values of 3 or greater defined medium to severe nicotine-dependent mothers. Lifetime never smokers were the reference group.

Covariates

Alcohol-dependence and drug-dependence seven-group design variables. Because the samples for the current project were from two separate offspring-of-twins designs for alcohol dependence and drug dependence in Data Collection Projects 1 and 2, respectively, the sampling design variables for these projects were included in all analyses to adjust for sampling bias. Specifically, we adjusted for sampling design by using a seven-group design variable based on father's and co-twins' alcohol-dependence and drug-dependence status and zygosity. Group 1 consisted of offspring born to fathers with drug dependence with and without alcohol dependence. Father's drug dependence was highly comorbid with alcohol dependence and, therefore, was considered together in drug-dependent fathers. Group 2 offspring were born to unaffected monozygotic twins whose co-twin had drug dependence with and without alcohol dependence. Group 3 offspring were born to unaffected dizygotic twin fathers whose co-twin had drug dependence with and without alcohol dependence. Group 4 offspring were born to fathers with alcohol dependence. Group 5 offspring had unaffected monozygotic twin fathers whose co-twin had alcohol dependence. Group 6 offspring had unaffected dizygotic twin fathers whose co-twin had alcohol dependence. Group 7 offspring were born to monozygotic and dizygotic twins without drug dependence and alcohol dependence.

Paternal psychopathology

Data from the 1992 father interviews were used to derive lifetime diagnosis of DSM-III-R criteria depression. Anxiety

disorders diagnosed included generalized anxiety, panic, and posttraumatic stress disorder diagnoses. The prevalence of specific anxiety disorders was not sufficient to model as separate predictor variables; therefore, we combined these variables into a single paternal anxiety predictor variable. Data from the 1992 Diagnostic Interview Schedule were also used for paternal diagnosis of DSM-III-R conduct disorder and antisocial personality disorder.

Maternal psychopathology was obtained from the two offspring-of-twins projects and included lifetime conduct-disorder and lifetime antisocial-personality-disorder symptom count, lifetime DSM Fourth Edition (DSM-IV; American Psychiatric Association, 1994), alcohol dependence, and lifetime DSM-IV depression.

Sociodemographic variables included offspring age, gender, paternal race (White vs. non-White), paternal and maternal education, and offspring report of father–mother marital status (married vs. divorced, separated, widowed, never married). We did not include the offspring's own education in regression models because it was dependent on offspring age. Because of missing maternal interview data for some offspring (9.3%), a dummy variable to reflect the missing status of a mother was constructed and included in the analysis.

Analyses

Before adopting the multinomial logistic regression model (i.e., generalized logistic regression model), each logistic regression model with the four-level offspring smoking outcome was tested to determine if the assumption of proportional odds was met (i.e., ordinal pattern of the four-level smoking-outcome variable). The test yielded a significant violation of the proportional odds model ($p < .05$), and the multinomial logistic regression model was adopted for all analyses.

Analyses began by testing if parental psychopathology had a univariate association with the four-level offspring smoking outcome and then testing if univariate associations remained significant in multivariate analyses. Finally, we tested if parental psychopathology was associated with the four-level offspring smoking outcome after controlling for genetic vulnerability for nicotine dependence imparted from parental smoking and significant parental psychiatric disorders from univariate analyses. All analyses adjusted for the alcohol-dependence and drug-dependence offspring-of-twins seven-group sampling design variables and sociodemographics.

Analyses were conducted using the SURVEYLOGISTIC procedure in SAS Version 9.0 (SAS Institute Inc., Cary, NC), which adjusts for error variance of nonindependent observations.

Results

Offspring were 21.4 years of age on average, approximately half of the 1,919 offspring were female (50.1%), most had White fathers (93.5%), and on average they had completed high school (years of education: $M = 12.5$, $SD = 2.7$). Parents were relatively well educated, 63.9% of fathers and 63% of mothers had greater than a high school education. Most (73.2%) biological parents were still married to each other. Among respondents, 11.1% of fathers had conduct disorder, 4.2% had antisocial personality disorder, 10.6% had depression, and 14.1% had an anxiety disorder. Among mothers, 26.0% were heavy, nicotine-dependent daily smokers (i.e., Heaviness of Smoking Index score ≥ 4); 10.1% had lifetime DSM-IV alcohol dependence; 12.0% had two or more symptoms of conduct disorder; 10.7% had two or more symptoms of antisocial personality disorder; and 31.0% had lifetime DSM-IV major depression.

There were 994 offspring born to fathers in Group 1 of the four-group paternal nicotine-dependence variable, 157 offspring born to Group 2, 191 born to Group 3, and 577 born to Group 4 fathers. In the seven-group sampling design variable, there were 455 offspring born to Group 1 fathers, 75 born to Group 2, 81 to Group 3, 548 to Group 4, 170 to Group 5, 148 to Group 6, and 440 to Group 7.

The mean ages of onset of trying cigarettes and regular smoking were 14 and 16 years, respectively. Among all offspring, 613 were classified as never having tried a cigarette, and 657 had ever tried a cigarette but did not progress beyond this smoking stage. Another 306 offspring had reached regular smoking status but were not nicotine dependent, and 311 were nicotine dependent by FTND criteria. The distribution of offspring smoking outcomes by predictor variables is shown in Table 1.

Because the sampling design variable was included in all modeling, we report the significant association between the paternal drug-dependence and alcohol-dependence variable and offspring smoking outcomes in Table 2. Before inclusion of the four-group paternal nicotine-dependence variable, offspring of alcohol-dependent fathers were significantly more likely to have ever tried a cigarette (odds ratio [OR] = 1.39, 95% CI [1.03, 1.87]), and offspring with drug-dependent or alcohol-dependent fathers were significantly more likely to be regular smokers (OR = 1.92, 95% CI [1.29, 2.86]) and have FTND-criteria nicotine dependence (OR = 3.08, 95% CI [2.02, 4.70]). FTND was also more common in offspring of monozygotic twins whose co-twin had drug dependence or alcohol dependence (OR = 3.39, 95% CI [1.65, 6.95]) and more common in offspring of alcohol-dependent fathers (OR = 2.18, 95% CI [1.44, 3.29]).

As shown in Table 3, after adjusting for the drug-dependence/alcohol-dependence sampling design and for sociodemographic variables, there was no significant association between ever smoking and the four-group nicotine-dependence design and maternal Heaviness of Smoking Index score. Ever being a regular smoker significantly increased the odds of being an offspring from Group 1 as compared with Group 4 (OR = 1.54, 95% CI [1.03, 2.92]). Regular

TABLE 1. Distribution (%) of offspring smoking outcomes by sample characteristics

Variable	Never tried cigarette (n = 628)	Ever tried cigarette (n = 667)	Regular smoking (n = 310)	FTND[a] (n = 314)
Paternal conduct disorder				
No	33.7	35.1	15.9	15.4
Yes	24.9	32.9	18.3	23.9
Paternal ASPD				
No	33.3	35.3	16.0	15.5
Yes	18.8	23.8	21.3	36.3
Paternal depression				
No	33.6	35.1	16.1	15.1
Yes	24.6	32.0	16.8	26.6
Paternal anxiety				
No	34.0	34.3	15.9	15.8
Yes	25.2	37.4	17.8	19.6
Maternal alcohol dependence				
No	33.2	35.6	15.7	15.7
Yes	28.3	28.8	20.3	22.6
Maternal ≥2 conduct disorder symptoms				
No	34.0	35.2	15.5	15.3
Yes	25.7	31.9	19.5	23.0
Maternal ≥2 ASPD disorder symptoms				
No	33.3	35.2	16.5	14.9
Yes	27.7	31.1	13.1	28.2
Maternal depression				
No	34.6	34.3	15.8	15.3
Yes	27.9	36.1	16.7	19.4
Paternal ND risk group[b]				
1 (HG-HE)	27.8	33.1	17.3	21.8
2 (HG-LE)	32.5	29.3	18.5	19.8
3 (MG-LE)	39.8	33.5	15.7	11.0
4 (LG-LE)	39.0	39.5	13.7	7.8
Maternal Heaviness of Smoking Index				
Nonsmoker	36.7	35.1	14.4	13.9
Low	29.3	37.1	19.8	13.9
High	25.8	32.3	17.2	24.8
Paternal DD and AD risk groups[c]				
Grp. 1 father DD/AD	26.8	31.9	19.3	22.0
Grp. 2 MZ co-twin DD/AD	26.7	29.3	20.0	24.0
Grp. 3 DZ co-twin DD/AD	39.5	24.5	21.0	14.8
Grp. 4 father AD	30.3	38.0	14.2	17.5
Grp. 5 MZ co-twin AD	34.1	36.5	15.9	13.5
Grp. 6 DZ co-twin AD	37.8	35.8	13.5	12.8
Grp. 7 unaffected	39.3	35.5	14.8	10.5
Paternal race				
White	31.4	35.1	16.7	16.9
Other	52.0	30.4	8.8	8.8
Offspring gender				
Male	31.0	35.5	14.3	19.2
Female	34.4	34.0	17.9	13.6
Paternal education				
≤High school	32.6	35.8	15.3	16.3
>High school	32.7	34.1	16.8	16.5
Maternal education				
≤High school	29.4	35.5	14.6	20.5
>High school	34.6	34.4	17.0	14.1
Biological parents marital status				
Married	36.3	35.3	15.8	12.6
Div./sep./wid./never married	23.1	32.9	17.3	26.7
Offspring age				
≥24	23.6	38.2	17.6	20.6
21-23	20.5	37.7	23.1	18.6
18-20	29.2	33.8	17.7	19.4
16-17	52.7	31.3	8.0	8.04
12-15	74.2	22.7	2.5	0.51

Notes: FTND = The Fagerström Test for Nicotine Dependence; ASPD = antisocial personality disorder; ND = nicotine dependence; HG = high genetic; HE = high environmental; LE = low environmental; MG = medium genetic; LG = low genetic; DD = drug dependence; AD = alcohol dependence; Grp. = group; MZ = monozygotic; DZ = dizygotic; div./sep./wid. = divorced/separated/widowed. [a]Variables included in model if they were significantly associated with the

(*table continues*)

TABLE 2. Results of multinomial logistic regression models demonstrating the association between paternal drug-dependence (DD) and alcohol-dependence (AD) sampling design variable and offspring smoking outcomes

Paternal DD and AD risk groups[a]	Ever tried cigarette (n = 667) vs. never tried cigarette (n = 628) OR [95% CI]	Regular smoking (n = 310) vs. never tried cigarette (n = 628) OR [95% CI]	FTND (n = 314) vs. never tried cigarette (n = 628) OR [95% CI]
Grp. 1 father DD/AD (n = 455)	1.32 [0.95, 1.83]	**1.92 [1.29, 2.86]**	**3.08 [2.02, 4.70]**
Grp. 2 MZ co-twin DD/AD (n = 75)	1.22 [0.64, 2.33]	2.0 [0.96, 4.15]	**3.39 [1.65, 6.95]**
Grp. 3 DZ co-twin DD/AD (n = 81)	0.69 [0.38, 1.27]	1.41 [0.73, 2.73]	1.41 [0.67, 2.97]
Grp. 4 father AD (n = 548)	**1.39 [1.03, 1.87]**	1.25 [0.84, 7.86]	**2.18 [1.44, 3.29]**
Grp. 5 MZ co-twin AD (n = 170)	1.19 [0.78, 1.81]	1.24 [0.72, 2.13]	1.49 [0.83, 2.68]
Grp. 6 DZ co-twin AD (n = 148)	1.05 [0.68, 1.62]	0.95 [0.53, 1.71]	1.28 [0.69, 2.37]
Grp. 7 unaffected (n = 440)	1.0	1.0	1.0

Notes: **Bold text** = significant odds ratio. FTND = The Fagerström Test for Nicotine Dependence; OR = odds ratio; CI = confidence interval; Grp. = group; MZ = monozygotic; DZ = dizygotic. [a]Seven-group design based on father and co-twins AD and DD status and zygosity. Group 1 consisted of offspring born to fathers with drug dependence (DD) with and without alcohol dependence (AD). Group 2 offspring were born to unaffected MZ twins whose co-twin had DD with and without AD. Group 3 offspring were born to unaffected DZ twin fathers whose co-twin had DD with and without AD. Group 4 offspring were born to fathers with AD. Group 5—offspring had unaffected MZ twin fathers whose co-twin had AD. Group 6 offspring had unaffected DZ twin fathers whose co-twin had AD. Group 7 offspring were born to MZ and DZ twins without DD and AD.

smoking was associated with low and high maternal Heaviness of Smoking Index scores as compared with maternal never smoking (OR = 1.85, 95% CI [1.23, 2.77] and OR = 1.84, 95% CI [1.23, 2.75], respectively). FTND-criteria nicotine dependence was significantly associated with being an offspring of Group 1 and Group 2 fathers as compared with offspring of Group 4 fathers (OR = 2.79, 95% CI [1.81, 4.29] and OR = 2.20, 95% CI [1.15, 4.21], respectively). Offspring FTND-criteria nicotine dependence was associated with high maternal Heaviness of Smoking Index scores (OR = 2.72, 95% CI [1.82, 4.07]).

Before adjusting for the four-group nicotine-dependence design (and, therefore, before adjusting for genetic and environmental risk for nicotine dependence), results from separate multinomial models for each parental psychopathology adjusted for the drug-dependence/alcohol-dependence sampling design and sociodemographics are shown in Table 4. Ever trying a cigarette was significantly associated with maternal depression (OR = 1.33, 95% CI [1.01, 1.76]). Regular smoking was significantly associated with maternal alcohol dependence (OR = 1.43, 95% CI [1.04, 1.97]) and maternal conduct disorder (OR = 1.69, 95% CI [1.03, 2.79]). FTND-criteria nicotine dependence was significantly associated with paternal conduct disorder (OR = 1.64, 95% CI [1.01, 2.65]), paternal antisocial personality disorder (OR = 3.51, 95% CI [1.36, 9.06]), maternal alcohol dependence (OR = 2.25, 95% CI [1.55, 3.27]), maternal conduct disorder (OR = 1.91, 95% CI [1.16, 3.17]), maternal antisocial personality disorder (OR = 2.45, 95% CI [1.48, 4.06]), and maternal depression (OR = 1.67, 95% CI [1.17, 2.39]).

As shown in Table 5, after simultaneously adjusting for significant parental psychopathology, four-group nicotine-dependence design variables, maternal Heaviness of Smoking Index scores, and the seven-group drug-dependence/alcohol-dependence sampling design variables and sociodemographics, no parental psychopathology remained significantly associated with regular smoking. Offspring at high genetic risk and high environmental risk (paternal nicotine-dependence risk Group 1) and offspring at high genetic risk and low environmental risk (paternal nicotine-dependence risk Group 2) were significantly more likely to meet FTND criteria for nicotine dependence compared with offspring at low genetic and low environmental risk (paternal nicotine-dependence risk Group 4) (OR = 2.58, 95% CI [1.60, 4.14] and OR = 2.30, 95% CI [1.13, 4.71], respectively). Offspring at familial risk because of low maternal Heaviness of Smoking Index scores were more likely to be non-nicotine-dependent regular smokers (OR = 1.84, 95% CI [1.18, 2.86]), and offspring of mothers with high Heaviness of Smoking Index scores were more likely to meet FTND criteria for nicotine dependence (OR = 2.19, 95% CI [1.35, 3.53]) compared with offspring of

(Table 1. *continued*)

smoking outcome in univariate analyses. [b]Four-group design: Group 1—offspring at high genetic (HG) and high environmental (HE) risk because fathers are MZ and DZ twins with Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), ND; Group 2—offspring at high genetic (HG) and low environmental (LE) risk because fathers are unaffected MZ twins whose co-twin has DSM-III-R ND; Group 3—offspring at medium genetic (MG) and LE risk because fathers are unaffected DZ twins whose co-twin has DSM-III-R ND; Group 4—offspring at low genetic and LE because fathers are unaffected ND MZ and DZ control pairs. [c]Seven-group sampling design variable: seven-group design based on father and co-twins AD and DD status and zygosity. Group 1 consisted of offspring born to fathers with drug dependence (DD) with and without alcohol dependence (AD). Group 2 offspring were born to unaffected MZ twins whose co-twin had DD with and without AD. Group 3 offspring were born to unaffected DZ twin fathers whose co-twin had DD with and without AD. Group 4 offspring were born to fathers with AD. Group 5—offspring had unaffected MZ twin fathers whose co-twin had AD. Group 6 offspring had unaffected DZ twin fathers whose co-twin had AD, and Group 7 offspring were born to MZ and DZ twins without DD and AD.

TABLE 3. Results of multinomial logistic regression models testing the association between offspring smoking outcomes and parental nicotine-dependence (ND) risk groups[a] adjusted for sampling design[b] and sociodemographic variables[c]

Variable	Ever tried cigarette (n = 667) vs. never tried cigarette (n = 628) OR [95% CI]	Regular smoking (n = 310) vs. never tried cigarette (n = 628) OR [95% CI]	FTND (n = 314) vs. never tried cigarette (n = 628) OR [95% CI]
Paternal ND risk group			
1 (HG, HE) (n = 994)	1.05 [0.78, 1.42]	**1.54 [1.03, 2.92]**	**2.79 [1.81, 4.29]**
2 (HG, LE) (n = 157)	0.81 [0.49, 1.36]	1.51 [0.81, 2.82]	**2.20 [1.15, 4.21]**
3 (MG, LE) (n = 191)	0.71 [0.46, 1.11]	0.89 [0.50, 1.60]	1.07 [0.55, 2.09]
4 (LG, LE) (n = 577)	1.0	1.0	1.0
Maternal Heaviness of Smoking Index			
Nonsmoker	1.0	1.0	1.0
Low	1.31 [0.94, 1.83]	**1.85 [1.23, 2.77]**	1.34 [0.86, 2.10]
High	1.34 [0.97, 1.85]	**1.84 [1.23, 2.75]**	**2.72 [1.82, 4.07]**

Notes: **Bold text** = significant odds ratio. FTND = The Fagerström Test for Nicotine Dependence; OR = odds ratio; CI = confidence interval; HG = high genetic; HE = high environmental; LE = low environmental; MG = medium genetic; LG = low genetic. [a]Four-group design: Group 1—offspring at high genetic (HG) and high environmental (HE) risk because fathers are monozygotic (MZ) and dizygotic (DZ) twins with Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), ND; Group 2—offspring at high genetic (HG) and low environmental (LE) risk because fathers are unaffected MZ twins with DSM-III-R ND; Group 3—offspring at medium genetic (MG) and LE risk because fathers are unaffected DZ with DSM-III-R ND; Group 4—offspring at low genetic and LE because fathers are unaffected ND MZ and DZ control pairs. [b]Adjusted for seven-group sampling design variable: Seven-group design based on father's and co-twins' alcohol-dependence (AD) and drug-dependence (DD) status and zygosity. Group 1 consisted of offspring born to fathers with DD with and without AD. Group 2 offspring were born to unaffected MZ twins whose co-twin had DD with and without AD. Group 3 offspring were born to unaffected DZ twin fathers whose co-twin had DD with and without AD. Group 4 offspring were born to fathers with AD. Group 5—offspring had unaffected MZ twin fathers whose co-twin had AD. Group 6 offspring had unaffected DZ twin fathers whose co-twin had AD. Group 7 offspring were born to MZ and DZ twins without DD and AD. [c]Adjusted for offspring age, gender, paternal race (White vs. non-White), paternal and maternal education and biological parents' marital status and missing maternal data.

nonsmoking mothers. Genetic and environmental vulnerability for drug dependence/alcohol dependence was not associated with risk for any smoking outcome. White race was associated with ever trying a cigarette (OR = 2.09, 95% CI [1.31, 3.34]), regular smoking (OR = 3.75, 95% CI [1.81, 7.75]), and FTND-criteria nicotine dependence (OR = 3.41, 95% CI [1.56, 7.49]). Male gender was associated with FTND-criteria nicotine dependence (OR = 1.79, 95% CI [1.29, 2.49]). Increasing age of offspring was associated with increasing odds of ever smoking,

TABLE 4. Multinomial models measuring the association between offspring smoking outcomes and parental psychiatric disorders adjusted for sampling design[a] and sociodemographic variables[b]

Variable	Ever tried cigarette (n = 667) vs. never tried cigarette (n = 628) OR [95% CI]	Regular smoking (n = 310) vs. never tried cigarette (n = 628) OR [95% CI]	FTND (n = 314) vs. never tried cigarette (n = 628) OR [95% CI]
Paternal conduct disorder	1.12 [0.75, 1.70]	1.33 [0.81, 2.16]	**1.64 [1.01, 2.65]**
Paternal ASPD	1.17 [0.50, 2.75]	2.45 [0.89, 6.74]	**3.51 [1.36, 9.06]**
Paternal depression	1.03 [0.66, 1.60]	1.06 [0.60, 1.86]	1.35 [0.81, 2.25]
Paternal anxiety	1.25 [0.87, 1.79]	1.10 [0.69, 1.75]	1.05 [0.65, 1.68]
Maternal alcohol dependence	1.14 [0.80, 1.62]	**1.43 [1.04, 1.97]**	**2.25 [1.55, 3.27]**
Maternal ≥2 conduct disorder symptoms	1.23 [0.83, 1.81]	**1.69 [1.03, 2.79]**	**1.91 [1.16, 3.17]**
Maternal ≥2 ASPD disorder symptoms	1.11 [0.73, 1.69]	1.07 [0.59, 1.92]	**2.45 [1.48, 4.06]**
Maternal depression	**1.33 [1.01, 1.76]**	1.34 [0.95, 1.90]	**1.67 [1.17, 2.39]**

Notes: **Bold text** = significant odds ratio; FTND = The Fagerström Test for Nicotine Dependence; OR = odds ratio; CI = confidence interval; ASPD = antisocial personality disorder. [a]Seven-group sampling design variable: Seven-group design based on father's and co-twins' alcohol-dependence (AD) and drug-dependence (DD) status and zygosity. Group 1 consisted of offspring born to fathers with DD with and without AD. Group 2 offspring were born to unaffected monozygotic (MZ) twins whose co-twin had DD with and without AD. Group 3 offspring were born to unaffected dizygotic (DZ) twin fathers whose co-twin had DD with and without AD. Group 4 offspring were born to fathers with AD. Group 5—offspring had unaffected MZ twin fathers whose co-twin had AD. Group 6 offspring had unaffected DZ twin fathers whose co-twin had AD. Group 7 offspring were born to MZ and DZ twins without DD and AD. [b]Adjusted for offspring age, gender, paternal race (White vs. non-White), paternal and maternal education, biological parents' marital status, and missing maternal data.

TABLE 5. Multinomial models measuring the association between offspring smoking outcomes and parental psychiatric disorders, familial nicotine-dependence (ND) risk group, sampling design variables, and sociodemographics adjusted for significant[a] covariates

Variable	Ever tried cigarette (n = 667) vs. never tried cigarette (n = 628) OR [95% CI]	Regular smoking (n = 310) vs. never tried cigarette (n = 628) OR [95% CI]	FTND (n = 314) vs. never tried cigarette (n = 628) OR [95% CI]
Paternal conduct disorder	1.11 [0.65, 1.88]	0.97 [0.54, 1.74]	0.96 [0.44, 2.10]
Paternal ASPD	0.97 [0.35, 2.69]	2.33 [0.71, 7.62]	2.65 [0.77, 9.06]
Maternal alcohol dependence	0.91 [0.56, 1.48]	1.32 [0.73, 2.40]	1.18 [0.62, 2.25]
Maternal ≥2 conduct disorder symptoms	1.10 [0.72, 1.67]	1.33 [0.78, 2.28]	1.22 [0.70, 2.11]
Maternal ≥2 ASPD symptoms	0.92 [0.58, 1.45]	0.78 [0.43, 1.45]	1.57 [0.89, 2.77]
Maternal depression	1.32 [0.97, 1.80]	1.25 [0.84, 1.86]	1.22 [0.78, 1.91]
Paternal ND risk group[b]			
1 (HG-HE)	1.04 [0.75, 1.43]	1.44 [0.93, 2.24]	**2.58 [1.60, 4.14]**
2 (HG-LE)	0.81 [0.46, 1.42]	1.44 [0.74, 2.83]	**2.30 [1.13, 4.71]**
3 (MG-LE)	0.74 [0.46, 1.17]	0.96 [0.52, 1.80]	1.07 [0.51, 2.23]
4 (LG-LE)	1.0	1.0	1.0
Maternal Heaviness of Smoking Index			
Nonsmoker	1.0	1.0	1.0
Low	1.29 [0.92, 1.83]	**1.84 [1.18, 2.86]**	1.34 [0.83, 2.17]
High	1.26 [0.88, 1.80]	1.55 [0.98, 2.45]	**2.19 [1.35, 3.53]**
Maternal data missing	1.0	1.0	1.0
Maternal data not missing	1.59 [0.90, 2.80]	0.88 [0.45, 1.69]	0.93 [0.49, 1.79]
Paternal DD and AD risk groups[c]			
Grp. 1 father DD/AD	1.19 [0.78, 1.81]	1.30 [0.75, 2.25]	1.18 [0.66, 2.11]
Grp. 2 MZ co-twin DD/AD	1.14 [0.49, 2.62]	1.66 [0.74, 3.71]	1.59 [0.61, 4.14]
Grp. 3 DZ co-twin DD/AD	0.72 [0.36, 1.46]	1.25 [0.56, 2.80]	0.75 [0.29, 1.91]
Grp. 4 father AD	1.32 [0.90, 1.93]	1.05 [0.63, 1.75]	1.35 [0.79, 2.30]
Grp. 5 MZ co-twin AD	1.21 [0.71, 2.04]	1.09 [0.55, 2.17]	1.22 [0.60, 2.51]
Grp. 6 DZ co-twin AD	1.33 [0.80, 2.22]	1.08 [0.52, 2.24]	1.43 [0.67, 3.06]
Grp. 7 unaffected	1.0	1.0	1.0
Paternal race			
White	**2.09 [1.31, 3.34]**	**3.75 [1.81, 7.75]**	**3.41 [1.56, 7.49]**
Offspring gender			
Male	1.24 [0.97, 1.59]	0.99 [0.73, 1.37]	**1.79 [1.29, 2.49]**
Paternal education			
≤High school	1.0	1.0	1.0
>High school	0.93 [0.71, 1.23]	1.00 [0.71, 1.43]	0.97 [0.67, 1.39]
Maternal education			
≤High school	1.0	1.0	1.0
>High school	0.78 [0.58, 1.06]	1.16 [0.79, 1.72]	0.72 [0.48, 1.09]
Biological parents marital status			
Married	**0.71 [0.51, 0.98]**	0.72 [0.47, 1.11]	**0.39 [0.26, 0.60]**
Div./sep./wid./never married	**1.0**	1.0	**1.0**
Offspring age			
≥24	**6.28 [4.13, 9.55]**	**25.25 [9.55, 66.76]**	**179.73 [21.7, 999.99]**
21-23	**7.23 [4.60, 11.35]**	**39.43 [14.67, 105.99]**	**216.75 [25.70, 999.99]**
18-20	**4.18 [2.75, 6.36]**	**17.85 [6.66, 47.82]**	**153.10 [18.18, 999.99]**
16-17	**2.02 [1.27, 3.23]**	**4.68 [1.63, 13.45]**	**28.43 [3.28, 246.89]**
12-15	**1.0**	**1.0**	**1.0**

Notes: **Bold text** = significant odds ratio. FTND = The Fagerström Test for Nicotine Dependence; ASPD = antisocial personality disorder; HG = high genetic; HE = high environmental; LE = low environmental; MG = medium genetic; LG = low genetic; DD = drug dependence; AD = alcohol dependence; Grp. = group; MZ = monozygotic; DZ = dizygotic; div./sep./wid. = divorced/separated/widowed. [a]Variables included in model if they were significantly associated with the smoking outcome in univariate analyses. [b]Four-group design: Group 1—offspring at HG and HE risk because fathers are MZ and DZ twins with Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), ND; Group 2—offspring at HG and LE risk because fathers are unaffected MZ twins whose co-twin has DSM-III-R ND; Group 3—offspring at MG and LE risk because fathers are unaffected DZ twins whose co-twin has DSM-III-R ND; Group 4—offspring at LG and LE risk because fathers are unaffected ND MZ and DZ control pairs. [c]Seven-group sampling design variable: Seven-group design based on father and co-twins AD and DD status and zygosity. Group 1 consisted of offspring born to fathers with drug dependence (DD) with and without alcohol dependence (AD). Group 2 offspring were born to unaffected MZ twins whose co-twin had DD with and without AD. Group 3 offspring were born to unaffected DZ twin fathers whose co-twin had DD with and without AD. Group 4 offspring were born to fathers with AD. Group 5—offspring had unaffected MZ twin fathers whose co-twin had AD. Group 6 offspring had unaffected DZ twin fathers whose co-twin had AD. Group 7 offspring were born to MZ and DZ twins without DD and AD.

regular smoking, and FTND-criteria nicotine dependence. Last, offspring were less likely to ever try a cigarette (OR = 0.71, 95% CI [0.51, 0.98]) and meet FTND-criteria nicotine dependence (OR = 0.39, 95% CI [0.26, 0.60]) if their parents remained married to each other.

Discussion

In the present offspring-of-twins design, regular smoking and FTND-criteria nicotine dependence were associated with high familial genetic vulnerability for nicotine dependence, and ever trying a cigarette was not associated with familial risk for nicotine dependence. Before adjusting for familial vulnerability for nicotine dependence, ever smoking was associated with maternal depression; regular smoking was associated with maternal alcohol dependence and conduct disorder; and FTND-criteria nicotine dependence was associated with paternal conduct disorder and antisocial personality disorder and with maternal alcohol dependence, conduct disorder, antisocial personality disorder, and depression. No psychopathology assessed in this cohort remained significantly associated with ever smoking, regular smoking, and FTND-criteria nicotine dependence after controlling for genetic and environmental vulnerability to parental nicotine dependence.

Parental nicotine dependence largely accounts for the association between parental psychopathology and offspring regular smoking and nicotine dependence. However, we note that the point estimates in our fully adjusted model for the association between father antisocial personality disorder and offspring regular smoking and nicotine dependence were large (OR = 2.33 and 2.65, respectively), as was the point estimate for the association between maternal antisocial personality disorder and offspring nicotine dependence (OR = 1.57). Although not significant, it is possible that a larger cohort would have resulted in positive significant associations between parental antisocial personality disorder and offspring smoking, even after accounting for familial vulnerability. The role of parental antisocial behavior is well established in previous research (Herndon and Iacono, 2005; Hicks et al., 2004; Johnson et al., 2006). We believe the present analyses extend the literature, because our data indicate that the association is partly mediated by familial contributions to offspring regular smoking and nicotine dependence, which is consistent with Hicks et al.'s (2004) twin-family study that indicates common familial vulnerability accounts for the transmission of conduct disorder and alcohol and drug dependence.

Limitations

Paternal psychiatric disorders were diagnosed according to DSM-III-R criteria and mother and offspring disorders were diagnosed by DSM-IV criteria. It was beyond the scope of the data collection to re-assess all psychiatric disorders in fathers. It is unlikely that the effect of father's disorders would have been different if they were derived for lifetime DSM-IV. Indeed, the DSM-III-R criteria for nicotine dependence remained a robust significant predictor of offspring regular smoking and nicotine dependence. We were also limited to analysis of maternal conduct-disorder and antisocial-personality-disorder symptoms, because data were not collected to derive a full diagnostic variable for conduct disorder in mothers. The association between two or more conduct-disorder symptoms and antisocial-personality-disorder symptoms is likely a conservative measure of the association between full diagnosis of conduct disorder and offspring smoking outcomes. The Vietnam Era Twin Registry cohort has limited variation in race. Because of the inaccurate self-reported race evident in the offspring data, we were limited to using paternal race, which was overwhelmingly White. Conclusions regarding the association between paternal psychopathology and offspring nicotine dependence are limited because not all offspring have passed through the age of risk for regular smoking and nicotine dependence. Future analyses of longitudinal data will determine if our current observations hold as offspring age.

Strengths

The offspring-of-twins design permits both (a) a test of familial influences, and (b) when examined within the multivariate model, an assessment of the direct effect of covariates that are otherwise confounded by shared familial vulnerability (e.g., parental psychopathology is correlated with paternal nicotine dependence). Additional strengths include the large sample size and nonclinical sample that enhance generalizability to other community-based adolescent and young-adult populations. In fact, the prevalence of nicotine dependence in the current cohort of regular smokers (50%) is consistent with findings from similarly aged respondents to the National Epidemiologic Survey of Alcoholism and Related Conditions, in which 54% of smokers 18-25 years of age were nicotine dependent (Goodwin et al., 2009). Last, the structured method of data collection reduced the chance for interviewer bias.

Conclusions

Nonfamilial factors of race, parent's intact marital status, and increasing offspring age explained the risk for smoking initiation in this cohort. Familial vulnerability accounts for much of the risk of regular smoking and nicotine dependence. In this offspring-of-twins design, paternal psychiatric disorders did not remain independent predictors of ever smoking, offspring regular smoking, and nicotine dependence after accounting for genetic and environmental liability.

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