Nicotine & Tobacco Research Volume 10, Number 4 (April 2008) 567–578

Correlates of cigarette smoking during pregnancy and its genetic and environmental overlap with nicotine dependence

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Received 19 April 2007; accepted 13 September 2007

Cigarette smoking during pregnancy (CSDP) is associated with a number of negative outcomes in the offspring. Therefore, clarifying the correlates of CSDP and the extent to which CSDP is associated with nicotine dependence is an important step toward reducing its rate in the general population. Using data from 1,134 adult Australian female monozygotic and dizygotic twin pairs, we explored the associations between CSDP and sociodemographic and psychiatric correlates and between CSDP and patterns of cigarette smoking. Further, we examined the role of heritable and environmental influences on CSDP and investigated whether these latent risk factors are shared with a predisposition to nicotine dependence. Women smoking during an entire pregnancy reported heavier dependence and more unsuccessful quit attempts, compared with the community sample of mothers and with women who smoked during only part of a pregnancy. Educational attainment, weekly church attendance, spousal current smoking, and nicotine dependence also were associated with CSDP. Heritable influences explained 34% of the variation in CSDP, with the remainder related to nonshared environmental factors. A large proportion of the genetic influences on CSDP were shared with *DSM*-III-R nicotine dependence, with little overlap across the nonshared environmental influences. A lifetime history of difficulty with smoking cessation, in conjunction with social background and psychiatric comorbidity, especially during pregnancy, needs to be considered by treatment providers when counseling expectant mothers about the potential risks of CSDP.

Introduction

Cigarette smoking during pregnancy

Cigarette smoking is a major public health concern associated with significant morbidity and mortality (Centers for Disease Control and Prevention [CDC], 2002). According to the CDC (2004), cigarette smoking during pregnancy (CSDP) was reported by 11.4% of all women giving birth in the United States in 2002. Because of its proposed association with poor physiological and psychological outcomes in the offspring, eliminating the deleterious effects of CSDP is considered a key goal of the Healthy People 2010 initiative (U.S. Department of Health and Human Services, 2000).

Research has highlighted the association between CSDP on child outcomes, such as low birth weight (Bada et al., 2005; Knopik et al., 2005; Salihu, Aliyu, & Kirby, 2005) and possibly conduct disorder (D'Onofrio et al., 2008; Maughan, Taylor, Caspi, & Moffitt, 2004; Silberg et al., 2003; Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002, Wakschlag, Pickett, Kasza, & Loeber, 2006) and attention-deficit/hyperactivity disorder (ADHD; Fergusson, Woodward, & Horwood, 1998; Knopik et al., 2006; Milberger, Biederman, Faraone, Chen, & Jones, 1996, 1997; Milberger, Biederman, Faraone, &

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ISSN 1462-2203 print/ISSN 1469-994X online

DOI: 10.1080/14622200801978672

Jones, 1998; Wakschlag et al., 2006). Despite the wide range of basic science and epidemiological research outlining the detrimental effects of CSDP, only a few studies have explored the etiology of CSDP itself. In the presence of widely available information on the negative consequences of cigarette smoking on fetal health, why do some women smoke during their pregnancy? What measured and unmeasured risk factors contribute to this behavior?

Cigarette smoking behaviors in women who smoke during a pregnancy

A lifetime history of difficulty quitting and staying smoke free, elevated levels of nicotine dependence (i.e., endorsing more *DSM*-IV symptoms of nicotine dependence), and increased nicotine withdrawal may contribute to CSDP. When compared with pregnant women who don't quit, pregnant smokers attempting to quit smoking during pregnancy report elevated levels of impatience, anger, and difficulty concentrating (Heil, Higgins, Mongeon, Badger, & Bernstein, 2006), which further exacerbates subsequent quit attempts. Additionally, women who continue to smoke during pregnancy tend to have higher mean Global Severity Index scores, with these mental health problems influencing and being influenced by inability to quit smoking (Solomon et al., 2006). Therefore, along with sociodemographic and psychiatric correlates, cigarette smoking behaviors may also affect CSDP.

Other correlates of CSDP

A number of sociodemographic correlates such as high educational attainment and high levels of religiosity may provide a protective influence whereas comorbid psychiatric disorders, such as depression, alcohol abuse or dependence, and conduct disorder may serve as risk factors. Fergusson et al. (1998) reported that women who lacked a formal education or were unskilled, who were young or with an unplanned pregnancy, used alcohol regularly or experimented with illicit drugs, were less emotionally responsive, and had experienced parental discord themselves were highly likely to smoke during their pregnancy. Maughan et al. (2004) reported similar associations between CSDP and maternal antisocial behavior, depression, and economic disadvantage. We also expected that being nicotine dependent might be a key correlate of CSDP.

Genetic effects on CSDP and its relationship with nicotine dependence

Little is known about genetic contributions to CSDP. One study supported the role of heritable influences on CSDP (D'Onofrio et al., 2003) but did not address whether these latent genetic factors specifically influenced CSDP or were in fact a reflection of genetic influences on the closely related phenotype of nicotine dependence. In adult samples, substantial heritable influences have been reported for nicotine dependence (Kendler et al., 1999; Lessov et al., 2004; Sullivan & Kendler, 1999) and for smoking persistence (Madden et al., 1999; Madden, Pedersen, Kaprio, Koskenvuo, & Martin, 2004). We hypothesized that there would be substantial overlap between the genetic and environmental risk factors that make women vulnerable to CSDP and those influencing her liability to nicotine dependence.

In the present study, we used data from adult Australian female twins to address the following questions: (a) Which sociodemographic and psychiatric correlates are associated with CSDP? (b) How do the patterns of cigarette smoking behavior vary in women who smoke during pregnancy, compared with a community sample of mothers and with those women who don't smoke during even one pregnancy? (c) To what extent do heritable and latent environmental risk factors contribute to individual differences in CSDP? (d) To what extent are these genetic and environmental risk factors for CSDP shared with those influencing a vulnerability to nicotine dependence?

Method

Sample

The data for this study were drawn from a twin register supported by the Australian National Health and Medical Research Council (Heath et al., 2001; Heath, Madden, Slutske, & Martin, 1995; Jardine, Martin, & Henderson, 1984; Martin et al., 1985). The Australian Twin Registry (ATR) is a volunteer panel of same-sex monozygotic (MZ) and dizygotic (DZ) twins and opposite-sex dizygotic twin pairs. Figure 1 presents the flow of data collection for the present study. Cohort 1 includes twins born before 1965, who were aged 18 years or older and eligible to complete mailed questionnaire surveys conducted in 1980–1982 and 1988–1989 (Jardine et al., 1984). As shown in Figure 1, during 1992–1994, a reduced and telephone-modified version of the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA) was administered to Cohort 1 (Bucholz et al., 1994; Heath et al., 1997; Hesselbrock, Easton, Bucholz, Schuckit, & Hesselbrock, 1999). This interview, known as the Phase I interview, gathered diagnostic information on alcohol abuse and dependence, major depressive disorder, conduct disorder, social anxiety, and panic disorder. However, the Phase I interview did not include a detailed assessment of cigarette smoking behavior or CSDP.

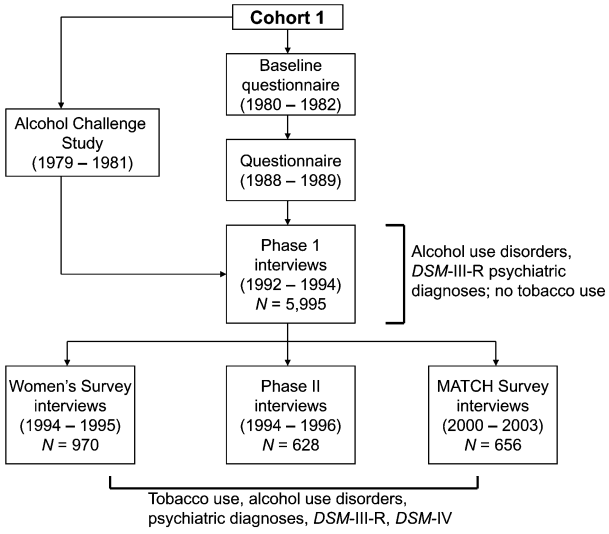

Figure 1. Flowchart of data collection for tobacco use behaviors and cigarette smoking during pregnancy (CSDP) in adult Australian women. Data from Phase II were excluded from current analyses as this interview did not include an assessment of duration of CSDP (full or part).

Data on CSDP, as well as diagnostic assessments for a lifetime history of nicotine dependence, were collected subsequently on two subsamples of women drawn from Cohort 1. To augment diagnostic data from the Phase I interview, the Women's Survey collected detailed information on cigarette smoking behavior, including CSDP, from a subset of 970 Cohort I female twins from pairs where neither member of the twin pair had a lifetime history of *DSM*-III-R alcohol dependence at the prior interview assessment (Madden et al., 1997). The other subsample, from the MATCH survey (Heath et al., 2003; Knopik et al., 2006), was a subset of 656 female twins from Cohort 1, with high-risk over-sampling for twin pairs where at least one twin had a history of *DSM*-IV alcohol abuse or dependence. Only female twin pairs in which at least one twin had children aged 11–23 years were included. Full-length interviews, using the SSAGA, were readministered during the MATCH survey to all participants.

To complement the Women's Survey, nicotine-related data on twin pairs in which one twin met criteria for *DSM*-III-R alcohol dependence at Phase II (Madden et al., 1997) also were collected on 628 individuals (276 women) during Phase II interviews. While the ascertainment for MATCH and Phase II were similar (with MATCH women being mothers of adolescent children), the CSDP section from Phase II did not include comprehensive data on smoking during the full pregnancy and hence have not been used for this study. A total of 268 women were assessed in both interviews (i.e., participated in both MATCH and the Women's Survey). We also used data from the 1988–1989 questionnaire administered to all Cohort I participants, which included self-report questions on educational attainment, frequency of church attendance, parental education, and experiencing traumatic life events. For these analyses, any female twins who reported never having been pregnant at the time of their most recent interview were excluded, including 150 women from the Women's Survey (after exclusion, $n=820$) and 74 women from the MATCH survey who were not the biological mother of their offspring (after exclusion, $n=582$). Therefore, our total sample for the present study consisted of 1,134 women (i.e., 1402–268 women in the Women's and MATCH surveys), with 621 members of MZ pairs, 459 members of DZ twin pairs, and 54 twins with unknown zygosity.

Measures

Cigarette smoking during pregnancy. Patterns of CSDP were assessed only in individuals with a lifetime history of regular cigarette smoking, defined in the MATCH survey as smoking 100 or more cigarettes in their lifetime and in the Women's Survey as lifetime weekly smoking for a period of 6 months or longer. Using the 268 women who participated in both the MATCH and Women's surveys, we determined that these varying definitions of regular smoking were equivalent, with less than 3% reporting lifetime regular smoking in one study but not the other. For our analyses, CSDP was coded as a three-level variable (0=pregnant but never smoked during even one pregnancy, 1=pregnant and smoked cigarettes during any pregnancy but not for the full duration for any pregnancy, and 2=pregnant and smoked cigarettes for the entire duration of any one pregnancy).

Cigarette smoking behaviors. All cigarette smoking behaviors were based on lifetime self-report and were not restricted to assessments during pregnancy alone. *DSM*-III-R nicotine dependence was coded as 0 if the twin was not a regular smoker (regular smoking defined as smoking 100 or more cigarettes or smoking weekly in their lifetime), as 1 if they reported a history of regular smoking but did not subsequently meet criteria for *DSM*-III-R nicotine dependence, and as 2 if they had a lifetime history of *DSM*-III-R nicotine dependence.

Other measures assessing lifetime cigarette smoking behavior that were used as correlates included:

- A lifetime history of heavy smoking (i.e., smoking 20 or more cigarettes per day during heaviest period of smoking);
- A lifetime history of daily smoking;
- Current/persistent smoking (i.e., smoked as recently as the last 6 months);
- A lifetime measure of maximum cigarettes smoked during a single 24-hr period;

- Total number of times successfully quit smoking for 2 weeks or longer;
- A lifetime history of a failed attempt to quit or cut back;
- Withdrawal symptoms, defined as the total number of *DSM*-IV withdrawal symptoms endorsed (range=1–8);
- A lifetime history of relapse to smoking for relief from withdrawal symptoms;
- *DSM*-IV nicotine dependence symptoms, defined as the total number of *DSM*-IV dependence criteria endorsed (range=1–7);
- The two-item Heaviness of Smoking Index (HSI; range=0–6; Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989).

All continuous measures were standardized to a mean of 0 and a variance of 1 for the regression analyses.

Sociodemographic correlates. Three sociodemographic correlates were examined: educational attainment of (a) the participant and (b) the participant's parents (0=primary schooling only, 1=primary and secondary schooling and/or apprenticeship/diploma, 2=tertiary schooling, including technical college or university degree); and (b) weekly church attendance, collected from the 1988–1989 questionnaire (Figure 1).

Traumatic life events. A variable that reflected experiencing four or more stressful or traumatic life events (e.g., loss of property or employment; divorce; infertility or loss of pregnancy; life-threatening illness or accidents; illness, injury, or death of a loved one; and physical or sexual assault) across the lifetime of an individual was used, also from the 1988–1989 questionnaire.

Psychiatric correlates. From the interviews, computerized diagnostic algorithms were used to code lifetime (not pregnancy-specific) diagnoses of nicotine dependence, alcohol abuse and alcohol dependence, major depressive disorder, and childhood conduct disorder, all in accordance with *DSM*-III-R criteria (American Psychiatric Association, 1987). A lifetime nondiagnostic assessment of social anxiety also was included, as were assessments of a lifetime history of repeated panic attacks, lifetime marijuana use (lifetime use of marijuana even once), and lifetime illicit drug use (using cocaine, sedatives, stimulants, opiates, or hallucinogens even once in their lifetime). Current spousal smoking was also coded as a dichotomous measure.

Statistical analyses

Patterns of cigarette smoking and CSDP in the general population. To examine whether aspects of cigarette smoking behavior itself varied across regular cigarette smokers in the general population and those women who smoked during part of, or an entire pregnancy, we used our sample from the Women's and MATCH surveys. Descriptive statistics were computed for regular smokers who ever reported a pregnancy (n=481 of 1,134, or participants representing 54.5% of those who ever tried a cigarette) and for regular smokers with no CSDP (n=67), with CSDP for part of the pregnancy (n=202) or with CSDP for the entire pregnancy (n=212). Multinomial logistic regressions were conducted to examine the association between each of these measures and CSDP.

Sociodemographic and psychiatric correlates and CSDP. To examine the association between sociodemographic and psychiatric correlates and CSDP, we used multinomial logistic regression with the robust Huber-White variance estimator to adjust the standard errors for familial clustering. Both univariate and multivariate models were fit while controlling for zygosity. Post hoc Wald chi-square tests were used to determine whether the associations between women who smoked for part of a pregnancy and those who smoked during an entire pregnancy differed statistically. All analyses were performed using Stata version 8.2.

During interviews, women who did not report a lifetime history of regular smoking were skipped out of the section on CSDP. Therefore, two versions of CSDP were used in the regression analyses: (a) Women without a history of regular cigarette smoking were coded as 0 (collapsed into the category denoting women who did not smoke at all during any pregnancy)—this method allowed us to use the full sample of 1,134 women, and (b) women without a lifetime history of regular smoking were coded as structurally missing and these analyses were conducted on 481 women. Comparing results from (a) and (b), we can informally comment on how the heterogeneity in the group of "unaffected" women, which formed the reference group for logistic regression, altered the association between CSDP and its correlates. If, for instance, a correlate were associated with regular smoking in general but did not associate specifically with CSDP after accounting for regular smoking, then we would expect to find a statistically significant association with (a) but not with (b), where the latter excluded nonregular smokers. In contrast, if a correlate were associated with regular smoking and CSDP, then its association with (a) and (b) would be significant (given adequate power).

Twin analyses

Heritability of CSDP. Data from MZ and DZ twin pairs can be used to disentangle the extent to which

latent genetic, shared environmental, and nonshared environmental factors influence individual differences in CSDP. Genetic factors (A) are correlated 100% and 50% in MZ and DZ pairs, respectively. Shared environmental influences (C), or those factors that make members of a twin pair more similar to each other (e.g., common peer influences), are assumed to be shared 100%, irrespective of zygosity. Nonshared (E) factors make members of a twin pair more distinct from each other, are uncorrelated across twins, and include measurement error. Heritability may be defined as the proportion of the total variance in CSDP (A+C+E) that can be attributed to genetic factors (A/A+C+E). A rough estimate of heritability may be obtained by comparing the correlation between CSDP in MZ and DZ twin pairs; in this case, heritability of CSDP is simply two times the difference between the MZ and DZ correlations. This estimate also can be obtained using the raw data and a statistical software package.

We used data from complete and incomplete twin pairs to estimate the extent to which additive A, C, and E latent factors contributed to individual differences in CSDP. Data on 1,134 women, with nonregular smokers set to missing, were used; and the maximum-likelihood estimator was used to account for these missing data. All twin modeling was conducted using the statistical software package Mx (Neale, 2004). Thresholds were adjusted for significant covariates from the logistic regression models (Table 2).

Overlap between CSDP and nicotine dependence. To examine the extent to which genetic and environmental factors influencing CSDP overlap with factors influencing nicotine dependence, we needed to jointly examine the role of common and specific A, C, and E on these two phenotypes. However, an individual's liability to CSDP and nicotine dependence cannot be assessed in those who never smoke regularly. Therefore, to examine this overlap, we used the hierarchical bivariate genetic model (Heath, Martin, Lynskey, Todorov, & Madden, 2002). The model is illustrated in Figure 2. In this model, regular smokers are divided into those with and without a lifetime history of nicotine dependence, influenced by genetic, shared environmental, and nonshared environmental factors represented by a_{11}, c_{11}, and e_{11}. CSDP is then missing in nonregular smokers but is assessed in regular smokers (as shown by the bar underlying the boxes for CSDP in Figure 2). The genetic and environmental influences on CSDP can now be partitioned into two sources: those that overlap with *DSM*-III-R nicotine dependence (as measured by the correlations Rg, Rc, and Re) and those that are specific to CSDP. In Figure 2, a_{22}, c_{22}, and e_{22} represent the total genetic, shared environmental, and nonshared environmental effects on CSDP. Using this model, we can measure the extent to which the covariation between CSDP and *DSM*-III-R nicotine dependence is related to genetic (Rg), shared environmental (Rc), and nonshared environmental (Re) factors. As for the univariate model, thresholds for CSDP and nicotine dependence were adjusted by including all covariates that were significantly associated with CSDP in the logistic regression analyses (Table 2).

Results

Sample characteristics

The sample of Australian mothers from the Women's and MATCH surveys (i.e., women reporting at least one pregnancy) included 261 and 188 complete MZ and DZ pairs and 236 members of incomplete twin pairs (N=1,134). The mean age of the sample was 39.8 years (95% *CI* 32–49). Of those women who reported ever being pregnant, approximately 42% (481) reported a lifetime history of regular smoking. About 42% and 44% reported CSDP for part of or for their entire pregnancy, respectively. Other characteristics of this sample are available in Heath et al. (1997). As the sample of Australian mothers used in this study draws from two complementary samples (without and with a history of alcoholism), the final sample approximates a general community sample. In our sample, 55% of ever-smokers reported a lifetime history of regular smoking. This finding is consistent with estimates from two general population samples of Australian women, same-aged and reporting at least a single pregnancy, from the same cohort. The first is a sample combining the Women's Survey and Phase II (Agrawal et al., 2006), and the second consists of women from the same cohort who were selected to represent a general Australian community sample (Saccone et al., 2007). In both samples, the prevalence of regular smoking was 56%–61%, which is consistent with our estimate.

Consistency of CSDP and retrospective reporting

Among regular smokers, 15% reported having never smoked during any pregnancy, 48% had smoked during an entire pregnancy, and the remainder (37%) reported smoking for part of a pregnancy. Limited variation in CSDP across pregnancies allowed us to combine data across them. For instance, in MATCH, only seven women who had smoked during their entire first pregnancy reported smoking only during the first trimester of their second pregnancy, whereas three women reported the reverse trend. The patterns of CSDP in the Women's Survey were similar, with a preponderance

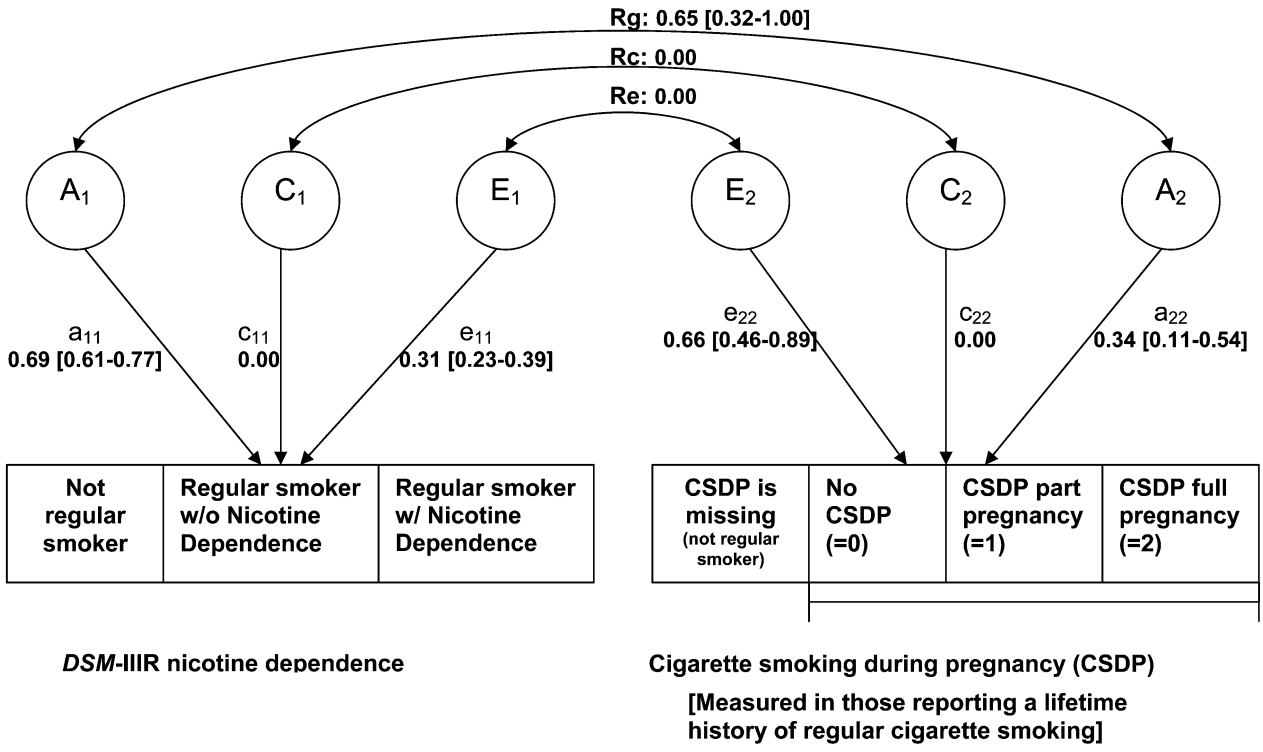

Figure 2. Path diagram, including standardized estimates with their 95% confidence limits (highlighted), showing the bivariate hierarchical model used to estimate the extent of genetic and environmental overlap between cigarette smoking during pregnancy (CSDP) and *DSM*-III-R nicotine dependence. Circles denote latent genetic factors (A_1, A_2 for *DSM*-III-R nicotine dependence and CSDP), environmental factors shared by members of twin pairs (C_1, C_2 for *DSM*-III-R nicotine dependence and CSDP), and environmental factors specific to each twin (E_1, E_2 for *DSM*-III-R nicotine dependence and CSDP), whereas rectangles denote measured or observed phenotypes. CSDP was measured in only two of the three nicotine dependence categories, in regular smokers with and without *DSM*-III-R nicotine dependence. Double-headed arrows represent the extent of genetic (Rg), shared environmental (Rc), and unique environmental (Re) correlation between nicotine dependence and CSDP. All estimates are squared and standardized. The estimates a_{22}, c_{22}, and e_{22} represent the total genetic, shared environmental, and nonshared environmental influences on CSDP. For the genetic influences, the estimate is a combination of genetic factors shared (42%) with nicotine dependence, and those specific to (58%) to CSDP.

of women reporting consistent CSDP across all pregnancies (up to five, in some instances). Heath et al. (2003), using the MATCH survey data, have shown high reliability across self-reported CSDP and twin sister informant ratings on CSDP, using a definition of CSDP similar to the one used in the present study. Reich, Todd, Joyner, Neuman, and Heath (2003), using data from Missouri twins, also showed very high reliability and stability across 6- to 18-month follow-up (κ=.95) for retrospective recall of CSDP.

Patterns of cigarette smoking and CSDP

Table 1 shows descriptive statistics (prevalence and means) for several aspects of cigarette smoking in regular cigarette smokers from the combined Women's Survey and MATCH samples. When regular smoking women (who also reported being pregnant) were stratified by CSDP, women who did not smoke during any pregnancy were found to be similar to women who smoked for part of a pregnancy on daily and persistent smoking, mean number of nicotine dependence symptoms, withdrawal symptoms, quit attempts lasting 2 weeks or longer, and smoking for withdrawal relief. However, women who smoked during even part of their pregnancy were more likely to report a lifetime history of heavy smoking and failed quit attempts and had higher mean HSI scores. These estimates also were quite similar when including only those who had ever tried to quit smoking. However, women who smoked during an entire pregnancy reported significantly higher lifetime estimates of smoking, more withdrawal and dependence, and more failed quit attempts, when compared with the community sample of mothers, with those women who never smoked during part of even one pregnancy, or with those women who smoked during part of a pregnancy. When compared with women who never smoked during any pregnancy, women who smoked during a full pregnancy were nearly eight

Table 1. Descriptive statistics showing patterns of cigarette smoking behavior in regular cigarette smokers from MATCH and Women's Survey participants (N=1,134; 481 regular smokers representing 42% of the population, or 54.5% of ever-smokers[a]). Also shown are relative risk ratios and statistical tests of association between CSDP and smoking behaviors.

	Regular smokers reporting a pregnancy (n=481)	No CSDP (n=67)	CSDP: part pregnancy (n=202)		CSDP: full pregnancy (n=212)	
Characteristic	Prevalence or mean with standard deviation	Prevalence or mean with standard deviation	Prevalence or mean with standard deviation	Relative risk ratio	Prevalence or mean with standard deviation	Relative risk ratio
Daily smoking	86.5%	71.6%	79.7%	1.6 (0.81–2.30)	97.6%	16.4 (5.8–45.9)*
Current/persistent smoking	49.7%	35.8%	34.2%	0.9 (0.51–1.69)	68.9%	4.0 (2.2–7.2)*
Heavy smoking	42.6%	17.9%	30.2%	2.0 (1.0–3.9)*	62.3%	7.6 (3.8–15.0)*
Mean HSI score	2.2 (1.8)	1.1 (1.3)	1.5 (1.7)	1.5 (1.0–2.2)*	3.2 (1.7)	4.1 (2.8–5.9)*
Mean withdrawal symptoms	2.5 (2.2)	2.0 (1.8)	2.1 (2.1)	1.1 (0.8–1.5)	3.1 (2.2)	1.8 (1.3–2.3)*
Mean *DSM*-III-R nicotine dependence symptoms	2.8 (1.5)	2.1 (1.4)	2.5 (1.5)	1.3 (0.9–1.8)	3.4 (1.4)	2.5 (1.8–3.5)*
Maximum cigarettes smoked in 24 hr	27.9 (13.9)	23.2 (13.3)	23.9 (12.8)	1.1 (0.7–1.6)	33.2 (13.3)	2.3 (1.6–3.5)*
Failed quit/cut back	61.8%	40.3%	54.5%	1.8 (1.0–3.2)*	75.5%	4.6 (2.6–8.1)*
Mean number of times quit or cut back for 2 weeks or more	4.7 (10.4)	6.6 (16.7)	5.6 (11.8)	0.9 (0.8–1.2)	3.4 (4.7)	0.6 (0.4–1.0)*
Relapse to smoking for withdrawal relief	32.0%	16.4%	22.8%	1.5 (0.7–3.1)	45.8%	4.3 (2.2–8.6)*

Note. CSDP, cigarette smoking during pregnancy. Reference group is "No CSDP." All relative risk ratios in column labeled "CSDP: full pregnancy" are statistically different from the relative risk ratios in the column labeled "CSDP: part pregnancy." [a]Prevalence of regular smoking in mothers who have ever smoked a cigarette is 54.5%, which is comparable with prevalence of regular smoking in a community sample of same-aged women (56.6%; Agrawal et al., 2006). *$p<.05$.

times more likely to be lifetime heavy smokers and five times more likely to report a failed quit or cut-back attempt. Women who had smoked during an entire pregnancy reported fewer quit attempts lasting 2 weeks or longer and were more than four times more likely to have smoked for withdrawal relief. In addition, the association between aspects of cigarette smoking and CSDP were significantly greater in those smoking during a full versus part of one pregnancy.

Sociodemographic and psychiatric correlates and CSDP

Results for analyses conducted with 1,134 women (with nonregular smokers included) and with 481 regular smokers (nonregular smokers as missing) are presented in Table 2. Being an MZ twin was not associated with increased risk for CSDP. Women who attended church on a weekly basis and those with higher educational attainment were less likely to smoke during their pregnancy, whereas women with a current spouse who smoked were more likely to smoke during part of or an entire pregnancy, with the association being stronger in women who had smoked through an entire pregnancy; Wald chi-square test for equality $\chi^2_{(1)}=4.96$.

When nonregular smokers were included as unaffecteds, a number of psychiatric correlates were associated with CSDP. Note that this variable compares women who smoked during part of or an entire pregnancy with those who either did not smoke regularly (or at all) or with those who smoked regularly but not during a pregnancy. Lifetime marijuana and other illicit drug use (only with CSDP for part of a pregnancy), experiencing traumatic life events, alcohol abuse or dependence, social anxiety (only with CSDP for a full pregnancy), and conduct disorder were associated with CSDP. In addition, the strongest correlate of CSDP was *DSM*-III-R nicotine dependence. This finding is not surprising, given the heterogeneity of the reference group (included nonregular smokers). Compared with nonregular smokers, regular smokers are clearly at increased risk for nicotine dependence and, hence, the high relative risk ratios.

However, as shown in the lower section of Table 2, the association between CSDP and nicotine dependence was not entirely related to regular smoking in general. When analyses were conducted only in those who smoked regularly (i.e., the reference group comprised of regular smokers with no history of CSDP), in addition to church attendance, educational attainment, and spousal smoking, *DSM*-III-R nicotine dependence was still associated with CSDP in both the univariate and multivariate models. In contrast, excluding nonregular smokers eliminated associations between other psychiatric correlates and CSDP.

Table 2. Relative risk ratios (RRR) and 95% Confidence Intervals (C.I.) for the association between cigarette smoking during pregnancy (CSDP) and socio-demographic and psychiatric correlates in adult Australian women.

	CSDP (not entire pregnancy)				CSDP (entire pregnancy)			
	Univariate model		Multivariate model		Univariate model		Multivariate model	
Correlate	*RRR*	95% *CI*	*RRR*	95% *CI*	*RRR*	95% *CI*	*RRR*	95% *CI*
	Non–regular smokers included							
Zygosity	0.97	0.65–1.45	1.20	0.77–1.86	1.45	0.99–2.11	1.41	0.88–2.26
Educational attainment	0.81	0.63–1.05	0.67*	0.49–0.93	0.48*	0.37–0.61	0.40*	0.29–0.56
Paternal education	1.13	0.79–1.29	1.09	0.77–1.53	1.08	0.86–1.35	1.30	0.91–1.83
Maternal education	1.13	0.80–1.36	1.00	0.69–1.43	0.92	0.70–1.19	0.70	0.46–1.06
Weekly church attendance	0.29*	0.15–0.48	0.40*	0.21–0.74	0.16*	0.08–0.33	0.19*	0.07–0.50
Spousal current smoking	1.95*	1.31–2.89	1.36	0.82–2.26	3.73*	2.56–5.41	2.96*	1.77–4.93
Lifetime marijuana use	4.96*	3.41–7.14	3.27*	2.01–5.32	4.30*	2.95–6.25	2.44*	1.42–4.19
Other illicit drug use	2.21*	1.44–3.34	0.90	0.49–1.67	1.52	0.97–2.35	0.68	0.35–1.31
Traumatic life events (4+)	1.80*	1.10–2.96	0.98	0.52–1.85	2.08*	1.25–3.47	1.03	0.49–2.12
Nicotine dependence	29.50*	16.40–53.05	14.83*	8.09–27.02	49.32*	25.88–85.26	30.07*	15.97–56.62
Alcohol abuse/ dependence	3.00*	1.73–5.20	1.78	0.87–3.67	2.76*	1.56–4.89	1.41	0.66–2.94
Social anxiety	1.63	0.83–3.21	1.25	0.51–3.08	2.58*	1.33–4.57	2.50	0.98–6.40
Repeated panic attacks	1.73	0.31–2.13	1.67	0.55–21.48	1.47	0.59–2.89	1.40	0.54–3.61
Conduct disorder	2.81*	1.59–4.97	1.10	0.51–2.37	5.10*	3.00–8.66	2.40*	1.09–5.27
Major depressive disorder	1.24	0.85–1.75	1.00	0.64–1.56	1.05	0.85–1.50	1.52	0.98–2.66
	Non–regular smokers excluded							
Zygosity	0.97	0.65–1.45	0.85	0.34–2.16	1.45	0.99–2.11	0.91	0.37–2.26
Educational attainment	0.98	0.65–1.50	0.97	0.63–1.50	0.56*	0.36–0.86	0.53*	0.33–0.85
Paternal education	0.88	0.62–1.26	1.06	0.68–1.65	0.88	0.60–1.22	1.21	0.77–1.89
Maternal education	0.77	0.52–1.13	0.90	0.56–1.45	0.63	0.42–0.94	0.68	0.41–1.62
Weekly church attendance	0.29*	0.13–0.65	0.41*	0.18–0.96	0.16*	0.06–0.40	0.22*	0.07–0.65
Spousal current smoking	1.51	0.75–3.04	1.40	0.68–2.89	2.92*	1.47–5.81	3.11*	1.50–6.48
Marijuana use	1.33	0.76–2.33	1.25	0.62–2.50	1.77	0.66–2.06	0.93	0.45–1.95
Other illicit drug use	0.84	0.44–1.62	0.55	0.25–1.20	0.58	0.30–1.10	0.46	0.20–1.03
Traumatic life events (4+)	1.02	0.95–2.30	1.13	0.46–2.73	1.17	0.53–2.58	1.19	0.47–3.04
Nicotine dependence	1.25	0.69–2.27	1.18	0.61–2.29	2.56*	1.42–4.58	2.33*	1.20–4.52
Alcohol abuse/ dependence	3.16	0.95–10.57	2.82	0.75–10.72	2.94	0.88–9.83	1.98	0.54–7.27
Social anxiety	2.45	0.54–11.16	1.17	0.22–6.08	4.02	0.90–17.99	2.54	0.53–12.22
Repeated panic attacks	3.10	0.68–14.09	4.23	0.95–18.85	2.70	0.58–12.65	2.93	0.59–14.58
Conduct disorder	1.09	0.53–1.76	0.62	0.23–1.67	2.00	0.87–4.64	1.28	0.45–3.62
Major depressive disorder	1.26	0.68–2.33	1.23	0.64–2.36	1.09	0.59–2.03	1.62	0.30–2.29

Note. All variables were included in multivariate model. Reference group for all analyses was 0=never smoked during any pregnancy.
*$p \leqslant .05$.

Heritability of CSDP and overlap with DSM-III-R nicotine dependence

Our measure of CSDP, with nonregular smokers set to missing, satisfied the assumption of multivariate normality; $\chi^2_{(5)MZ}=2.9$; $\chi^2_{(5)DZ}=2.5$. When nonregular smokers were coded as 0, the CSDP measure satisfied the assumption of multivariate normality but only in MZ pairs; $\chi^2_{(5)MZ}=4.3$; $\chi^2_{(5)DZ}=15.5$. Hence we opted for the CSDP measure with nonregular smokers coded as missing. Univariate analyses revealed that heritable influences (A) contributed to 34% (95% *CI* 11%–60%) of the total variance in CSDP, whereas nonshared environmental factors (E) explained the remaining 66% (95% *CI* 40%–89%) of the variance. We found no statistical evidence for shared environmental factors (C) on the liability to CSDP; constraining

these factors to 0 did not produce a change in model fit; $\chi^2_{(1)}=0.11$.

To fit the bivariate genetic model in Figure 2, we first tested whether *DSM*-III-R nicotine dependence had an underlying normal distribution, which it did; $\chi^2_{(5)MZ}=10.4$; $\chi^2_{(5)DZ}=7.5$. We found no evidence for shared environmental influences on CSDP or on nicotine dependence ($\chi^2_{(3)}=0$); c_{11}, c_{22}, and Rc could be constrained to 0 (Figure 2). Also we found no change in model fit when Re (i.e., the overlap of nonshared environmental influences across CSDP and nicotine dependence) was constrained to 0 ($\chi^2_{(1)}=0.01$). Therefore, the liability to nicotine dependence in this community sample of mothers was related to heritable factors (contributing to 69% of the total variance) and nonshared environmental factors (contributing to 31% of the total variance).

Our best-fitting model of nicotine dependence and CSDP revealed a substantial overlap between the genetic influences on CSDP and those on *DSM*-III-R nicotine dependence (Rg=0.65); nearly 42% (0.65×0.65) of the genetic variance in CSDP was shared with genetic factors influencing *DSM*-III-R nicotine dependence with the remaining 58% related to genetic factors specific to CSDP. In addition, all of the nonshared environmental influences on CSDP (i.e., those factors that make members of a twin pair more distinct from each other) did not overlap with the nonshared environmental factors on *DSM*-III-R nicotine dependence, implying that the covariance (of 0.48) between CSDP and nicotine dependence is related to common genetic liability. In addition, the variance specific to CSDP was attributable to genetic (23%) and nonshared environmental (77%) factors.

Discussion

Cigarette smoking behaviors and CSDP

A majority of clinical studies highlight that dependent smokers have greater difficulty quitting in general (Shiffman, Waters, & Hickcox, 2004), and quitting during pregnancy does not appear to be an exception (Heil et al., 2006). This finding begs the question: Are women who smoke during an entire pregnancy different from a community sample of mothers in their cigarette smoking patterns? Our analyses revealed that smoking during an entire pregnancy was associated with heavier, more frequent, and long-term smoking, with fewer successful quit or cut-back attempts and with increased risk for relapse. Women who smoked during a full pregnancy not only were different from the general population in their increased smoking involvement but also demonstrated a greater inability to quit smoking, potentially related to their increased dependence vulnerability, compared with women who smoked for part of a pregnancy only. In fact, even when number of nicotine dependence criteria endorsed was controlled for, a lifetime history of inability to quit or cut back successfully was associated with smoking during a full pregnancy but not with smoking during part of a pregnancy.

Correlates of CSDP

Several epidemiological studies have focused on the sociodemographic characteristics of CSDP (Heaman & Chalmers, 2005; Jesse & Reed, 2004; Mohsin & Bauman, 2005; Whalen et al., 2006). Therefore, our finding of the positive association with educational attainment and the negative relationship with weekly church attendance, and CSDP, is well supported by the literature. In regular smokers only we did not find a significant association between other psychiatric correlates and CSDP, which may have two possible causes. First, as indicated by broad confidence limits (Table 2), our sample conditioned for regular smoking may have been somewhat small to detect associations with low-prevalence psychiatric correlates (e.g., alcoholism or conduct disorder). Second, prior studies reporting the association between psychiatric correlates and CSDP neglected to test whether this association is mediated by the prior conditional stage of regular smoking. In our analyses, when nonregular smokers were excluded from the reference group, we found no association between psychopathology and CSDP. One reason for this finding is that, when those who didn't report a lifetime (i.e., not pregnancy-specific) history of regular smoking were included in the reference group of unaffecteds, the reference group was heterogeneous and included (a) never or occasional smokers with no CSDP and (b) regular smokers with no CSDP. Therefore, any comparison with this reference group includes an indirect test of whether the psychiatric or sociodemographic correlate is associated with onset of regular smoking itself (and not CSDP alone). Thus, in addition to affording a larger sample size, the latter comparison is also a more global test of correlates of regular smoking in general. Using subsets of regular smokers with and without a history of CSDP allows for a more formal test of whether the correlates specifically associate with CSDP, but this approach substantially reduces the sample size.

Genetic influences on CSDP

Our findings are consistent with D'Onofrio et al. (2003), who previously found evidence for moderate heritable influences on CSDP, with no clear evidence for shared environmental influences. It is important here to clarify that these genetic factors or heritable

influences are latent and may refer to a number of biological mechanisms such as genes for impulse-disinhibition or risk-taking (Bardo, Donohew, & Barrington, 1996), genes associated with altered nicotine metabolism, genes for hormonal dysregulation during pregnancy, and interactions across all of these biological pathways. Although we did not find evidence that environmental factors shared across members of a twin pair influenced CSDP, we found that along with genetic vulnerability, latent environmental influences (e.g., nonshared peer and spouse support or obstetric advice to quit smoking during pregnancy) complicate quit attempts and shape a woman's predisposition to CSDP. Our finding that spousal smoking is a potent correlate of CSDP, even when indexed by smoking status of the current spouse, is a particularly interesting one with potential methodological and clinical implications. We have previously demonstrated that substantial evidence supports assortative mating for regular smoking and nicotine dependence in this sample (Agrawal et al., 2006). Therefore, the possibility exists that nonrandom mating with respect to cigarette smoking is genetically influenced and, in turn, may impact CSDP.

DSM-*III-R nicotine dependence and CSDP*

Despite being somewhat limited by power, findings from our bivariate genetic model show that, in regular cigarette smokers, genetic factors that contribute to the risk for nicotine dependence also contribute significantly to CSDP (cross-trait genetic correlation of .65, with an upper confidence limit of 1.0). Our analyses also revealed that environmental factors specific to CSDP (and not shared with nicotine dependence, or across members of a twin pair) contribute significantly to its etiology. These putative environmental correlates (which likely include socioeconomic status, stressful life events, and peer and partner support) may include pregnancy-specific risk and protective factors. To some extent, these individual-specific environmental factors also may reflect measurement error, or unreliability in women's reports of their CSDP (and, presumably, nicotine dependence). In our sample of 268 women who participated in both MATCH and the Women's Survey, reliability for both CSDP (κ=.74) and nicotine dependence were good (κ=.67), suggesting that the effects of measurement error are modest. A previous study, using cotwins' reports of their twin's CSDP, also has shown that women who smoke during their entire pregnancy rarely report not doing so (Heath et al., 2003). Although our analyses suggest that a significant proportion of the additive genetic and only a modest proportion of the nonshared environmental influences on CSDP are shared with nicotine dependence, these findings must be interpreted with some caution because of the relatively small sample size. Replications in other samples will provide support in favor of this hypothesis.

Here we demonstrate a substantial phenotypic and genetic relationship between nicotine dependence and CSDP. However, our study has five important limitations. First, our findings relate to a sample of adult White women in their early thirties to late forties at the time of interviews and may not extrapolate to other ethnic or sociodemographic samples or to other cohorts of mothers. Second, we were somewhat restricted by power to clearly distinguish the role of additive genetic from shared environmental influences on CSDP. Neale, Eaves, and Kendler (1994) have shown this confounding of estimates to be a problem for threshold traits in smaller twin samples. Third, spousal smoking as reported in the Women's Survey may not reflect the smoking status of the spouse who was the biological father of the offspring (in Women's Survey only) or the spouse who cohabitated with the twin mother during her pregnancy. Although we cannot be certain, it is quite likely that the current spouse of the twin also cohabitated with her during the pregnancy, given that more than 92% of the women reported a single intact marriage at the time of their interview. Because we do not have the age at each pregnancy in the Women's Survey, our ability to address causal hypotheses regarding other important covariates (e.g., traumatic life events or depression) also is similarly limited. Fourth, retrospective recall may have influenced the twins' reports of CSDP; however, Heath et al. (2003) have shown that this is unlikely to be the case. Finally, although MATCH was oversampled for alcohol-related problems, and MATCH participants reported somewhat higher levels of regular smoking (44% vs. 38% in the Women's Survey), our twin models were unlikely to be severely affected by the oversampling given that thresholds were adjusted for all significant correlates of CSDP, including alcohol abuse and dependence.

Notwithstanding these limitations, our results demonstrate that social background, psychiatric correlates, and a lifetime history of heavy smoking and of difficulty quitting or staying smoke-free contribute to CSDP. Expectant mothers attempting to quit smoking may be challenged by their predisposition to nicotine dependence, and treatment providers are urged to consider this constellation of risk and protective influences in assisting pregnant women.

Acknowledgments

Arpana Agrawal is supported by grants DA023668, DA12854, and AA13321; Valerie Knopik is supported by grant DA17671; and Michele Pergadia is supported by grant DA019951. This research also

is supported by grants AA11998 and AA015210 and funds to Pamela Madden from the Alcoholic Beverages Medical Research Foundation. The authors thank Dixie Statham for supervising interviews and data collection. They have no conflicts of interest to disclose.

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