

Disentangling the relationships between maternal smoking during pregnancy and co-occurring risk factors

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Background. Maternal smoking during pregnancy (SDP) has been studied extensively as a risk factor for adverse offspring outcomes and is known to co-occur with other familial risk factors. Accounting for general familial risk factors has attenuated associations between SDP and adverse offspring outcomes, and identifying these confounds will be crucial to elucidating the relationship between SDP and its psychological correlates.

Method. The current study aimed to disentangle the relationship between maternal SDP and co-occurring risk factors (maternal criminal activity, drug problems, teen pregnancy, educational attainment, and cohabitation at childbirth) using a population-based sample of full- ($n=206\,313$) and half-sister pairs ($n=19\,363$) from Sweden. Logistic regression models estimated the strength of association between SDP and co-occurring risk factors. Bivariate behavioral genetic models estimated the degree to which associations between SDP and co-occurring risk factors are attributable to genetic and environmental factors.

Results. Maternal SDP was associated with an increase in all co-occurring risk factors. Of the variance associated with SDP, 45% was attributed to genetic factors and 53% was attributed to unshared environmental factors. In bivariate models, genetic factors accounted for 21% (non-drug-, non-violence-related crimes) to 35% (drug-related crimes) of the covariance between SDP and co-occurring risk factors. Unshared environmental factors accounted for the remaining covariance.

Conclusions. The genetic factors that influence a woman’s criminal behavior, substance abuse and her offspring’s rearing environment all influence SDP. Therefore, the intergenerational transmission of genes conferring risk for antisocial behavior and substance misuse may influence the associations between maternal SDP and adverse offspring outcomes.

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Introduction

Nicotine is the most commonly abused substance by mothers during pregnancy (22.9%; Office of Applied Studies, 2007) and maternal smoking during pregnancy (SDP) is robustly associated with numerous adverse outcomes in offspring, making it a significant public health concern. These outcomes include perinatal health problems, such as lower birthweight (Rice *et al.* 2009; Thapar *et al.* 2009), spontaneous abortion, fetal mortality and sudden infant death syndrome

(see Ernst *et al.* 2001 for review). Maternal SDP is also associated with psychological problems, such as cognitive delays (Batty *et al.* 2006; Lambe *et al.* 2006; Lundberg *et al.* 2010), attention-deficit hyperactivity disorder (ADHD; Thapar *et al.* 2009; Lindblad & Hjern, 2010), conduct disorder (CD; Silberg *et al.* 2003; Brion *et al.* 2010), antisocial behavior (ASB; Rice *et al.* 2009; D’Onofrio *et al.* 2010a; Paradis *et al.* 2010) and substance use disorders (Brennan *et al.* 2002). Research has consistently supported a causal relationship for SDP with many perinatal health problems, but evidence has been inconsistent for its relationship with psychological problems (Rice *et al.* 2009; Thapar *et al.* 2009).

Several studies evaluating the associations between SDP and psychological problems have investigated potential confounds. These studies have shown that

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SDP is not an isolated risk factor, but rather mothers engaging in SDP also have lower levels of educational attainment (Gilman *et al.* 2008a), less annual income (Maughan *et al.* 2004; Monuteaux *et al.* 2006), more substance use problems (Batty *et al.* 2006), engagement in ASB (Maughan *et al.* 2004) and a greater probability of having children with men engaging in ASB (Maughan *et al.* 2004). Thus, to fully test whether these relationships are causal, more rigorous studies accounting for confounds between SDP and psychological outcomes have been necessary (Rutter *et al.* 2001).

Among the research accounting for such confounds, there seems to be a pattern in which studies accounting for specific, measured confounds [e.g. parental education and socio-economic status (SES)] show attenuated but still significant associations between SDP and psychological outcomes (Kandel *et al.* 1994; Weissman *et al.* 1999; Wakschlag *et al.* 2006; Langley *et al.* 2007; Neuman *et al.* 2007; Wiebe *et al.* 2009; Ekblad *et al.* 2010; Espy *et al.* 2010; Wakschlag *et al.* 2010). However, studies accounting for general, unmeasured familial confounds (i.e. capturing all genetic and environmental factors) show these associations to be fully attenuated (Silberg *et al.* 2003; Gilman *et al.* 2008b; D'Onofrio *et al.* 2010a,b; Kuja-Halkola *et al.* 2010; Lindblad & Hjern, 2010; Lundberg *et al.* 2010). For example, Silberg *et al.* (2003) found a model of intergenerational transmission of CD liability (i.e. offspring liability due to the presence of maternal CD) to better fit data than a model of direct effects from SDP on offspring CD liability. Consistent with these findings, *in vitro* fertilization studies, in which mothers were not biologically related to the offspring but provided the prenatal and postnatal environments, have found no relationship between SDP and ADHD or ASB (Rice *et al.* 2009; Thapar *et al.* 2009). Thus, what was once considered a causal relationship seems better explained by familial confounds.

The quasi-experimental research suggests that the specific, measured confounds explicitly included in many epidemiological studies are only part of the picture. Identifying the familial confounds is crucial to elucidating the association between SDP and its psychological correlates, allowing research to move beyond the uncertainty of the nature of these relationships (Rutter *et al.* 2001). The aim of the current study was to facilitate the identification of such familial confounds by determining the degree to which genetic and environmental factors account for the relationship between SDP and behavioral correlates of maternal SDP–maternal ASB, substance use problems, and other maternal risk factors for offspring (teen pregnancy, cohabitation status and low level of education).

The current study disentangled these relationships using a large, population-based sample, which is particularly beneficial for investigating low base rate behavior (e.g. 0.9% of women are convicted of violent crimes; Frisell *et al.* 2011). In addition, family members with varying degrees of genetic relatedness were identified to test multivariate behavioral genetic models. To our knowledge, only one other published study has included SDP in a multivariate behavioral genetic model (Agrawal *et al.* 2008). In that study, genetic factors accounted for 34% of the variance in SDP and 42% of the covariance between SDP and nicotine dependence. Given that the phenotypes in the current study (e.g. externalizing outcomes) are less related to SDP than nicotine dependence, we hypothesized that genetic factors would account for a smaller, but significant, proportion of the covariance in all multivariate behavioral genetic models. This hypothesis is consistent with multivariate research showing that externalizing disorders have a common underlying factor that is primarily composed of genetic influences (Krueger *et al.* 2002). This hypothesis is also consistent with a passive gene–environment correlation, wherein mothers are providing the prenatal environment, in addition to the postnatal environment and genetic transmission of other risk factors (Plomin *et al.* 1977).

Method

Sample

We analyzed a population-based sample, based on data from multiple nationwide registers maintained by Swedish government agencies and research institutes. The information in these registers was linked using a unique identification (ID) number assigned to each individual. In addition, ID numbers of family members (e.g. biological parents, offspring) were available, allowing familial relationships (e.g. sibling) and genetic relatedness (e.g. sharing one or both parents) to be determined.

Birth data

The Multi-Generation Register contains identifying information (e.g. ID number) of the biological and adoptive parents of each child born in Sweden since 1932 (Statistics Sweden, 2006). The Swedish Medical Birth Register contains data collected throughout the pregnancy and at childbirth for over 99% of all births in Sweden since 1973 (Centre for Epidemiology, 2003). Data were merged from the Swedish Medical Birth Register and the Multi-Generation Register to match each mother with her children and pregnancy/childbirth data (e.g. maternal SDP, maternal age at

birth, cohabitation status) and to match each mother with her own parents and sisters.

Data for co-occurring risk factors

The Swedish National Crime Register, held by the National Council for Crime Prevention, contains information about the nature of every conviction in Sweden since 1973, including data on the number of offenses, date of the crime, and sentencing. The Hospital Discharge Register contains information about the nature of hospitalizations in Sweden since 1973, including psychiatric diagnoses from the ICD-10 (WHO, 1992; Centre for Epidemiology, 2005). The Register of Education contains information about the highest level of educational attainment for each individual since 1990 (Statistics Sweden). Data were merged from the National Crime Register, Hospital Discharge Register and Register of Education to obtain data for maternal criminal, psychiatric and educational phenotypes respectively.

Data for exclusion criteria

The Cause of Death Register, kept by the National Board of Health and Welfare, contains information about all registered deaths since 1952. The Migration Register, held by Statistics Sweden, contains information from registered migrations, including dates of immigrating to, or emigrating from, Sweden. Data were merged from the Cause of Death Register and the Migration Register to determine which individuals were deceased or had emigrated and should be excluded from data analyses.

Total sample

Several inclusion criteria were applied to the sample. First, given this study's focus on maternal SDP, participants were restricted to females with at least one biological child born after SDP data became available in 1982. Birth-related data (e.g. SDP, maternal age) were retained from the first childbirth of each mother. There were 1 600 609 mothers for whom such data were available. Second, mothers born after 1995 were excluded from analyses, as they had not yet entered the high-risk period for some co-occurring risk factors (e.g. substance use problems) as of the last wave of data collection. Third, individuals belonging to a multiple birth set (e.g. twins, triplets), or who either were deceased or had emigrated out of Sweden as of the last wave of data collection, were excluded from analyses. Therefore, the current sample comprised mothers who were born before 1995, had given birth in Sweden after 1982, and were still living in Sweden as of 2009. There were 1 193 080 mothers meeting the exclusion criteria.

The ID numbers of each mother's parents (i.e. maternal and paternal ID numbers) were then used to construct families. First, mothers with common maternal ID numbers were grouped into maternal families (i.e. sisters with the same mother were grouped together). There were 924 946 maternal families available in the data set. Second, the two oldest sisters of each maternal family were identified and retained for subsequent steps; that is, each family consisted of the two oldest sisters who had at least one biological child. Third, paternal ID numbers were used to determine the genetic relatedness of each sister pair. Full sisters were identified as having the same paternal ID number (i.e. sharing 50% of segregating genes) and half sisters were identified as having different paternal ID numbers (i.e. sharing 25% of segregating genes). Sisters without paternal ID numbers (i.e. for whom genetic relatedness was unknown) or who were adopted into different families (i.e. sister pairs that may not have been raised together) were excluded from analyses.

In total, there were 225 676 maternal families with a sister pair meeting all criteria, of which there were 206 313 (91.42%) full- and 19 363 (8.58%) half-sister pairs. Mothers' average age at the end of follow-up (2009) was 44.02 (s.d. = 8.60) years.

Variables

Maternal SDP

Maternal SDP was assessed by self-report at the first antenatal visit and measured on a three-point ordinal scale as a non-smoker (0 cigarettes/day), moderate smoker (1–9 cigarettes/day) or heavy smoker (≥ 10 cigarettes/day). Self-reports of SDP during antenatal visits have been shown to be valid compared to retrospective self-reports (i.e. after pregnancy; Jacobson *et al.* 2002) and bioassays (e.g. serum cotinine levels; Pickett *et al.* 2009). For example, a large majority (94%) of maternal self-reports of non-smoking are in agreement with serum cotinine levels (Lindqvist *et al.* 2002). In the current sample, 14.17% of mothers engaged in moderate SDP and 7.58% engaged in heavy SDP (21.76% of the total sample). Notably, mothers from half-sister pairs reported considerably higher rates of any SDP (33.91%) than those from full-sister pairs (20.62%), which reflects an increased prevalence of environmental risk factors (e.g. lower SES) and adverse offspring outcomes (e.g. poorer educational outcomes) in blended families (Ginther & Pollak, 2004).

Criminal convictions

Criminal histories were based on the Swedish Penal Code. Convictions were categorized as violent,

drug-related, substance-related driving or other offenses. In addition, the date of conviction was used to determine the individual's age when the crime was committed. To simplify analyses, only data for the first conviction of each type of criminal offense were retained for each individual.

Violent crime was defined as attempted/completed murder, manslaughter and filicide, aggravated assault, gross violation of a person's integrity, kidnapping and illegal constraint, illegal coercion and threat, harassment, aggravated robbery, aggravated arson, and/or threats or violence against an officer. Drug crime was defined as offenses related to the manufacturing and/or distribution of illicit drugs. Driving crime was defined as offenses related to operating a motor vehicle under the influence of a controlled substance. Other crimes consisted of any non-violent and non-drug-related conviction. In the current sample of mothers, there was at least one lifetime conviction related to violent crime in 1.11%, drug crime in 0.74%, driving crime in 1.03%, and other crime in 8.65%. In total, 11.07% had at least one conviction of any type.

Psychiatric hospitalizations

Diagnoses during psychiatric hospitalizations were based on the ICD-10. Only hospitalizations related to alcohol or drug use were analyzed, as internalizing disorders have not been associated with SDP (Brion et al. 2010). Again, the date of discharge from the hospital was used to determine the individual's age when hospitalized, and only the first psychiatric discharge for alcohol- or drug-related hospitalizations was retained. In the current sample, there was at least one lifetime hospitalization in 1.33% related to alcohol use, 0.95% related to drug use, and 1.92% related to any substance use.

Other maternal risk factors

Maternal teen pregnancy status was determined by the mother's age at the birth of her first child. The average age of first childbirth was 27.04 (s.d. = 4.95) years, and 4.56% of mothers had teen pregnancies. Maternal cohabitation status was based on whether the mother reported living with her spouse or partner at the time of her first childbirth. Of the mothers in the current study, 6.86% reported not living with a spouse or partner.

Education was based on the highest level of educational attainment for each mother. The Register of Education categorizes each person into one of seven levels. Low level of educational attainment was assessed by combining the first two categories (no education beyond primary and lower secondary school: 9.50% in the current study).

Data analysis

Logistic regression

Logistic regression models were used to identify the strength of association between SDP and co-occurring risk factors. Logistic regression models were fitted using SAS version 9.2 (SAS Institute Inc., USA). PROC SURVEYLOGISTIC was used to account for familial clustering. Dummy-coded variables were created to compare moderate and heavy SDP to no smoking. In addition, polychoric correlations were used to determine the within- and cross-sister associations involving SDP and co-occurring risk factors, with full- and half-sister dyads being analyzed separately to help explore the degree to which genetic and environmental factors may influence each trait and the associations with SDP (Neale & Cardon, 1992).

Univariate behavioral genetic analyses

Structural equation models (SEMs) were fitted to estimate the degree to which variance in each phenotype is associated with additive genetic (A), common environmental (C), and unshared environmental (E) factors. This is done by using genetically informed data and imposing variance and covariance constraints, from which latent variables are assumed to represent the biometrical (ACE) factors (e.g. constraining sibling correlations of the A factors to 0.5 for full siblings and 0.25 for half siblings). Thus, behavioral genetic models estimated the covariances between full- (calculated as $0.5 \cdot A + C$) and half-sibling pairs (calculated as $0.25 \cdot A + C$) and the percentage of phenotypic variance attributable to the biometrical factors. This approach is similar to that of the classical twin study (Neale & Cardon, 1992; Prescott, 2004).

Given that all phenotypes were categorical, thresholds were estimated instead of means for all manifest variables. Finally, age at the last wave of data collection was included as a covariate for all phenotypes. All behavioral genetic analyses were conducted using Mplus version 6.1 (Muthén & Muthén, 2010).

Bivariate behavioral genetic analyses

Finally, SEMs were fitted to estimate the degree to which covariances between SDP and co-occurring risk factors are associated with the biometrical factors. The bivariate model was based on the Cholesky decomposition approach (see Fig. 1), from which three triangular matrices containing parameter estimates for the biometrical factors are derived (Neale & Cardon, 1992; Loehlin, 1996). In bivariate models, each matrix contains three elements, two on the diagonal accounting for the variance in each phenotype (e.g. SDP and a

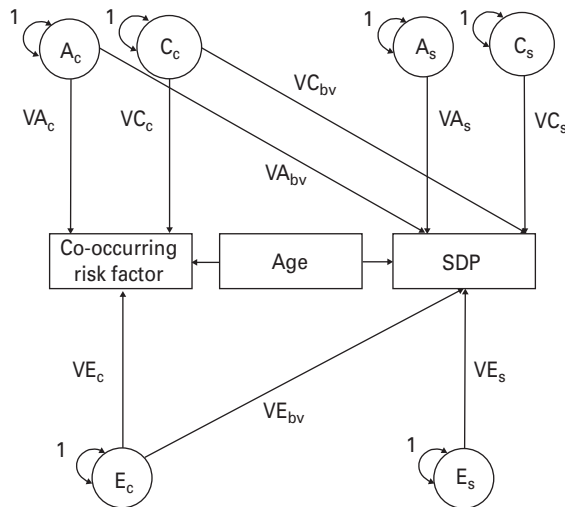


Fig. 1. Bivariate behavioral genetic model of genetic and environmental factors accounting for covariance in maternal smoking during pregnancy (SDP) and behavioral correlates. In this study we examined bivariate behavioral genetic models using the Cholesky decomposition approach. Both SDP and the co-occurring risk factor entered into each model were regressed on mother's age, to account for risk/opportunity for the phenotype to occur (e.g. criminal conviction, psychiatric hospitalization). Models were used to obtain estimates of the proportion of covariance between SDP and each co-occurring risk factor associated with genetic and environmental factors. The variances for all latent variables (A, C, and E) were fixed to 1. Standard errors were derived from the following equations, which were entered into a Model Constraint command in Mplus. Adapted from the *Mplus User's Guide*, examples 5.19 and 7.28 (Muthén & Muthén, 2010). Shared Environment (C) was fixed to zero in the bivariate models. Subscripts refer to latent variables and parameters for SDP (_s) and the co-occurring risk factor (_c), as well the bivariate parameters (_{bv}). Parameter estimates were calculated as follows: $A = VA_c \times VA_{bv}$, $E = VE_c \times VE_{bv}$, $Covariance = A + C(0)$, $H^2 = A / (A + E) =$ proportion of covariance attributed to genetic factors, $E^2 = E / (A + E) =$ proportion of covariance attributed to environmental factors.

co-occurring risk factor) and one on the off-diagonal accounting for the covariance between both phenotypes. Thus, the variances and covariance are decomposed into the biometrical factors. Model constraints and parameterizations were similar to those used in the univariate model, and age was again included as a covariate for both phenotypes.

Results

Association measures

The frequencies of all co-occurring risk factors by level of SDP engagement and the corresponding odds ratios (ORs) obtained from logistic regression models are

shown in Table 1. The ORs indicated that the risk factors were significantly more likely to occur in mothers engaging in moderate or heavy SDP, relative to those engaging in no SDP. The largest effects were for crimes and hospitalizations related to substance abuse (OR 7.5–13.6), and the smallest effects were for other crimes (i.e. non-drug, non-violent convictions; OR 2.2). Of note, teen pregnancy was more strongly associated with moderate SDP than heavy SDP, which may be due to teenagers having less time to acquire more severe smoking habits than older mothers.

Polychoric correlations of SDP with co-occurring risk factors are shown in Table 2 using within-sister (e.g. correlations of a mother's engagement in SDP with her own criminal convictions) and cross-sister phenotypic correlations for full- and half-sister pairs (e.g. correlations of a mother's engagement in SDP with her sister's criminal convictions). The strongest within-sister correlations were for drug-related convictions ($r=0.43$), driving convictions ($r=0.38$) and substance-related psychiatric hospitalizations ($r=0.37$ – 0.39). As expected, the strongest cross-sister correlate of each mother's SDP was her sister's engagement in SDP ($r=0.45$ for full, $r=0.24$ for half). All cross-sister correlations were higher for full- than half-sister pairs, suggesting that genetic factors influence SDP and the association between SDP and each risk factor.

Univariate behavioral genetic analyses

Estimates of the proportion of variance associated with genetic and environmental factors in SDP and co-occurring risk factors are presented in Table 3. The variance in SDP was influenced primarily by additive genetic (45%) and unshared environmental factors (53%), with shared environment having a non-significant influence (2%). All co-occurring risk factors were most strongly associated with unshared environmental factors (i.e. environmental factors affecting sisters differently), which accounted for at least 50% of the variance in all phenotypes. In addition, a substantial amount of variance in all co-occurring risk factors was due to genetic factors, ranging from 19% (non-cohabitation) to 42% (low level of educational attainment). Shared environmental factors (i.e. environmental factors affecting siblings similarly) were associated with any convictions (6%), teen pregnancy (7%), non-cohabitation (8%) and low level of educational attainment (4%), but showed negligible influences on all other phenotypes. Notably, common environmental factors were near 10% for some phenotypes (e.g. violence- and drug-related convictions), but these were low base rate occurrences and had large standard errors resulting in estimates that were not significantly different from zero.

Table 1. Frequencies and odds ratios (ORs) of co-occurring risk factors as a function of smoking during pregnancy (SDP) in mothers

Behavioral correlate	Frequency (%)			OR (95% CI)	
	No SDP	Moderate SDP	Heavy SDP	Moderate SDP	Heavy SDP
Criminal convictions					
Violent	0.6	2.6	3.9	4.9 (4.6–5.3)	7.3 (6.7–7.8)
Drug	0.2	2.1	3.2	8.8 (8.0–9.6)	13.6 (12.4–15.0)
Driving	0.5	2.5	3.9	5.4 (5.0–5.8)	8.6 (8.0–9.3)
Other	7.3	12.8	14.8	1.9 (1.8–1.9)	2.2 (2.2–2.3)
Any	8.4	18.7	23.5	2.5 (2.5–2.6)	3.3 (3.2–3.4)
Psychiatric diagnoses					
Alcohol	0.7	2.9	4.8	4.4 (4.2–4.7)	7.6 (7.1–8.1)
Illicit drug	0.4	2.3	3.6	5.5 (5.1–5.9)	8.8 (8.2–9.6)
Any substance	1.0	4.3	6.8	4.6 (4.4–4.9)	7.5 (7.1–8.0)
Other maternal characteristics					
Teen pregnancy	3.3	9.4	8.6	3.1 (3.0–3.2)	2.8 (2.7–2.9)
Non-cohabitation	4.8	12.2	16.9	2.7 (2.6–2.8)	4.0 (3.9–4.2)
Low educational attainment	6.4	18.2	23.2	3.3 (3.2–3.4)	4.4 (4.3–4.6)

CI, Confidence interval.

ORs are calculated relative to the non-SDP group.

Table 2. Cross-trait polychoric correlations of smoking during pregnancy (SDP) with co-occurring risk factors, using within- and cross-sister correlations

Correlation type	SDP	Criminal conviction				Psychiatric hospitalization			Other maternal risk factors			
		Violent	Drug	Driving	Other	Any	Drug	Alcohol	Any	Teen pregnancy	No cohabitation	Low education
Within-sister	*	0.36	0.43	0.38	0.19	0.30	0.37	0.38	0.39	0.26	0.32	0.37
Full sisters	0.45	0.23	0.25	0.23	0.12	0.18	0.21	0.22	0.22	0.16	0.17	0.26
Half sisters	0.24	0.11	0.13	0.09	0.08	0.11	0.08	0.12	0.11	0.06	0.06	0.13

All correlations were conducted with the three-category SDP measure.

Bivariate behavioral genetic analyses

Estimates of the proportion of covariance between SDP and co-occurring risk factors associated with genetic and environmental factors are presented in Table 4. Shared environment was fixed to zero for all models because of its negligible influence on SDP and to ensure interpretable parameter estimates across all models (e.g. sums of the biometrical parameters would account for 100% of the covariance in each model).

Unshared environmental factors accounted for the largest proportion of covariance between SDP and all co-occurring risk factors. Additive genetic factors were also associated with a significant proportion of the covariance between SDP and all phenotypes, as these estimates ranged from 21% (non-violence-, non-drug-related offenses) to 35% (drug-related

convictions). The proportion of covariance attributed to genetic factors was particularly high for substance-related phenotypes (30–35%), including driving-related convictions (i.e. driving under the influence) and substance-related psychiatric hospitalizations. Shared genetic liability also accounted for a relatively large proportion of the covariance between SDP and other co-occurring risk factors (28–35%), such as low maternal educational attainment. In sum, the genetic factors that influence a woman's criminal behavior, substance abuse and the environment she provides for her offspring also influence SDP.

Discussion

The current study used multivariate behavioral genetic models to elucidate the relationship between

Table 3. Parameter estimates of genetic and environmental factors accounting for the variance of smoking during pregnancy (SDP) and co-occurring risk factors from univariate behavioral genetic models

Behavioral correlate	Additive genetic	Shared environment	Unshared environment
SDP	0.45 (0.02)	0.02 (0.01) ^{N.S.}	0.53 (0.01)
Criminal convictions			
Violent	0.29 (0.09)	0.09 (0.06) ^{N.S.}	0.63 (0.04)
Drug	0.30 (0.09)	0.11 (0.06) ^{N.S.}	0.59 (0.04)
Driving	0.24 (0.15) ^{N.S.}	0.05 (0.09) ^{N.S.}	0.71 (0.07)
Other	0.25 (0.05)	0.00 (0.03) ^{N.S.}	0.75 (0.02)
Any	0.24 (0.04)	0.06 (0.02)	0.70 (0.02)
Psychiatric diagnoses			
Alcohol	0.39 (0.09)	0.00 (0.05) ^{N.S.}	0.60 (0.04)
Illicit drug	0.28 (0.10)	0.09 (0.06) ^{N.S.}	0.63 (0.04)
Any substance	0.40 (0.07)	0.00 (0.04) ^{N.S.}	0.60 (0.03)
Other maternal characteristics			
Teen pregnancy	0.37 (0.04)	0.07 (0.02)	0.56 (0.01)
Non-cohabitation	0.19 (0.06)	0.08 (0.03)	0.73 (0.03)
Low educational attainment	0.42 (0.03)	0.04 (0.02)	0.55 (0.01)

Standard errors are given in parentheses.

N.S. denotes parameter estimate non-significant from zero.

Table 4. Parameter estimates of genetic and environmental factors accounting for the covariance for smoking during pregnancy (SDP) with co-occurring risk factors from bivariate behavioral genetic models

Behavioral correlate	Additive genetic	Unshared environment
Criminal convictions		
Violent	0.33 (0.01)	0.67 (0.01)
Drug	0.35 (0.01)	0.65 (0.01)
Driving	0.30 (0.01)	0.70 (0.01)
Other	0.21 (0.01)	0.80 (0.01)
Any	0.27 (0.00)	0.73 (0.00)
Psychiatric diagnoses		
Alcohol	0.31 (0.01)	0.70 (0.01)
Illicit drug	0.32 (0.01)	0.69 (0.01)
Any substance	0.32 (0.01)	0.68 (0.01)
Other maternal characteristics		
Teen pregnancy	0.34 (0.00)	0.66 (0.00)
Non-cohabitation	0.28 (0.01)	0.72 (0.01)
Low educational attainment	0.35 (0.00)	0.66 (0.00)

Standard errors are given in parentheses.

maternal SDP and co-occurring familial risk factors, which previous studies have indicated are familial in nature. The co-occurrence of SDP and these risk factors was largely attributed to environmental factors (accounting for 65–80% of the covariance), with genetic factors playing a significant role and accounting

for the remaining covariance. As expected, genetic factors were associated with a smaller proportion of covariance between SDP and co-occurring risk factors (21–35%) than previously shown for SDP and nicotine dependence (42%; Agrawal *et al.* 2008).

Maternal SDP may be a proxy of behavioral dysregulation, such as problems with delayed gratification (Metcalf & Mischel, 1999) or an inability to control one's own behavior (e.g. dyscontrol; Widiger & Sankis, 2000), which may manifest in SDP and the other risk factors included in the current study (e.g. CD, substance abuse; Lau *et al.* 1995; Barkley, 1997). These results are consistent with previous research showing that externalizing disorders cluster under a single latent factor (Krueger & Markon, 2006; Lahey *et al.* 2009). Notably, an effect of SDP has not extended to emotional dysregulation (e.g. internalizing disorders; Wakschlag *et al.* 2006; Brion *et al.* 2010), suggesting that the risk factors associated with SDP are specific to behavioral dysregulation (Thapar *et al.* 2003; Huijbregts *et al.* 2008). Furthermore, poor inhibition and difficulty delaying gratification may be similar to the cognitive deficits found in ADHD (Solanto *et al.* 2001) and low levels of educational attainment. Therefore, many of the genetic effects involved in SDP and adverse psychological phenotypes are probably acting on executive functioning (e.g. decision making, planning), and the environmental effects may be counter to the benefits of social and emotional learning programs (Payton *et al.* 2000).

To our knowledge, only one other multivariate behavioral genetic study involving SDP has been conducted to date. Agrawal *et al.* (2008) conducted a twin study in which 42% of the covariance between the SDP and nicotine dependence was attributed to common genetic factors. Those findings are comparable to the substance-related phenotypes analyzed in the current study, in which the proportion of covariance attributed to genetic factors was slightly smaller (30–35%). Notably, multiple substance-related phenotypes in the current study were of those most strongly associated with the genetic influences of SDP. Although a common factor representing liability for substance abuse has been identified (as opposed to several, drug-specific factors; Han *et al.* 1999), the covariance attributed to genetic factors in Agrawal *et al.* (2008) may include influences on nicotine sensitivity and, thus, contribute to a larger proportion of covariance.

An important strength of the current analyses stems from using a large, population-based sample, in which numerous co-occurring risk factors of public interest are available. Many of the co-occurring risk factors included in the current study are rare events, requiring a large sample for adequate power in identifying effects. For example, violent criminal acts are rare occurrences in females, as are substance-related psychiatric hospitalizations (e.g. 1.9% of the current sample). Notably, even with a large sample of 225 676 families in the current study, phenotypes with a low base rate occurrence had relatively large standard errors for biometrical factors (e.g. see Table 3).

Multiple measures were also available across the domains of interest in the current study: criminal convictions, psychiatric hospitalizations and other characteristics of an offspring's rearing environment. This allows parameter comparisons to be made to identify consistencies or outliers. For example, all maternal characteristics (maternal teen pregnancy, cohabitation, educational attainment) had similar degrees of genetic influence shared with SDP. By contrast, there was an unexpectedly large difference between the proportions of covariance attributed to genetic factors for other crimes (i.e. non-violence-, non-drug-related; 21%) relative to violence- (34%) and drug-related crimes (35%). Whether this finding is anomalous or indicative of differences in causal underpinnings warrants further investigation.

An inherent characteristic of studies on maternal SDP, which is a limitation to the current study, is the use of a sample restricted to females. Specifically, there are gender differences for the heritability of externalizing behaviors, with genetic factors having a stronger influence on these phenotypes in men (Hicks *et al.* 2007). Given these differences, the estimates of the

genetic and environmental contributions to the covariance between SDP and externalizing phenotypes may not apply to males. Additional research is therefore needed to disentangle how the intergenerational transmission of maternal SDP may confer risk for adverse outcomes in male offspring.

These findings also do not identify specific genetic or environmental factors that contribute to SDP and/or co-occurring risk factors, and research in the fields of molecular genetics, neuroscience and the social sciences is needed to further the progress in this area. For example, several gene–environment interactions have been identified that involve SDP and may indicate genes that influence both SDP and these adverse psychological phenotypes (Neuman *et al.* 2007; Lotfipour *et al.* 2009; Wiebe *et al.* 2009). A basic knowledge of how these and other genes influence SDP and behavioral dysregulation is important for advancing understanding in this area.

Gene–environment interactions may also involve specific environmental factors, which moderate the heritability of phenotypes and/or the covariance among phenotypes associated with genetic factors. For example, a polymorphism protecting against alcohol dependence in Japanese populations has been identified (i.e. aldehyde dehydrogenase, *ALDH*), but this protective effect has declined as per capita alcohol consumption has increased in Japan (Higuchi *et al.* 1994). In the current study, data span a period when SDP became increasingly deviant (as the public awareness of the consequences of SDP increased), and, consequently, the relationship between SDP and co-occurring risk factors may have changed. We investigated this possibility, and the associations between SDP and co-occurring risk factors were moderated by secular changes. This interaction may be due to marked changes in the prevalence of SDP over this period (decreasing from 32% in 1982 to 7% in 2009). However, there was no difference in the heritability of SDP when our sample was split into two cohorts: those giving birth in 1982–1991 (47%) and those giving birth in 1992–2009 (46%).

A final limitation concerns the phenotypes used in the current study. Behavioral dysregulation manifests in numerous phenotypes that range greatly in severity, but many phenotypes in the current study reflect severe dysregulation (e.g. violent crime). The current findings, therefore, cannot be applied to less severe co-occurring risk factors, and future research should cover these areas.

Alternative models of SDP

Slotkin (1998) proposed three pathways by which SDP may influence a developing organism: (1) direct

effects on the maternal–fetal unit, such as hypoxia, vascular effects, placental effects and malnutrition in offspring; (2) neurodevelopmental insults causing behavioral dysregulation (for instance, through nicotine exposure); and (3) environmental risk factors co-occurring with SDP, including lower parental educational attainment. Much evidence has supported a causal link between SDP and effects on the maternal–fetal unit (e.g. increased pregnancy-related problems; Cnattingius, 2004; Johansson *et al.* 2009). Rigorously controlling for familial factors (e.g. the co-occurring environmental risk factors that Slotkin described), however, has attenuated the effect of SDP on neurobehavioral outcomes, which is inconsistent with the presence of neurodevelopmental effects (e.g. psychological problems; Knopik, 2009). The current study suggests another pathway through which SDP is associated with offspring psychological problems: co-occurring genetic risk factors that influence SDP and the environment in which offspring are reared. Thus, what Slotkin posited to be an effect of neurodevelopmental insults may be, at least partially, due to shared genetic liability. However, the lack of a direct effect of SDP on psychological outcomes does not negate the fact that SDP can lead to fatal consequences for offspring through direct effects on the maternal–fetal unit.

Implications

The aim of the current study was to further disentangle the relationship between SDP and co-occurring familial risk factors. The current results suggest that the genetic factors that influence a woman's criminal behavior, substance abuse, and the environment she provides for her offspring also influence SDP. Thus, it is possible that the intergenerational transmission of genes conferring risk for ASB and substance misuse, at least partially, influence the associations between maternal SDP and adverse offspring outcomes.

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Declaration of Interest

None.

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