Published in final edited form as:

Behav Genet. 2014 September ; 44(5): 456–467. doi:10.1007/s10519-014-9668-4.

Maternal smoking during pregnancy and adverse outcomes in offspring: genetic and environmental sources of covariance

Ralf Kuja-Halkola^{1,*}, Brian M. D’Onofrio², Henrik Larsson¹, and Paul Lichtenstein¹

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

²Department of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana, USA

Abstract

Maternal smoking during pregnancy (SDP) has been associated with several psychiatric outcomes in the offspring; studies have questioned whether the associations are causal, however. We analyzed all children born in Sweden between 1983 and 2009 to investigate the effect of SDP on multiple indicators of adverse outcomes in three areas: pregnancy outcomes (birth weight, preterm birth and being born small for gestational age), long-term cognitive abilities (low academic achievement and general cognitive ability) and externalizing behaviors (criminal conviction, violent criminal conviction and drug misuse). SDP was associated with all outcomes. Within-family analyses of the pregnancy outcomes were consistent with a causal interpretation as the associations persisted when siblings discordant for SDP were compared. For the cognitive and externalizing outcomes, the results were not consistent with causal effects; when comparing differentially exposed siblings none of the associations remained significant. In quantitative genetic models genetic factors explained the majority of the associations between SDP and cognitive and externalizing outcomes. The results suggest that the associations between SDP in mothers and cognition and externalizing behaviors in their offspring is primarily due to genetic effects that influence the behaviors in both generations.

Keywords

Smoking during pregnancy; Children of siblings; Sibling comparison; Cousin comparison; Extended family model

Background

Maternal smoking during pregnancy (SDP) has been associated with adverse pregnancy outcomes and long-term cognitive and behavioral difficulties in the offspring (e.g., ADHD and low cognitive functioning) in humans, as well as in animals (Cnattingius, 2004, Huizink and Mulder, 2006, Knopik, 2009). Researchers have suggested plausible biological

*Corresponding author: Ralf Kuja-Halkola, Karolinska Institutet, PO Box 281, 171 77 Stockholm, Sweden. ralf.kuja-halkola@ki.se. Preliminary partial results were presented at the 42nd Annual Meeting of the Behavior Genetics Association; June 24, 2012; Edinburgh, Scotland.

Conflict of Interest

Author Kuja-Halkola R, Author D’Onofrio BM, Author Larsson H and Author Lichtenstein P declare that they have no conflict of interest.

mechanisms, such as fetal restriction of nutrients and oxygen (Huizink and Mulder, 2006), alterations in neural development through nicotine binding to the nicotinic acetylcholine receptors in the fetal brain (Huizink and Mulder, 2006, Knopik, 2009), dysregulation of hypothalamic-pituitary-adrenal axis (Huizink and Mulder, 2006), and epigenetic effects (Knopik *et al.*, 2012). Although SDP seems to be causally related to pregnancy outcomes, the causality of its effects on long-term difficulties have been questioned (Knopik, 2009).

Many carefully designed observational studies on SDP and long-term outcomes have been carried out, e.g. by Paradis *et al.* (2011) investigating SDP and criminality at approximately 33 years of age while controlling for a number of measured covariates. Most observational studies that have compared unrelated individuals have found that SDP independently predicts offspring traits when controlling for parental characteristics that covary with SDP (reviews in Glantz and Chambers, 2006, Wakschlag *et al.*, 2002). However, a continuing concern is missing adjustments of important unmeasured confounders, such as maternal and paternal personality traits, intellectual abilities, and psychiatric problems that were either not included in the studies or were measured imprecisely, which has highlighted the need for other types of designs to resolve these issues (D'Onofrio *et al.*, 2013). For example, several twin studies have shown that SDP is a genetically influenced trait (Agrawal *et al.*, 2008, D'Onofrio *et al.*, 2003, Ellingson *et al.*, 2012) with heritability estimates ranging from 34% to 52%; the genetic factors that influence SDP are shared with criminal convictions and drug use (Ellingson *et al.*, 2012), as well as nicotine dependence (Agrawal *et al.*, 2008). Genetic factors passed down from parents to their offspring could, therefore, account for the statistical associations between SDP and offspring traits. Thus, we believe that a genetically sensitive approach to the analysis of the association between SDP and any heritable outcome is of high importance

Several quasi-experimental studies (e.g., comparisons of siblings differentially exposed to SDP and in-vitro fertilization studies) have suggested that the long-term associations are due to familial confounding, rather than being causal (D'Onofrio *et al.*, 2012, D'Onofrio *et al.*, 2010a, D'Onofrio *et al.*, 2010b, D'Onofrio *et al.*, 2008, Gilman *et al.*, 2008, Kuja-Halkola *et al.*, 2010, Lambe *et al.*, 2006, Langley *et al.*, 2012, Lundberg *et al.*, 2010, Thapar *et al.*, 2009), see review in D'Onofrio *et al.* (2013). The scientific community is, however, still far from a consensus regarding the question of causality (see e.g. Slotkin (2013)).

To date most of the quasi-experimental studies on SDP have not investigated the extent to which the familial factors that confound the associations are due to genetic and/or environmental effects. In vitro fertilization studies (Thapar *et al.*, 2009) have suggested that genetic factors confound the associations, but sibling-comparison studies cannot identify the source of familial confounding (Donovan and Susser, 2011, Lahey and D'Onofrio, 2010). Furthermore, researchers need to examine the assumptions and limitations in the designs they use because each design has limitations and assumptions. Ultimately, finding the sources responsible for the underlying associations between smoking during pregnancy and offspring outcomes is essential for prevention/intervention efforts, as well as informing subsequent basic research (D'Onofrio *et al.*, 2013).

In the current study we used family-based quasi-experimental methods, such as sibling-comparisons and Children of Siblings/Twins designs (D’Onofrio *et al.*, 2003, D’Onofrio *et al.*, 2013, Heath *et al.*, 1985, Silberg *et al.*, 2003), on total population data of 2.75 million Swedes, to test causal inferences and disentangle genetic and environmental effects of the association between SDP and outcomes in offspring. We studied three areas of possible adverse effects in offspring that have been related to SDP: pregnancy outcomes, long-term cognitive outcomes, and long-term externalizing outcomes. We also tested several fundamental assumptions of sibling-comparison designs to examine whether these would unduly influence our conclusions.

Methods

Subjects

We linked several nationwide Swedish registries maintained by government agencies using the unique personal identification number given to all Swedish citizens. These registries cover in principle the entire population (Ludvigsson *et al.*, 2009). The use of these databases has been approved by the ethics committee at Karolinska Institutet, Stockholm, Sweden.

We studied all individuals born in Sweden from January 1st 1983 to December 31st 2009, consisting of 2,754,626 children, because valid data on smoking during pregnancy is available with good coverage from 1983. However, because we studied different outcomes, the investigated associations were made on different cohorts; see Table 1 for number of individuals available for analyses for each outcome. All outcomes were followed until 2009.

Relationships

Using the Multi-Generation Register and the Swedish Twin Register, we constructed extended families of different sizes and relations. We randomly selected up to two sisters who were mothers in each extended family (except we chose all female twin pairs). Then, we randomly drew up to two of each mothers’ offspring, constructing up to two nuclear families within each extended family. We included nuclear families of three different types: single offspring, full-siblings and maternal half-siblings; and extended families of six different types: mothers without siblings, monozygotic twin mothers, dizygotic twin mothers, mothers who were full-siblings, and mothers who were maternal or paternal half-siblings.

Measures

Smoking during pregnancy—At the first antenatal visit for pregnant women, generally in the first trimester (before week 15), the nurse asked whether the mothers were smoking at that time. This is registered in the Swedish Medical Birth Register (MBR) (Centre for Epidemiology, 2012) and was coded as 0 (No) or 1 (Yes). A study found the self-reported SDP to be valid, with only 6% of reported non-smokers having cotinine levels indicating that they were actually smoking (Lindqvist *et al.*, 2002).

Outcomes—From the MBR we used **birth weight** (measured by midwives at the hospital after delivery), **gestational age** (in days and calculated using either ultrasound or time since

last menstrual period), and **preterm birth** (defined as being born gestational day 259 or earlier, but not before day 155 (week 22) where the birth was considered to be a late miscarriage, rather than a preterm birth). We defined being born **small for gestational age** as having birth weight in the lowest 10 per cent compared within gender and gestational day.

From the School Registry we collected grades in upper school, at approximate age 15. We created a binary variable to capture **low academic achievement**, using similar data as Lambe *et al.* (2006), although with a different operationalization; the lowest 10% were coded as a 1 and the rest as 0. Individual with missing grades, indicating non-completion of the compulsory first nine school years, were included in the poor performance group. We collected a measure of **general cognitive ability** (Frisell *et al.*, 2012b) from the Swedish Conscription Registry. The measure was recorded on a 9-grade scale, with hypothesized mean of 5 and standard deviation of 2. Military conscription was enforced by law until 2007 and was generally performed by men at 18 years of age. Only males that were between 17 to 20 years at conscription were included.

From the Crime Register we collected convictions of crimes in Swedish lower court. As a measure of **criminality** we used any conviction registered. For **violent criminality** we used convictions defined as in Frisell *et al.* (2011). In Sweden the age of criminal responsibility is fifteen, we limited the sub-cohort to cover individuals with at least five years at risk, and recorded convictions within this time period, i.e. between ages 15 and 20. Thus the sub-cohort covers offspring born between 1st January 1983 and 31st December 1989. In line with Kendler *et al.* (2012) we used a combination of diagnoses of alcohol/drug dependence from the Patient Register and drug-related convictions (including convictions for driving while intoxicated) from the Crime Register to get a measure of **drug/alcohol misuse**. The Patient Register contains diagnoses from all inpatient care instances that require hospitalization over-night, as well as admissions in outpatient settings since 2001. For these analyses we selected a sub-cohort with individuals at risk until age 22 and recorded drug/alcohol misuse as a one if there was a diagnosis or conviction before 22nd birthday, and as a zero otherwise, thus this sub-cohort consisted of individuals born between 1983 and 1987. For these externalizing behavioral outcomes the probability of observing an offense/diagnosis for any subject is dependent on time of follow up. The maximum ages was chosen to balance the probability of outcome with the number of eligible individuals. As a consequence, rather than analyzing convictions/diagnoses at any time in an individual's life, we are analyzing specific age-limited periods. For example, it is possible that early onset criminality has a higher genetic liability. Thus, this selection can have implication for generalization, and generalizations outside early onset criminality/drug abuse should be done with caution.

General cognitive ability and birth weight were treated as continuous variables in the analyses, whereas the other outcomes were treated as binary variables.

Covariates—We included three covariates from the MBR which we adjusted for in all analyses where applicable; gender of offspring, maternal age at childbirth, and birth year.

Statistical analyses

Ordinary regression: Establishing associations—We estimated the crude and covariate adjusted association between SDP and each outcome using linear (continuous outcomes) or logistic (binary outcomes) regressions. We used the statistical software R (R Development Core Team, 2012) base package for analyses.

Within family analyses: Investigating familial confounding—To investigate potential confounding by factors shared within families we performed within-family analyses. We studied siblings (where comparisons were made within full-siblings and within maternal half-siblings) and cousins (separately for full-cousins and half-cousins). For practical reasons, we selected a random pair of cousins per extended family in the analyses with continuous outcomes.

To estimate the within-family effects (Neuhaus and Kalbfleisch, 1998, Neuhaus and McCulloch, 2006), we performed conditional logistic regression for the binary outcomes, where each extended family was treated as a cluster in cousin comparisons, and nuclear families were treated as clusters in sibling comparisons. For the continuous outcomes, we included a pair-specific mean of the exposure as a covariate as well as a shared random intercept in a linear mixed model. Both methods produces a within-pair estimate that can be considered to be closer to the true, causal, parameter under certain assumptions (Frisell *et al.*, 2012a). All siblings and cousins were included in these analyses, regardless if they were concordant or discordant in SDP, since information from other included covariates contributes to the likelihood. We used the package survival (Therneau 2012) and the package lme4 (Bates *et al.*, 2012) in the statistical software R (R Development Core Team, 2012) to fit the models. Here, and in the ordinary regression analyses, missing values in SDP and outcome were handled by case-wise deletion.

Structural equation models: Estimating magnitude of genetic and environmental confounding—We then performed structural equation modeling (SEM) to investigate the source of potential familial confounding in a model we call the *ACMPE* model. We extended the standard models used in twin research, which decompose variance into genetic (*A*) and shared (*C*) and non-shared (*E*) environmental influences (Neale and Cardon, 1992), to include five variance sources for each phenotype (Table 2; Figure 1). The main difference between the *ACMPE* model and the standard twin model is (1) that we estimate an intergenerational bivariate association (i.e., one phenotype in parental generation and one in offspring generation) and (2) that the shared environment is decomposed into environments shared by mothers and cousins (*M*), fathers and full-siblings (*P*), and all children of one mother (*C*). The model is more extensively explained in Appendix A.

To exemplify the variance parameters aimed at capturing different environmental sources of variance and covariance we here present a hypothetical example of SDP, childrearing regimes and academic achievement. Note that all associations are made up.

The *C* parameter: A woman behaves affectively towards her children, a behavior she learned from experiences not shared with her sister. Affective parenting is correlated with lower

levels of SDP and makes all siblings in the nuclear family less liable to act out in school, which influences the offspring's higher academic achievements.

The *M* parameter: Two sisters were raised by parents who were very goal-oriented, pushing them to aim for good grades, a behavior correlated with higher levels of SDP. Both sisters act similarly as their parents, both by having higher levels of SDP, and pushing their own children. Thus, all cousins in the extended family tend to have high academic achievement.

The *P* parameter: A mother changes spouse between pregnancies, and the new spouse convinces her to quit smoking in her second pregnancy. The first child does not receive as much reinforcing feedback on her academic development by the father of the second child, making her perform worse academically.

The *E* parameter: A mother starts to smoke between first and second pregnancy, and continues while pregnant with her second child. The worse environment *in utero* restricts the neurological development of the second child, making her less mentally capable and therefore she performs academically worse (a scenario where SDP is causally affecting academic achievement).

We fitted this bivariate model separately for SDP and each outcome, and estimated all the covariance parameters. Thus, we partitioned the association between SDP and each offspring outcome into *A*, *C*, *M*, *P* and *E* factors and estimated how much of the correlation between SDP and outcome that is due to each factor.

To find a parsimonious model, where the number of parameters that fit the data is minimized without significant loss in explanatory power, we performed a series of likelihood ratio tests, where we excluded non-significant parameters in the outcomes (at α -level 0.05). We started with the parameter for the outcome with lowest value and the corresponding cross-phenotype parameter (e.g., paternal effect and its correlation with paternal effect in SDP), after elimination of pairs of parameters we continued with just the cross-phenotypic parameters in a similar fashion until all parameters in the model were significantly different from zero. The resulting model is called "best-fitting model". The within-phenotype *E*-parameters were not subject to significance testing since they contain random error. Because of potentially causal interpretation (D'Onofrio *et al.*, 2013, Kendler *et al.*, 1993, Turkheimer and Harden, Submitted) the cross-phenotypic *E*-parameter was included in the final model regardless of statistical significance. For the binary outcomes we used the liability-threshold model, where an underlying normal distribution is assumed for the liability of having the outcome. If an individual has a liability higher than an estimated threshold the variable is observed as 1, otherwise as 0. For each variable we allowed different types of families to have different means/prevalences by letting the mean in the assumed underlying normal distribution be different both for nuclear families and extended families (because the mean/prevalence of exposure and outcomes is different in, for example, full- and half-sibling families). Rather than investigating potential mediating or moderating effects of birth year, gender, and maternal age, we adjusted the means/prevalences of each variable for the covariates, where we included linear and quadratic terms for maternal age and birth year.

We used the package OpenMx (Boker *et al.*, 2011, Boker *et al.*, 2012) in the software R (R Development Core Team, 2012) to fit SEMs. All code is available on request from the corresponding author. Missing values in exposure and outcome were handled using full information maximum likelihood.

Sensitivity analyses

As in any statistical analysis, the within-sibling analyses (from which we aim at drawing the strongest causal inferences) rest on a number of assumptions. In Appendix B we investigate three of the assumptions which potentially may affect our analyses (generalizability of mothers who change their smoking pattern between pregnancies, carry-over effects, and sibling contagion effects), see D’Onofrio *et al.* (2013) for an in-depth description of issues in sibling comparisons.

Results

Descriptive

In Table 3 we present the means and prevalences of the outcomes for pregnancies where the mother did and did not smoke while pregnant, as well as when smoking status was missing. For all of the outcomes the values in the group where mothers smoked while pregnant compared were worse than when the mother did not smoke. The group missing SDP status has values in between the observed smokers and non-smokers, except for the preterm birth outcome, where the prevalence of preterm births is greater in the group missing SDP than in either of the non-missing groups. For further investigations of different patterns of smoking between pregnancies in the same mother see Appendix B and Appendix Table 6a–h.

Ordinary regression

Results from the ordinary cohort analyses for each outcome can be found in Table 4. Results from previous studies were confirmed; SDP was associated with each of the outcomes. For example, offspring to mothers who smoked during pregnancy weighed 201 grams less than offspring to mothers not smoking, and the association remained after controlling for the potential confounders (181 grams less).

Within analyses: Investigating familial confounding

We proceeded to perform within-family analyses, where we compared half-cousins, full-cousins, maternal half-siblings, and full-siblings respectively (Table 4). Our results were in line with previous research; the effect of SDP on pregnancy outcomes persisted in the within family analyses, although the estimates were somewhat attenuated. For example, even in the most controlled analyses (within full-siblings), a child where the mother smoked while pregnant was on average 92 grams lighter than his/her full-sibling born in a pregnancy where the mother did not smoke. In contrast, SDP seemed to have no direct effect on cognitive and externalizing outcomes when siblings discordant for smoking during pregnancy were compared. These results imply familial confounding for all of the long-term associations.

It should be noted that the within-sibling analyses are adjusting for unmeasured confounders assumed stable between pregnancies. To be a confounder a variable has to be related to the exposure as well as the outcome; such potential confounders may thus be viewed as stable *in the mother* (having an effect on the exposure) between pregnancies. An example of this is maternal genetic influences.

Structural equation models: Estimating magnitude of genetic and environmental confounding

We estimated how much of the variation in the outcomes that was due to each variance source in eight separate univariate models. To maximize power, in a separate model, we used the full 1983–2009 cohort to estimate fractions of explained variance for SDP. Table 5 presents the variance components from univariate models, and Appendix Table 1 presents the modelled values from which the variance components were derived. As can be seen additive genetic effects (i.e., the heritability) explained 69% of the variance for SDP, and between 27% and 86% of the variance in the outcomes.

We then used SEM to fit separate bivariate models for each outcome, parameter estimates and standard errors from the full bivariate models are presented in Appendix Table 2. We then identified the best-fitting model for each bivariate relationship (the resulting best-fitting models are presented in Appendix Table 3; decision steps are presented in Appendix Table 4a–h). The magnitude of the correlations, as well as the part of the correlations explained by each of the variance sources in the best-fitting model, are displayed in Figure 2. For comparative reasons we produced a figure, similar to Figure 2, which shows the correlation between SDP and the outcomes in the full model, before any model fitting was performed (Appendix Figure 1). The pattern of overlap differed between the pregnancy outcomes and the cognitive and externalizing outcomes. In all the associations between SDP and pregnancy outcomes, non-shared environmental effects, which are consistent with a causal inference, were important, explaining 12–20% of the total correlation. In contrast, non-shared environment factors only accounted for 0–4% of the observed associations with the cognitive and externalizing outcomes. Genetic factors explained a majority of the associations between SDP and the long-term outcomes, accounting for at least 74% of the correlations.

To exemplify the quantification of the correlations we here present the calculations for the SDP-low academic achievement association, following the approach outlined in Appendix A. The total covariance, which in this case is equivalent to correlation since both variables have a variance of 1, is (values from Appendix Table 3)

$$\begin{aligned} Cov(SDP_{ijk}, OUT_{ijk}) &= \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E \\ &= \frac{1}{2}0.810 \cdot 0.893 \cdot 0.598 + 0.344 \cdot 0.154 \cdot 0 + 0.267 \cdot 0.366 \cdot 0.623 + 0.296 \\ &\quad \cdot 0.105 \cdot 0.494 + 0.258 \cdot 0.185 \cdot (-0.018) \\ &= 0.216 + 0 + 0.061 + 0.015 - 0.001 = 0.292. \end{aligned}$$

Thus the fractions explained by the different variance sources are

$$\frac{(0.216+0+0.061+0.015-0.001)}{0.292}=0.742+0+0.209+0.053-0.003,$$

in the order *A*, *C*, *M*, *P* and *E*.

Sensitivity analyses

The within-sibling analyses utilize mothers who are discordant in SDP between pregnancies. If these mothers were very different from non SDP-discordant mothers, especially in the associations between SDP's the outcomes, our results may not generalize to other types of families. However, we found no support for SDP-discordant families being substantially different; we observed that the means/prevalences in outcome were roughly halfway between that of SDP-concordant non-smokers and smokers, indicating a liability in between the two concordant groups (Appendix Table 7). Further, if SDP-discordant families are not generalizable to the general population we would not expect the agreement with within-cousin comparison seen in Table 4. If the SDP status in the first pregnancy affected the outcome in the second pregnancy, either directly through carry-over effects (e.g., smoking may induce a biological change in the mother, which carries over to following pregnancies) or through sibling contagion effect (e.g., the first offspring engages in criminal activities and influences the second offspring to do the same) the assumptions of sibling comparison would be violated and the within-sibling estimate would be biased. For the cognitive/behavioral outcomes we found no support for such effects being present when we conducted bi-directional analyses (Appendix Table 8). As such, the results do not indicate that the assumptions in the sibling-comparison design, in as much as we could test them, account for the familial confounding of the associations between SDP and the long-term outcomes.

Discussion

Although SDP was associated with all outcomes in the domains we studied, in line with previous research (Cnattingius, 2004, Huizink and Mulder, 2006, Knopik, 2009), we found support for different sources being responsible for the associations. Consistent with causal interpretations, the associations between SDP and pregnancy outcomes persisted when we compared siblings discordant for SDP (although the effect size of the association with preterm birth was relatively limited). For the long-term cognitive and externalizing outcomes, however, the analyses were not consistent with causal associations; when we compared siblings discordant for SDP, none of the long-term associations remained large, or statistically significant.

Similar to our study, sibling-comparison studies of externalizing behavior (D'Onofrio *et al.*, 2008), school performance (D'Onofrio *et al.*, 2010b, Lambe *et al.*, 2006), substance use (D'Onofrio *et al.*, 2012), stress coping (Kuja-Halkola *et al.*, 2010), criminality (D'Onofrio *et al.*, 2010a), intellectual performance (Lundberg *et al.*, 2010), and ADHD (Skoglund *et al.*, 2013) have all suggested substantial familial confounding. Here, we took the analyses one step further and estimated the source of familial confounding. Consistent with the previously observed intra-generational correlation between SDP and maternal criminal behavior and

other co-occurring risk factors (Ellingson *et al.*, 2012), we found that genetic factors explained the main part of the associations with cognitive and externalizing outcomes in the offspring. These results are in line with the findings from family studies and in vitro fertilization studies of SDP and ADHD (Langley *et al.*, 2012, Thapar *et al.*, 2009). In a recent study on the association between SDP and conduct disorder using an adoption design, the results suggested that the association was not due to familial confounding during the postnatal period (Gaysina *et al.*, 2013). The finding, which is consistent with our results, suggests the familial confounding is due to factors present during the prenatal period (e.g., genes), rather than being exerted in the postnatal period.

One of the major strengths of the current study is the use of a populations based sample, where data has been collected prospectively. Furthermore we utilized the knowledge of familial relationships to estimate effects, which may be interpreted as being relatively free of confounding of factors shared within families. None of the sensitivity analyses indicated that the within-sibling results were due to the assumptions inherent in the sibling-comparison design that we were able to test. The extensive family information also allowed us to disentangle the relative contribution of genetic and environmental effects for the association between SDP and outcomes in offspring; sibling-comparison studies by themselves are unable to do so (D'Onofrio *et al.*, 2013). Furthermore we predicted multiple outcomes in each of the domains to avoid misrepresenting inferences, and we found converging results.

The measure of SDP was a yes/no at approximately fifteen weeks of gestation. Thus we did not investigate any dose-response relationship, neither in terms of how much the pregnant women smoked, nor for how long.

One of the reasons for writing this paper was to better understand the previously identified familial confounding for some of the SDP associations. To do this, we wanted to use the best available data. However, there were no methods developed for these types of family based analyses, and we therefore developed the method used in this paper. Admittedly, the parameterization used might not be the ultimately best one, especially not for the shared environmental parameters. We chose to separate the environment into variance parts *C*, *M*, *P*, and *E*. This is a somewhat arbitrary choice that might, or might not, be valid. In the best case scenario, we have captured the most important features of how environmental influences' on phenotypes are shared between relatives, and therefore estimates of cross-phenotypic additive genetic effects are unbiased. In the worst case scenario, our estimates of cross-phenotypic additive genetic effects are biased, but the within-family estimates testing causal inferences would remain unchanged. Further, we assume that maternal siblings have shared environmental effects (the *C* in offspring generation and *M* in parental generation), while paternal siblings have not. We do this since when parents divorce offspring tend to more often live with the mother (Statistics Sweden, 1994). However, we did not explicitly validate this assumption in the present data. Because the main source of confounding was genetic, we did not try to further evaluate the different shared environmental parameters, because that would most likely not contribute to different interpretations of the data. If these methods are used for other research questions, further method developments might be needed.

Model fitting of the quantitative genetic *ACMPE* model presented some problems because the method is novel and the software has not been used for similar types of data sets. This led to several drawbacks, first we were not able to fit the full bivariate models for the SDP-preterm birth and SDP-born small for gestational age associations since the models failed to converge. Instead we chose to use parameter estimates from separately fitted univariate models for SDP and outcomes in the bivariate analyses, where we estimated the cross-phenotype parameters. This may introduce bias, and spuriously increase precision in the parameters in the bivariate model. Second, we encountered problems in finding the global likelihood maximum. Focusing on finding the best fit for the models, we ran each model from a variety of starting values, and re-ran them from the previously fitted values, to ensure that a global likelihood maximum had been reached. The difficult optimization procedure, which solely focused on improvements in the likelihood, made the standard errors for some parameters not reliable (since the curvature of the likelihood around the fitted values, which is captured by the hessian matrix and used to calculate standard errors, obtained from a fitted model with starting values close to the final fitted values did not behave well for our models and data). To solve this problem we did not rely on standard errors in model fitting and inference from these models, rather, we used likelihood ratio tests (Appendix Tables 4a–h). We have neither considered dominant genetic effects nor assortative mating in our analyses. The measure for SDP is self-reported and may thus be subject to misclassification, which in turn leads to bias (toward null) of the associational estimates, which is particularly problematic for within-relative analyses (Frisell *et al.*, 2012a, McGue *et al.*, 2010). However, our exposure has been shown to be valid (Lindqvist *et al.*, 2002), and we were able to estimate robust associations with pregnancy outcomes within families, suggesting measurement error alone cannot account for the findings.

Prevention of SDP remains important; in our analyses we add further support of SDP being a causal risk factor for birth/pregnancy-related complications. However, we find no such support for adolescent/adult outcomes in the cognitive and behavioral problems. Nevertheless, the observed associations are real; mothers who smoke while pregnant have offspring with greater risk of many adverse outcomes throughout life. Our results suggest that the sources of the long-term associations originate in families (primarily due to shared genetic variation), however. Although this should **not** be interpreted as a deterministic feature, which is immune against interventional efforts, there are nevertheless important consequences. Understanding the underlying associations between SDP and offspring outcomes is necessary for appropriate prevention, intervention and future research efforts. For example, an imaging study was recently conducted where measurable differences between offspring of exposed and not exposed to SDP during reward anticipation were observed (Muller *et al.*, 2013). The potential for genetic variants passed down from mother was noted as a limitation but not examined further, in contrast to imaging work on schizophrenia and working memory (Karlsgodt *et al.*, 2007). Thus, Muller *et al.* cannot be certain that it is smoking that caused the observed differences or if the differences were caused by genetic variants passed down from the smoking mother. Thus, to avoid wasted resources, the information that genetic effects are of substantial importance for the association between SDP and long-term outcomes should be considered in intervention and prevention, as well as in basic (e.g., clinical neuroscience) research.

Acknowledgments

Financial support

The study was supported by grants from the National Institute of Child Health and Human Development (B.M.D., grant number HD061817); by the Swedish Research Council through the Swedish Initiative for Research on Microdata in the Social And Medical Sciences (SIMSAM) framework grant no 340-2013-5867, by the and Swedish Research Council for Health, Working Life and Welfare, and by the Swedish Prison and Probation Services.

References

- Agrawal A, Knopik VS, Pergadia ML, Waldron M, Bucholz KK, Martin NG, Heath AC, Madden PAF. Correlates of cigarette smoking during pregnancy and its genetic and environmental overlap with nicotine dependence. *Nicotine and Tobacco Research*. 2008; 10:567–578. [PubMed: 18418779]
- Bates, D.; Maechler, M.; Bolker, B. lme4: Linear mixed-effects models using S4 classes. 2012. [computer program]
- Boker S, Neale M, Maes H, Wilde M, Spiegel M, Brick T, Spies J, Estabrook R, Kenny S, Bates T, Mehta P, Fox J. OpenMx: An Open Source Extended Structural Equation Modeling Framework. *Psychometrika*. 2011; 76:306–317. [PubMed: 23258944]
- Boker, SM.; Neale, MC.; Maes, HH.; Wilde, MJ.; Spiegel, M.; Brick, TR.; Estabrook, R.; Bates, TC.; Mehta, P.; von Oertzen, T.; Gore, RJ.; Hunter, MD.; Hackett, DC.; Karch, J.; Brandmaier, AM. OpenMx User Guide, Release 1.2.0-1919. 2012.
- Centre for Epidemiology. The Swedish Medical Birth Register - A Summary of Content and Quality Socialstyrelsen. 2012.
- Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine & Tobacco Research*. 2004; 6(Suppl 2):S125–40. [PubMed: 15203816]
- D’Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *Am J Public Health*. 2013; 103(Suppl 1):S46–55. [PubMed: 23927516]
- D’Onofrio BM, Rickert ME, Langstrom N, Donahue KL, Coyne CA, Larsson H, Ellingson JM, Van Hulle CA, Iliadou AN, Rathouz PJ, Lahey BB, Lichtenstein P. Familial confounding of the association between maternal smoking during pregnancy and offspring substance use and problems. *Archives of General Psychiatry*. 2012; 69:1140–50. [PubMed: 23117635]
- D’Onofrio BM, Singh AL, Iliadou A, Lambe M, Hultman CM, Grann M, Neiderhiser JM, Langstrom N, Lichtenstein P. Familial confounding of the association between maternal smoking during pregnancy and offspring criminality: a population-based study in Sweden. *Archives of General Psychiatry*. 2010a; 67:529–38. [PubMed: 20439834]
- D’Onofrio BM, Singh AL, Iliadou A, Lambe M, Hultman CM, Neiderhiser JM, Langstrom N, Lichtenstein P. A quasi-experimental study of maternal smoking during pregnancy and offspring academic achievement. *Child Development*. 2010b; 81:80–100. [PubMed: 20331655]
- D’Onofrio BM, Turkheimer EN, Eaves LJ, Corey LA, Berg K, Solaas MH, Emery RE. The role of the children of twins design in elucidating causal relations between parent characteristics and child outcomes. *Journal of Child Psychology and Psychiatry*. 2003; 44:1130–44. [PubMed: 14626455]
- D’Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, Lahey BB. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. *Development and Psychopathology*. 2008; 20:139–64. [PubMed: 18211732]
- D’Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. The Critical Need for Family-Based, Quasi-Experimental Designs in Integrating Genetic and Social Science Research. *American Journal of Public Health*. 2013
- D’Onofrio BM, Turkheimer E, Eaves LJ, Corey LA, Berg K, Solaas MH, Emery RE. The role of the Children of Twins design in elucidating causal relations between parent characteristics and child outcomes. *Journal of Child Psychology & Psychiatry*. 2003; 44:1130–1144. [PubMed: 14626455]

- Donovan SJ, Susser E. Commentary: Advent of sibling designs. *International Journal of Epidemiology*. 2011; 40:345–349. [PubMed: 21450688]
- Ellingson JM, Rickert ME, Lichtenstein P, Langstrom N, D'Onofrio BM. Disentangling the relationships between maternal smoking during pregnancy and co-occurring risk factors. *Psychological Medicine*. 2012; 42:1547–57. [PubMed: 22115276]
- Frisell T, Lichtenstein P, Langstrom N. Violent crime runs in families: a total population study of 12.5 million individuals. *Psychological Medicine*. 2011; 41:97–105. [PubMed: 20334717]
- Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology*. 2012a; 23:713–20. [PubMed: 22781362]
- Frisell T, Pawitan Y, Langstrom N. Is the association between general cognitive ability and violent crime caused by family-level confounders? *PLoS One*. 2012b; 7:e41783. [PubMed: 22911856]
- Gaysina D, Fergusson DM, Leve LD, Horwood J, Reiss D, Shaw DS, Elam KK, Natsuaki MN, Neiderhiser JM, Harold GT. Maternal Smoking During Pregnancy and Offspring Conduct Problems: Evidence From 3 Independent Genetically Sensitive Research Designs. *JAMA Psychiatry*. 2013
- Gilman SE, Gardener H, Buka SL. Maternal smoking during pregnancy and children's cognitive and physical development: a causal risk factor? *American Journal of Epidemiology*. 2008; 168:522–31. [PubMed: 18653646]
- Glantz MD, Chambers JC. Prenatal drug exposure effects on subsequent vulnerability to drug abuse. *Dev Psychopathol*. 2006; 18:893–922. [PubMed: 17152406]
- Heath AC, Kendler KS, Eaves LJ, Markell D. The resolution of cultural and biological inheritance: informativeness of different relationships. *Behavior Genetics*. 1985; 15:439–65. [PubMed: 4074271]
- Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neuroscience & Biobehavioral Reviews*. 2006; 30:24–41. [PubMed: 16095697]
- Karlsgodt KH, Glahn DC, van Erp TG, Therman S, Huttunen M, Manninen M, Kaprio J, Cohen MS, Lonnqvist J, Cannon TD. The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects. *Schizophrenia Research*. 2007; 89:191–7.
- Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression. A causal analysis. *Archives of General Psychiatry*. 1993; 50:36–43. [PubMed: 8422220]
- Kendler KS, Sundquist K, Ohlsson H, Palmer K, Maes H, Winkleby MA, Sundquist J. Genetic and familial environmental influences on the risk for drug abuse: a national Swedish adoption study. *Archives of General Psychiatry*. 2012; 69:690–7. [PubMed: 22393206]
- Knopik VS. Maternal smoking during pregnancy and child outcomes: real or spurious effect? *Developmental Neuropsychology*. 2009; 34:1–36. [PubMed: 19142764]
- Knopik VS, Maccani MA, Francazio S, McGeary JE. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. *Development and Psychopathology*. 2012; 24:1377–1390. [PubMed: 23062304]
- Kuja-Halkola R, D'Onofrio BM, Iliadou AN, Langstrom N, Lichtenstein P. Prenatal smoking exposure and offspring stress coping in late adolescence: no causal link. *International Journal of Epidemiology*. 2010; 39:1531–40. [PubMed: 20719746]
- Lahey BB, D'Onofrio BM. All in the family: Comparing siblings to test causal hypotheses regarding environmental influences on behavior. *Current Directions in Psychological Science*. 2010; 19:319–323. [PubMed: 23645975]
- Lambe M, Hultman C, Torrang A, Maccabe J, Cnattingius S. Maternal smoking during pregnancy and school performance at age 15. *Epidemiology*. 2006; 17:524–30. [PubMed: 16878043]
- Langley K, Heron J, Smith GD, Thapar A. Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. *American Journal of Epidemiology*. 2012; 176:261–8. [PubMed: 22791738]

- Lindqvist R, Lendahls L, Tollbom O, Aberg H, Hakansson A. Smoking during pregnancy: comparison of self-reports and cotinine levels in 496 women. *Acta Obstetrica et Gynecologica Scandinavica*. 2002; 81:240–4. [PubMed: 11966481]
- Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *European Journal of Epidemiology*. 2009; 24:659–67. [PubMed: 19504049]
- Lundberg F, Cnattingius S, D’Onofrio B, Altman D, Lambe M, Hultman C, Iliadou A. Maternal smoking during pregnancy and intellectual performance in young adult Swedish male offspring. *Paediatric and Perinatal Epidemiology*. 2010; 24:79–87. [PubMed: 20078833]
- McGue M, Osler M, Christensen K. Causal Inference and Observational Research: The Utility of Twins. *Perspectives on Psychological Science*. 2010; 5:546–556. [PubMed: 21593989]
- Muller KU, Mennigen E, Ripke S, Banaschewski T, Barker GJ, Buchel C, Conrod P, Fauth-Bühler M, Flor H, Garavan H, Heinz A, Lawrence C, Loth E, Mann K, Martinot JL, Pausova Z, Rietschel M, Strohle A, Struve M, Walaszek B, Schumann G, Paus T, Smolka MN. Altered reward processing in adolescents with prenatal exposure to maternal cigarette smoking. *JAMA Psychiatry*. 2013; 70:847–56. [PubMed: 23784668]
- Neale, MC.; Cardon, LR. *Methodology for genetic studies of twins and families*. Kluwer Academic Publishers; Dordrecht ; Boston: 1992.
- Neuhaus JM, Kalbfleisch JD. Between- and within-cluster covariate effects in the analysis of clustered data. *Biometrics*. 1998; 54:638–645. [PubMed: 9629647]
- Neuhaus JM, McCulloch CE. Separating between- and within-cluster covariate effects by using conditional and partitioning methods. *Journal of the Royal Statistical Society Series B-Statistical Methodology*. 2006; 68:859–872.
- Paradis AD, Fitzmaurice GM, Koenen KC, Buka SL. Maternal smoking during pregnancy and criminal offending among adult offspring. *J Epidemiol Community Health*. 2011; 65:1145–50. [PubMed: 21081311]
- R Development Core Team. R: A language and environment for statistical computing. 2012. [computer program]
- Silberg J, Rutter M, D’Onofrio B, Eaves L. Genetic and environmental risk factors in adolescent substance use. *Journal of Child Psychology and Psychiatry*. 2003; 44:664–76. [PubMed: 12831111]
- Skoglund C, Chen Q, D’Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. *J Child Psychol Psychiatry*. 2013 In press.
- Slotkin TA. Maternal smoking and conduct disorder in the offspring. *JAMA Psychiatry*. 2013; 70:901–2. [PubMed: 23884399]
- Statistics Sweden. *Demografiska rapporter*. Vol. 1994. Stockholm: 1994. Fakta om den svenska familjen; p. 2
- Thapar A, Rice F, Hay D, Boivin J, Langley K, van den Bree M, Rutter M, Harold G. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. *Biological Psychiatry*. 2009; 66:722–7. [PubMed: 19596120]
- Therneau, T. R package version 2.36-14. 2012. A Package for Survival Analysis in S. [computer program]
- Turkheimer, E.; Harden, KP. Behavior genetic research methods: Testing quasi-causal hypotheses using multivariate twin data. In: Reis, HT.; Judd, CM., editors. *Handbook of Research Methods in Personality and Social Psychology*. Cambridge University Press; (Submitted)
- Wakschlag LS, Pickett KE, Cook E Jr, Benowitz NL, Leventhal BL. Maternal smoking during pregnancy and severe antisocial behavior in offspring: a review. *Am J Public Health*. 2002; 92:966–74. [PubMed: 12036791]

Appendix

Appendix A: Description of the ACMPE model

Each phenotype, either exposure or outcome, is assumed to be caused by the variance sources A , C , M , P , E and possible some covariates. Let i ($=1, 2, \dots, N$; N =number of extended families) be extended family number, j ($=1, 2$) be nuclear family number, and k ($=1, 2$) be offspring number. Let y_{ijk}^{SDP} be maternal smoking during pregnancy and y_{ijk}^{OUT} be the outcome and x_{ijk}^{SDP} and x_{ijk}^{OUT} be covariates, for individual k within nuclear family j and extended family i . Let SDP_{ijk} and OUT_{ijk} be the residuals; the unexplained variance in y_{ijk}^{SDP} and y_{ijk}^{OUT} when adjusted for covariates x_{ijk}^{SDP} and x_{ijk}^{OUT} . Furthermore, let A_{ijk}^{SDP} , C_{ijk}^{SDP} , M_{ijk}^{SDP} , P_{ijk}^{SDP} , and E_{ijk}^{SDP} be random effects representing the previously defined variance sources for SDP (the exposure), and A_{ijk}^{OUT} , C_{ijk}^{OUT} , M_{ijk}^{OUT} , P_{ijk}^{OUT} , and E_{ijk}^{OUT} be random effects representing the variance sources for the outcome. These random effects are assumed normally distributed with mean zero. Finally, let β_{SDP} and β_{OUT} be regression coefficients for the covariates on the phenotypic values respectively. For brevity the model is here described using the unity link, as used for continuous variables; however for binary variables the liability threshold model is used (similar to using a probit link), the model generalizes to this situation. The observed phenotypes within an individual are defined by the equation

$$\begin{bmatrix} y_{ijk}^{SDP} \\ y_{ijk}^{OUT} \end{bmatrix} = \begin{bmatrix} x_{ijk}^{SDP} \beta_{SDP} + SDP_{ijk} \\ x_{ijk}^{OUT} \beta_{OUT} + OUT_{ijk} \end{bmatrix},$$

where the residuals SDP_{ijk} and OUT_{ijk} are decomposed into random effects:

$$\begin{bmatrix} SDP_{ijk} \\ OUT_{ijk} \end{bmatrix} = \begin{bmatrix} A_{ijk}^{SDP} + C_{ijk}^{SDP} + M_{ijk}^{SDP} + P_{ijk}^{SDP} + E_{ijk}^{SDP} \\ A_{ijk}^{OUT} + C_{ijk}^{OUT} + M_{ijk}^{OUT} + P_{ijk}^{OUT} + E_{ijk}^{OUT} \end{bmatrix}.$$

Intercepts may depend on extended and nuclear family types, if so then indicators of family types are included in x_{ijk} , and the intercepts regression coefficients are included in the β vectors. It should be noted that these parameters are estimated simultaneously with the random effects.

We use extended families consisting of two nuclear families, and each nuclear family consists of one or two offspring of the same mother. Thus an extended family may consist of 4 individuals, each with two phenotypes:

$$\begin{bmatrix} SDP_{i11} \\ OUT_{i11} \\ SDP_{i12} \\ OUT_{i12} \\ SDP_{i21} \\ OUT_{i21} \\ SDP_{i22} \\ OUT_{i22} \end{bmatrix} = \begin{bmatrix} A_{i11}^{SDP} + C_{i11}^{SDP} + M_{i11}^{SDP} + P_{i11}^{SDP} + E_{i11}^{SDP} \\ A_{i11}^{OUT} + C_{i11}^{OUT} + M_{i11}^{OUT} + P_{i11}^{OUT} + E_{i11}^{OUT} \\ A_{i12}^{SDP} + C_{i12}^{SDP} + M_{i12}^{SDP} + P_{i12}^{SDP} + E_{i12}^{SDP} \\ A_{i12}^{OUT} + C_{i12}^{OUT} + M_{i12}^{OUT} + P_{i12}^{OUT} + E_{i12}^{OUT} \\ A_{i21}^{SDP} + C_{i21}^{SDP} + M_{i21}^{SDP} + P_{i21}^{SDP} + E_{i21}^{SDP} \\ A_{i21}^{OUT} + C_{i21}^{OUT} + M_{i21}^{OUT} + P_{i21}^{OUT} + E_{i21}^{OUT} \\ A_{i22}^{SDP} + C_{i22}^{SDP} + M_{i22}^{SDP} + P_{i22}^{SDP} + E_{i22}^{SDP} \\ A_{i22}^{OUT} + C_{i22}^{OUT} + M_{i22}^{OUT} + P_{i22}^{OUT} + E_{i22}^{OUT} \end{bmatrix}.$$

The covariance between subjects, both within and across phenotypes, is dependent on their relation, both genetic and environmental. In Appendix Table 5 the correlation between random variables A , C , M , P , and E within and across phenotypes are tabulated. Here a_s^2 is the variance of A_{ijk}^{SDP} , a_o^2 ditto for A_{ijk}^{OUT} , c_s^2 is the variance of C_{ijk}^{SDP} , c_o^2 ditto for C_{ijk}^{OUT} , et cetera. The parameter r_A captures the genetic overlap between exposure and outcome, r_C captures the overlap for environmental C part, et cetera.

Appendix Table 5 shows covariance within individual and across relatives, both within each phenotype and across phenotypes. It can be seen that environments are assumed shared across phenotypes, and therefore across generations, by simple prolongation of how it looks within each generation. Note that all covariances between variance sources, both within and across phenotypes, are assumed to be zero, e.g.

$Cov(A_{ijk}^{SDP}, C_{ijk}^{SDP}) \equiv 0$, $Cov(C_{ijk}^{SDP}, M_{ijk}^{OUT}) \equiv 0$, and $Cov(M_{ijk}^{OUT}, P_{ijk}^{OUT}) \equiv 0$. The SEM is shown in part as path diagrams in Appendix Figure 2 where an extended family structure of a family with one offspring in “Nuclear family 1” and a family with two offspring in “Nuclear family 2” are depicted. Each variance source is shown separately; however, they are simultaneously estimated.

In the SEM an expected covariance matrix is specified, this covariance matrix is specific to any combination of siblings in nuclear families with any combination of mothers who are siblings in extended families. Since we allow for one to four individuals in the offspring generation (one: mothers without siblings with one offspring; four: two mothers who are siblings, each mother with two offspring) the extended families may be accompanied by an expected covariance matrix of dimensions ranging from 2×2 to 8×8 .

We can derive all covariances between phenotypes in one subject with that of another in the same extended family using Appendix Table 5 (or Appendix Figure 2), both between and within phenotypes;

Within an individual, note that off-diagonals are symmetric:

$$\begin{bmatrix} Var(SDP_{ijk}) & Cov(SDP_{ijk}, OUT_{ijk}) \\ Cov(OUT_{ijk}, SDP_{ijk}) & Var(OUT_{ijk}) \end{bmatrix} = \begin{bmatrix} a_s^2 + c_s^2 + m_s^2 + p_s^2 + e_s^2 & \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E \\ \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E & a_o^2 + c_o^2 + m_o^2 + p_o^2 + e_o^2 \end{bmatrix}.$$

Between full siblings, the k' sub-index is the complement of k :

$$\begin{bmatrix} \text{Cov}(SDP_{ijk}, SDP_{ijk'}) & \text{Cov}(SDP_{ijk}, OUT_{ijk'}) \\ \text{Cov}(OUT_{ijk}, SDP_{ijk'}) & \text{Cov}(OUT_{ijk}, OUT_{ijk'}) \end{bmatrix} = \begin{bmatrix} a_s^2 + c_s^2 + m_s^2 + p_s^2 & \\ \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P & \frac{1}{2}a_o^2 + c_o^2 + m_o^2 + p_o^2 \end{bmatrix}.$$

Between half siblings:

$$\begin{bmatrix} \text{Cov}(SDP_{ijk}, SDP_{ijk'}) & \text{Cov}(SDP_{ijk}, OUT_{ijk'}) \\ \text{Cov}(OUT_{ijk}, SDP_{ijk'}) & \text{Cov}(OUT_{ijk}, OUT_{ijk'}) \end{bmatrix} = \begin{bmatrix} a_s^2 + c_s^2 + m_s^2 & \\ \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M & \frac{1}{4}a_o^2 + c_o^2 + m_o^2 \end{bmatrix}.$$

Between cousins where mothers are MZ twins, the j' sub-index is the complement of j , and “.” is used to indicate any of possible values at sub-index:

$$\begin{bmatrix} \text{Cov}(SDP_{ijk}, SDP_{ij'.}) & \text{Cov}(SDP_{ijk}, OUT_{ij'.}) \\ \text{Cov}(OUT_{ijk}, SDP_{ij'.}) & \text{Cov}(OUT_{ijk}, OUT_{ij'.}) \end{bmatrix} = \begin{bmatrix} a_s^2 + m_s^2 & \\ \frac{1}{2}a_s a_o r_A + m_s m_o r_M & \frac{1}{4}a_o^2 + m_o^2 \end{bmatrix}.$$

Between cousins where mothers are DZ twins or full siblings:

$$\begin{bmatrix} \text{Cov}(SDP_{ijk}, SDP_{ij'.}) & \text{Cov}(SDP_{ijk}, OUT_{ij'.}) \\ \text{Cov}(OUT_{ijk}, SDP_{ij'.}) & \text{Cov}(OUT_{ijk}, OUT_{ij'.}) \end{bmatrix} = \begin{bmatrix} \frac{1}{2}a_s^2 + m_s^2 & \\ \frac{1}{4}a_s a_o r_A + m_s m_o r_M & \frac{1}{8}a_o^2 + m_o^2 \end{bmatrix}.$$

Between cousins where mothers are maternal half siblings:

$$\begin{bmatrix} \text{Cov}(SDP_{ijk}, SDP_{ij'.}) & \text{Cov}(SDP_{ijk}, OUT_{ij'.}) \\ \text{Cov}(OUT_{ijk}, SDP_{ij'.}) & \text{Cov}(OUT_{ijk}, OUT_{ij'.}) \end{bmatrix} = \begin{bmatrix} \frac{1}{4}a_s^2 + m_s^2 & \\ \frac{1}{8}a_s a_o r_A + m_s m_o r_M & \frac{1}{16}a_o^2 + m_o^2 \end{bmatrix}.$$

Between cousins where mothers are paternal half siblings:

$$\begin{bmatrix} \text{Cov}(SDP_{ijk}, SDP_{ij'.}) & \text{Cov}(SDP_{ijk}, OUT_{ij'.}) \\ \text{Cov}(OUT_{ijk}, SDP_{ij'.}) & \text{Cov}(OUT_{ijk}, OUT_{ij'.}) \end{bmatrix} = \begin{bmatrix} \frac{1}{4}a_s^2 & \\ \frac{1}{8}a_s a_o r_A & \frac{1}{16}a_o^2 \end{bmatrix}.$$

From this we may assemble any constellation of families included in the model. As an example, let extended family 1 be a mother with one offspring, let extended family 2 be a mother with two full sibling offspring, and let the mothers be maternal half siblings; the expected covariance matrix looks like

$$\begin{aligned}
& \text{Cov} \left(\begin{bmatrix} SDP_{i11} \\ OUT_{i11} \\ SDP_{i21} \\ OUT_{i21} \\ SDP_{i22} \\ OUT_{i22} \end{bmatrix} \right) \\
&= \begin{bmatrix} \text{Var}(SDP_{i11}) & \text{Cov}(OUT_{i11}, SDP_{i11}) & \text{Cov}(SDP_{i21}, SDP_{i11}) & \text{Cov}(OUT_{i21}, SDP_{i11}) & \text{Cov}(SDP_{i22}, SDP_{i11}) & \text{Cov}(OUT_{i22}, SDP_{i11}) \\ \text{Cov}(OUT_{i11}, SDP_{i11}) & \text{Var}(OUT_{i11}) & \text{Cov}(OUT_{i21}, SDP_{i11}) & \text{Var}(OUT_{i21}) & \text{Cov}(OUT_{i22}, SDP_{i11}) & \text{Cov}(OUT_{i22}, OUT_{i21}) \\ \text{Cov}(SDP_{i21}, SDP_{i11}) & \text{Cov}(OUT_{i21}, SDP_{i11}) & \text{Var}(SDP_{i21}) & \text{Cov}(OUT_{i21}, SDP_{i21}) & \text{Cov}(SDP_{i22}, SDP_{i21}) & \text{Cov}(SDP_{i22}, OUT_{i21}) \\ \text{Cov}(OUT_{i21}, SDP_{i11}) & \text{Var}(OUT_{i21}) & \text{Cov}(OUT_{i21}, SDP_{i21}) & \text{Var}(OUT_{i21}) & \text{Cov}(OUT_{i22}, SDP_{i21}) & \text{Cov}(OUT_{i22}, OUT_{i21}) \\ \text{Cov}(SDP_{i22}, SDP_{i11}) & \text{Cov}(SDP_{i22}, OUT_{i21}) & \text{Cov}(SDP_{i22}, SDP_{i21}) & \text{Cov}(SDP_{i22}, OUT_{i21}) & \text{Var}(SDP_{i22}) & \text{Cov}(OUT_{i22}, SDP_{i22}) \\ \text{Cov}(OUT_{i22}, SDP_{i11}) & \text{Cov}(OUT_{i22}, OUT_{i21}) & \text{Cov}(OUT_{i22}, SDP_{i21}) & \text{Cov}(OUT_{i22}, OUT_{i21}) & \text{Cov}(OUT_{i22}, SDP_{i22}) & \text{Var}(OUT_{i22}) \end{bmatrix} \\
&= \begin{bmatrix} \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E & \frac{1}{8}a_s a_o r_A + m_s m_o r_M & \frac{1}{16}a_o^2 + m_o^2 & \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E & \dots \\ \frac{1}{8}a_s a_o r_A + m_s m_o r_M & \frac{1}{16}a_o^2 + m_o^2 & \frac{1}{8}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E & \dots \\ \frac{1}{16}a_o^2 + m_o^2 & \frac{1}{8}a_s a_o r_A + m_s m_o r_M & \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E & \dots \\ \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots \end{bmatrix}
\end{aligned}$$

In the *ACMPE* model there are a number of parameters which may be estimated:

- The intercepts and covariate regression parameters; β_{SDP} and β_{OUT} .
- The variance of random parameters A , C , M , P , and E for exposure and outcome;
 $a_s^2, c_s^2, m_s^2, p_s^2, e_s^2, a_o^2, c_o^2, m_o^2, p_o^2$, and e_o^2 .
- The cross-phenotype correlation parameters; r_A, r_C, r_M, r_P , and r_E .

For each variable, both exposure and outcomes, we may use the above defined variance, e.g.

$$\text{Var}(OUT_{ijk}) = a_o^2 + c_o^2 + m_o^2 + p_o^2 + e_o^2,$$

to estimate the fraction of variance explained by each variance source. For example, the narrow sense heritability for an outcome, i.e. the fraction of variance explained by additive genetic factors, may be expressed as

$$\text{narrow sense heritability} = \frac{a_o^2}{\text{Var}(OUT_{ijk})}.$$

Above we derived that the covariance between SDP and outcome within an individual is

$$\text{Cov}(SDP_{ijk}, OUT_{ijk}) = \frac{1}{2}a_s a_o r_A + c_s c_o r_C + m_s m_o r_M + p_s p_o r_P + e_s e_o r_E.$$

The amount of explained covariance between phenotypes, within individual, per variance source is the particular source divided by the total amount of covariance, e.g.

$$\text{explained covariance due to additive genetics} = \frac{\frac{1}{2}a_s a_o r_A}{\text{Cov}(SDP_{ijk}, OUT_{ijk})}.$$

Appendix B: Generalizability of mothers who change smoking status between pregnancies; carry-over and contagion effects

Within sibling comparison analyses may be regarded as having an estimated effect that is closer to a causal effect compared to ordinary between individual analyses. Nevertheless, as all statistical models, comparisons within siblings rely on a number of assumptions, discussed in detail in D’Onofrio *et al.* (2013). We here address three assumptions which we believe are most important for our study.

Generalizability. Are women who change their smoking behavior between two pregnancies different?

The within sibling comparisons utilize siblings discordant for exposure to smoking while in utero. If mothers who change their smoking status between pregnancies are very different (i.e., in terms of how smoking during pregnancy (SDP) affects the outcome) from those who do not, the results of our analyses may not be generalizable to groups of women who do not change their smoking status between pregnancies. Appendix Tables 6a–h present the proportions and means in the outcomes for each possible combination of SDP in the offspring (where we used the first-and second-born of each mother having her first child in 1983 or later, and having at least two children in exposure periods defined as in the main article).

To investigate the generalizability of pairs discordant for SDP to pairs concordant, we calculate the concordant proportions/means and an expected value for the discordant pairs (Appendix Table 7). We realize that “expected value” is scale-dependent, so we consider additive scale and multiplicative scale in our analyses. The expected value was calculated under the assumption that SDP had a linear effect (either additive scale [unity link] or a multiplicative scale [logit link], where applicable) for both offspring in the nuclear family, regardless if the mother smoked in the offspring’s pregnancy or his/her sibling’s.

As can be seen in the table, for all associations the observed prevalences and means in the outcomes for SDP-discordant pairs were roughly halfway between that of SDP-concordant pairs. All values were closer to the predicted values than to the observed values in any of the concordant pairs. This pattern is what is expected if SDP is an expression of maternal characteristics (e.g., genes) and/or the association is causal. Thus, the data suggest that the SDP discordant mothers carry a liability that is in between the liabilities of the concordant mothers or that the association is causal, or a combination them between.

Further, if discordant siblings were very different from the general population we would not expect within sibling results to be in agreement with results comparing cousins (Table 4 in

the main paper). Taken together, our analyses don't provide any evidence for the hypothesis that SDP results from discordant mothers should not be generalizable to other mothers.

Carry-over and contagion effects. Does smoking behavior in first pregnancy influence the next pregnancy?

Another issue is whether there are carry-over effects from child 1 to child 2, that is, when the exposure status of sibling 1 (SDP_1) affects the outcome of sibling 2 (OUT_2) directly; for example, later born offspring to mothers who had their first child born during adolescence were affected by the effect of the adolescent child-bearing regardless of the mothers age at their own birth, maybe because environmental factors specifically associated with early maternal age of first child (e.g., diminished financial and social resources in families in which the mother had her first child at an early age (Coyne *et al.* 2013)). The carry-over effects should be distinguished from the contagion effects, which occurs when the outcome of sibling 1 (OUT_1) affects the outcome of sibling 2 (OUT_2). An example would be if criminal behavior of an older sibling would influence criminality in the younger siblings. We note that both of these potential effects would introduce an association between SDP_1 and OUT_2 through a pathway which is assumed to be non-existing in the sibling analyses. Thus, if no carry-over or contagion effect exists we would expect the association between the SDP_1 and OUT_2 to be of the same magnitude as the association between SDP_2 on OUT_1 . On the other hand, if carry-over or contagion effects are important, the effect of SDP_1 on OUT_2 should be stronger than the effect of SDP_2 on OUT_1 .

To investigate carry-over and contagion effects we tested whether the SDP_1 - OUT_2 association differed from the SDP_2 - OUT_1 association by including an interaction term between being first born and SDP in one pregnancy on the outcome in the other pregnancy (after controlling for the effects of being first-born; Appendix Table 8).

As evident in Appendix Table 8, in none of the associations where our analyses suggested that familial confounding was responsible for the entire association (i.e., all the cognitive/behavioral outcomes) there were no evidence for carry-over or contagion effects (note that for Low academic achievement, the indication is that child 2 influence child 1 rather than the other way around). We only observe significant interaction effects of the SDP_1 - OUT_2 association being stronger than the SDP_2 - OUT_1 association in pre-term birth and born small for gestational age. Thus, our main conclusion that smoking during pregnancy seem to be associated to adolescent cognitive capacity and late adolescent behavioral/conduct problems only due to genetic transmission of common susceptibility genes do not seem to be affected by violation of carry-over or contagion effects.

References Appendix B

- Coyne CA, Langstrom N, Rickert ME, Lichtenstein P, D'Onofrio BM. Maternal age at first birth and offspring criminality: using the children of twins design to test causal hypotheses. *Development and Psychopathology*. 2013; 25(1):17–35. [PubMed: 23398750]
- D'Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *American Journal of Public Health*. 2013; 103(Suppl 1):S46–55. [PubMed: 23927516]

Figure 1.
A representation of the *ACMPE* model.
Note: The figure represents the covariance between maternal smoking during pregnancy (SDP; indicated by sub-index “S”) and an outcome (OUT; indicated by sub-index “O”) within an individual.

Figure 2.

Correlations between maternal smoking during pregnancy and outcomes in offspring and parts of the correlations explained by different sources of variance

Note: Results from the best-fitting models, for full models see Appendix Figure 1. Due to computational issues the model for the association between SDP and preterm birth, as well as with being born small for gestational age, was fitted in three steps; first SDP and outcomes were fitted separately, then the results from model fitting were used in the cross-phenotype analyses.

Appendix Figure 1.

Correlations between maternal smoking during pregnancy and outcomes in offspring and parts of the correlations explained by different sources of variance

Note: These are the results from the full models, without model fitting steps performed. Due to computational issues the model for the association between SDP and preterm birth, as well as with being born small for gestational age, was fitted in three steps; first SDP and outcomes were fitted separately, then the results from model fitting were used in the cross-phenotype analyses.

Appendix Figure 2.

Path diagram representations for each variance source separately.

Note: g_m , genetic relation of mothers. g_o , genetic relation of siblings in offspring generation.

Sub-index 11 refers to offspring 1 in nuclear family 1, sub-index 21 refers to offspring 1 in nuclear family 2, and sub-index 22 refers to offspring 2 in nuclear family 2.

Table 1

Number of individuals for each outcome analyzed

	Sub-cohort				Families
	From registers	Birth years cohort ^a	Available	After elimination ^b (% of available)	
Birth weight, Preterm birth, and Born small for gestational age	Medical Birth Register	1983–2009	2,754,626	2,658,974 (96.5)	1,823,697 (66.2)
Low academic achievement	National School Register	1983–1995	1,409,909	1,124,858 (79.8)	869,553 (61.7)
General cognitive ability ^d	Military Conscription Register	1983–1992	429,335	299,450 (69.7)	257,268 (59.9)
Criminality	National Crime Register	1983–1989	712,484	670,953 (94.2)	546,208 (76.7)
Violent criminality	National Crime Register	1983–1989	712,484	669,973 (94.0)	545,537 (76.6)
Drug misuse	National Crime Register, Patient Register	1983–1987	486,353	481,044 (98.9)	398,705 (82.0)

^aYears when individuals can be included in sub cohort.

^bExcluding individuals with missing values for gender, birth date and/or maternal age at childbirth, who had no possibility of getting outcome (e.g., was not at conscription), and individuals who died/emigrated.

^cExcluding individuals as in ^b plus exclusion criteria; non-identifiable parents, twins in offspring generation, only inclusion of up to two siblings per nuclear family, only two mothers per extended family.

^dOnly males in sub cohort.

Table 2

Parameters in quantitative genetic model; interpretation in each generation

Parameter	Parent generation	Offspring generation
<i>A</i> (Additive genetic)	Additive genetics	Additive genetics
<i>C</i> (Common environment)	Environment unique to one mother	Environment shared between siblings
<i>M</i> (Maternal environment)	Environment shared between sisters who are mothers	Environment shared between cousins
<i>P</i> (Paternal environment)	Spouse effect	Paternal effect
<i>E</i> (Non-shared environment)	Environment unique to each pregnancy	Unique individual environment

Table 3

Means and prevalences for outcomes in pregnancies where the mother was not smoking, was smoking, and where smoking status is missing

	Mean/prevalence (95% confidence interval) per smoking status		
Outcome	SDP=0	SDP=1	SDP=missing
Birth weight (grams)	3588 (3587, 3589)	3388 (3386, 3390)	3496 (3493, 3500)
Preterm birth	4.6% (4.6%, 4.7%)	6.1% (6.0%, 6.2%)	7.7% (7.6%, 7.9%)
Born small for gestational age	4.9% (4.8%, 4.9%)	11.4% (11.3%, 11.5%)	6.3% (6.1%, 6.4%)
Low academic achievement	6.9% (6.9%, 7.0%)	17.5% (17.4%, 17.7%)	11.2% (10.9%, 11.4%)
General cognitive ability (9-point score)	5.29 (5.28, 5.30)	4.65 (4.64, 4.67)	5.07 (5.03, 5.10)
Criminality	8.0% (7.9%, 8.1%)	14.7% (14.5%, 14.9%)	11.2% (10.9%, 11.5%)
Violent criminality	1.3% (1.3%, 1.3%)	3.8% (3.7%, 3.9%)	2.5% (2.4%, 2.6%)
Drug misuse	4.2% (4.1%, 4.3%)	8.6% (8.4%, 8.7%)	6.4% (6.1%, 6.7%)

Note: Values are from the analytic samples (column “After elimination” in Table 1).

Table 4

Effects of maternal smoking during pregnancy on outcome, both unrelated (cohort) analyses and within relative analyses; Estimate (95% confidence interval)

	Effect measure	Cohort		Within relatives			
		Crude	Adjusted	Half-cousins	Full-cousins	Half-siblings	Full-siblings
Birth weight (grams)	Regression coefficients	-201 (-203, -198)	-181 (-184, -179)	-205 (-218, -191)	-185 (-192, -177)	-135 (-146, -123)	-92 (-97, -86)
Preterm birth	Odds ratio	1.34 (1.31, 1.36)	1.29 (1.27, 1.32)	1.23 (1.14, 1.34)	1.19 (1.14, 1.26)	1.18 (1.04, 1.34)	1.21 (1.12, 1.30)
Born small for gestational age	Odds ratio	2.52 (2.48, 2.55)	2.45 (2.41, 2.48)	2.41 (2.23, 2.59)	2.29 (2.19, 2.39)	1.83 (1.63, 2.06)	1.64 (1.54, 1.75)
Low academic achievement	Odds ratio	2.84 (2.80, 2.89)	2.67 (2.63, 2.71)	1.91 (1.74, 2.09)	1.62 (1.54, 1.70)	1.07 (0.92, 1.25)	0.93 (0.87, 1.01)
General cognitive ability ^a (9-point score)	Regression coefficients	-0.63 (-0.65, -0.62)	-0.57 (-0.59, -0.55)	-0.24 (-0.43, -0.04)	-0.27 (-0.35, -0.18)	-0.03 (-0.41, 0.36)	-0.00 (-0.10, 0.09)
Criminality	Odds ratio	1.98 (1.95, 2.02)	1.90 (1.86, 1.94)	1.62 (1.40, 1.87)	1.32 (1.23, 1.42)	0.92 (0.67, 1.28)	0.95 (0.86, 1.05)
Violent criminality	Odds ratio	3.02 (2.90, 3.14)	2.77 (2.66, 2.89)	2.07 (1.57, 2.73)	1.59 (1.37, 1.86)	0.82 (0.45, 1.51)	0.94 (0.75, 1.17)
Drug misuse	Odds ratio	2.13 (2.07, 2.19)	2.00 (1.94, 2.05)	1.55 (1.25, 1.93)	1.47 (1.32, 1.64)	0.83 (0.47, 1.46)	0.92 (0.78, 1.07)

Note: All models except Crude model, adjusted for gender, birth year in categories (for birth weight in three year intervals; for preterm birth and born small for gestational age in four year intervals; for low academic achievement in two year intervals; for general cognitive ability, criminality, violent criminality and drug misuse in 1 year intervals; all starting in 1983), and maternal age at childbirth in categories (for birth weight <17, 17–19, then two year intervals, 42–44 and >44; for preterm birth <20, then four year intervals, >44; for born small for gestational age <20, then three year intervals, 44–45, >45; for low academic achievement <19, then four year intervals, >42; for general cognitive ability <19, then two year intervals, >39; for criminality, violent criminality and drug misuse <20, then five year intervals, >39).

^aSub-cohort includes only males.

Table 5

Variance explained by each variance source (95% confidence intervals)

Maternal phenotype	Additive genetics	Environment unique to one mother	Environment shared between sisters who are mothers	Spouse effect	Environment unique to each pregnancy
Maternal smoking during pregnancy ^a	69% (67%, 70%)	3% (2%, 4%)	4% (3%, 5%)	16% (15%, 16%)	8% (8%, 9%)
Offspring phenotype	Additive genetics	Environment shared between siblings	Environment shared between cousins	Paternal effect	Unique individual environment
Birth weight	50% (47%, 53%)	16% (15%, 17%)	7% (7%, 8%)	0% (0%, 0%)	27% (26%, 28%)
Preterm birth	27% (19%, 35%)	24% (21%, 27%)	8% (6%, 9%)	0% (0%, 0%)	41% (37%, 46%)
Born small for gestational age	43% (34%, 52%)	16% (12%, 19%)	7% (6%, 9%)	0% (0%, 0%)	34% (29%, 38%)
Low academic achievement	86% (78%, 94%)	1% (–1%, 3%)	12% (11%, 14%)	0% (–1%, 1%)	1% (–4%, 5%)
General cognitive ability	33% (26%, 39%)	19% (10%, 29%)	0% (0%, 0%)	1% (–8%, 10%)	46% (43%, 50%)
Criminal convictions	39% (19%, 60%)	2% (–5%, 9%)	4% (1%, 7%)	0% (0%, 0%)	54% (43%, 66%)
Violent criminal convictions	63% (42%, 84%)	2% (–5%, 8%)	6% (2%, 11%)	0% (0%, 0%)	29% (16%, 42%)
Drug/alcohol misuse	35% (30%, 40%)	6% (4%, 8%)	3% (1%, 4%)	1% (1%, 2%)	56% (51%, 60%)

Note: Estimates are from univariate models. Wald-type confidence intervals, hence negative values may exist in intervals. Parameters were fitted using the non-squared, and, if applicable, non-standardized variance parameters, therefore standard errors are calculated using the delta method.

^aCalculated using the full 1983–2009 cohort.

Appendix Table 1

ACMPE univariate modelled parameters [parameter estimate (standard error)]

Maternal phenotype	a_s	c_s	m_s	p_s	e_s
Maternal smoking during pregnancy ^a	.831 (.007)	.171 (.021)	.197 (.010)	.396 (.004)	.290
Offspring phenotype	a_o	c_o	m_o	p_o	e_o
Birth weight	.392 (.005)	.221 (.003)	.147 (.002)	.000 (.014)	.288 (.003)
Preterm birth	.517 (.039)	.492 (.015)	.276 (.014)	.001 (.078)	.643
Born small for gestational age	.658 (.035)	.398 (.022)	.270 (.015)	.002 (.068)	.579
Low academic achievement	.927 (.023)	.107 (.041)	.349 (.010)	.057 (.046)	.067
General cognitive ability	1.058 (.028)	.816 (.052)	.000 (.114)	.218 (.197)	1.258 (.014)
Criminal convictions	.627 (.023)	.140 (.051)	.208 (.027)	.000 (.117)	.737
Violent criminal convictions	.793 (.050)	.129 (.139)	.254 (.055)	.001 (.390)	.539
Drug/alcohol misuse	.591 (.023)	.241 (.020)	.159 (.023)	.110 (.014)	.745

Note: The e -parameters for binary phenotypes are defined as remaining variance after estimation of other parameters and are therefore void of standard errors.

^aCalculated using the full 1983–2009 cohort.

Appendix Table 2

ACMPE full model results [parameter estimate (standard error)]

	Within SDP					Within outcome					Between phenotypes				
	α_S	ϵ_S	m_S	β_S	ϵ_S	α_O	ϵ_O	m_O	β_O	ϵ_O	r_A	r_C	r_M	r_P	r_E
Birth weight	0.823 (0.003)	0.262 (0.003)	0.213 (0.003)	0.354 (0.003)	0.288	0.394 (0.003)	0.207 (0.003)	0.147 (0.001)	0.035 (0.003)	0.300 (0.003)	-0.046 (0.003)	-0.773 (0.001)	-0.679 (0.003)	-1.000 (0.005)	-0.244 (0.001)
Preterm birth ^a	0.828 (0.008)	0.183 (0.015)	0.202 (0.017)	0.394 (0.003)	0.290	0.514 (0.048)	0.494 (0.019)	0.277 (0.015)	0.002 (0.075)	0.644	NA	NA	NA	NA	NA
Born small for gestational age ^a	0.828 (0.008)	0.183 (0.015)	0.202 (0.017)	0.394 (0.003)	0.290	0.660 (0.015)	0.396 (0.015)	0.270 (0.011)	0.002 (0.075)	0.578	NA	NA	NA	NA	NA
Low academic achievement	0.810 (0.000)	0.344 (0.000)	0.267 (0.000)	0.296 (0.000)	0.258	0.893 (0.000)	0.154 (0.000)	0.366 (0.000)	0.105 (0.000)	0.185	0.598 (0.001)	0.024 (0.006)	0.623 (0.001)	0.494 (0.009)	-0.018 (0.001)
General cognitive ability	0.813 (0.022)	0.263 (0.020)	0.307 (0.019)	0.313 (0.016)	0.278	1.076 (0.033)	0.819 (0.023)	0.097 (0.019)	0.212 (0.012)	1.244 (0.016)	-0.536 (0.010)	-0.071 (0.014)	-0.327 (0.008)	-0.980 (0.010)	-0.030 (0.010)
Criminality	0.802 (0.029)	0.351 (0.030)	0.290 (0.038)	0.291 (0.011)	0.254	0.573 (0.024)	0.203 (0.024)	0.222 (0.018)	0.076 (0.030)	0.759	1.000 (0.099)	-0.693 (0.090)	0.009 (0.120)	0.511 (0.498)	0.000 (0.016)
Violent criminality	0.782 (0.017)	0.370 (0.020)	0.314 (0.019)	0.297 (0.012)	0.255	0.795 (0.061)	0.000 (0.155)	0.272 (0.042)	0.057 (0.073)	0.538	0.654 (0.228)	0.795 (0.147)	0.421 (0.481)	0.522 (0.816)	0.024 (0.039)
Drug misuse	0.835 (0.001)	0.293 (0.001)	0.260 (0.001)	0.296 (0.001)	0.250	0.600 (0.001)	0.256 (0.001)	0.146 (0.000)	0.088 (0.000)	0.738	0.591 (0.001)	0.190 (0.000)	0.743 (0.001)	0.182 (0.000)	0.000 (0.000)

Abbreviations: SDP, maternal smoking during pregnancy. NA, not applicable.

Note: Standard errors may be misleading due to constraints put on the optimizer when fitting the model. The ϵ -parameters for binary phenotypes are defined as remaining variance after estimation of other parameters and are therefore void of standard errors.

^aDue to computational issues SDP and outcome were fitted separately.

Appendix Table 3

ACMPE best-fitting model results [parameter estimate (standard error)]

	Within SDP					Within outcome					Between phenotypes				
	δ_S	δ_S	m_S	p_S	ϵ_S	ϕ_0	ϵ_0	m_0	p_0	ϕ_0	ϵ_A	ϵ_C	rM	rP	rE
Birth weight	0.823 (0.003)	0.262 (0.003)	0.213 (0.003)	0.354 (0.003)	0.288	0.394 (0.003)	0.207 (0.003)	0.147 (0.001)	0.035 (0.003)	0.300 (0.003)	-0.046 (0.003)	-0.773 (0.001)	-0.679 (0.003)	-1.000 (0.005)	-0.244 (0.001)
Preterm birth ^a	0.828 (0.008)	0.183 (0.015)	0.202 (0.017)	0.394 (0.003)	0.290	0.514 (1.314)	0.494 (0.003)	0.277 (0.002)	0	0.644	0.045 (0.131)	0.212 (0.170)	0.385 (0.248)	0	0.048 (0.012)
Born small for gestational age ^a	0.828 (0.008)	0.183 (0.015)	0.202 (0.017)	0.394 (0.003)	0.290	0.660 (0.006)	0.396 (0.004)	0.270 (0.005)	0	0.578	0.536 (1.321)	1.006 (1.414)	-0.138 (3.247)	0	0.172 (0.706)
Low academic achievement ^b	0.810	0.344	0.267	0.296	0.258	0.893	0.154	0.366	0.105	0.185	0.598	0	0.623	0.494	-0.018
General cognitive ability	0.820 (0.047)	0.283 (0.071)	0.295 (0.070)	0.289 (0.027)	0.278	1.114 (0.026)	0.825 (0.020)	0	0	1.228 (0.014)	-0.555 (0.048)	-0.301 (0.093)	0	0	-0.034 (0.020)
Criminality	0.808 (0.006)	0.344 (0.006)	0.282 (0.006)	0.295 (0.006)	0.254	0.385 (0.006)	0.192 (0.006)	0.227 (0.020)	0	0.755	1.000 (0.002)	-0.887 (0.017)	0	0	-0.001 (0.013)
Violent criminality	0.802 (0.028)	0.349 (0.030)	0.286 (0.036)	0.297 (0.010)	0.255	0.899 (0.018)	0	0	0	0.438	0.691 (0.027)	0	0	0	0.026 (0.019)
Drug outcome	0.850 (0.005)	0.290 (0.005)	0.229 (0.005)	0.381 (0.005)	0.249	0.730 (0.005)	0	0	0	0.683	0.635 (0.005)	0	0	0	-0.002 (0.005)

Abbreviations: SDP, maternal smoking during pregnancy.

Note: Standard errors may be misleading due to constraints put on the optimizer when fitting the model. The ϵ -parameters for binary phenotypes are defined as remaining variance after estimation of other parameters and are therefore void of standard errors. All values significant, on a 5%-level, except when a “0” is stated, where they are non-significant in a likelihood ratio test and have been removed from model. ϵ -parameters are not subject to significance tests. rE is included in final model regardless of significance.

^a Due to computational issues the model was fitted in three steps; first SDP and outcome were fitted separately, then the results from model fitting were used in the cross-phenotype analyses.
^b No valid standard errors could be obtained from the optimization.

Appendix Table 4a

Likelihood ratio tests for smoking during pregnancy and birth weight

Model name	Number of estimated parameters	-2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE – ACMPE	40	4108980.3	NA
ACME – ACME	38	4109054.1	<0.001
ACPE – ACPE	38	4109917.0	<0.001
AMPE – AMPE	38	4109821.6	<0.001
CMPE – CMPE	38	4109241.9	<0.001
ACMPE – CMPE	39	4108984.5	0.039
ACMPE – ACPE	39	4108998.2	<0.001
ACMPE – ACME	39	4109054.3	<0.001
ACMPE – AMPE	39	4109070.6	<0.001
ACMPE – ACMP	39	4111042.7	<0.001

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE – ACMPE, where the first five letters tells us which of the variance parameters in birth weight that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 and e_o^2), and the five last letters tells us which of the cross-phenotype parameters that are included (i.e., r_A , r_C , r_M , r_P , and r_E). All of the variance parameters in maternal smoking during pregnancy are included in all models.

Appendix Table 4b

Likelihood ratio tests for preterm birth

Model name	Number of estimated parameters	–2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE	17	714467.6	NA
ACME	16	714467.6	1
ACE	15	714554.3	<0.001
AME	15	714644.1	<0.001
CME	15	714501.1	<0.001

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Due to computational issues only the outcome phenotype was tested for significance. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE, where the letters tells us which of the variance parameters in preterm birth that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 , and e_o^2).

Appendix Table 4c

Likelihood ratio tests for being born small for gestational age

Model name	Number of estimated parameters	-2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE	17	808894.7	NA
ACME	16	808894.7	1
ACE	15	808986.0	<0.001
AME	15	808975.9	<0.001
CME	15	808994.6	<0.001

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Due to computational issues only the outcome phenotype was tested for significance. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE, where the letters tells us which of the variance parameters in being born small for gestational age that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 and e_o^2).

Appendix Table 4d

Likelihood ratio tests for smoking during pregnancy and low academic achievement

Model name	Number of estimated parameters	–2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE – ACMPE	39	1298228.9	NA
ACME – ACME	37	1298279.4	<0.001
AMPE – AMPE	37	1298270.4	<0.001
ACPE – ACPE	37	1298563.5	<0.001
CMPE – CMPE	37	1298296.0	<0.001
ACMPE – AMPE	38	1298229.9	0.900
ACMPE – AME	37	1298283.1	<0.001
ACMPE – MPE	37	1298425.3	<0.001
ACMPE – APE	37	1298295.3	<0.001
ACMPE – AMP	37	1298229.9	1

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE – ACMPE, where the first five letters tells us which of the variance parameters in low academic achievement that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 and e_o^2), and the five last letters tells us which of the cross-phenotype parameters that are included (i.e., r_A , r_C , r_M , r_P , and r_E). All of the variance parameters in maternal smoking during pregnancy are included in all models.

Appendix Table 4e

Likelihood ratio tests for smoking during pregnancy and general cognitive functioning

Model name	Number of estimated parameters	-2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE – ACMPE	38	1154273.6	NA
ACPE – ACPE	36	1154275.8	0.327
ACE – ACE	34	1154278.3	0.289
AE – AE	32	1154790.9	<0.001
CE – CE	32	1154927.5	<0.001
ACE – AE	33	1154339.4	<0.001
ACE – CE	33	1154626.1	<0.001
ACE – AC	33	1154321.9	<0.001

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE – ACMPE, where the first five letters tells us which of the variance parameters in general cognitive functioning that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 , and e_o^2), and the five last letters tells us which of the cross-phenotype parameters that are included (i.e., r_A , r_C , r_M , r_P , and r_E). All of the variance parameters in maternal smoking during pregnancy are included in all models.

Appendix Table 4f

Likelihood ratio tests for smoking during pregnancy and criminal convictions

Model name	Number of estimated parameters	-2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE – ACMPE	39	847607.1	NA
ACME - ACME	37	847607.9	0.692
AME – AME	35	847877.4	<0.001
ACE – ACE	35	847675.9	<0.001
CME – CME	35	847640.0	<0.001
ACME – ACE	36	847607.9	1
ACME – AE	35	847619.3	<0.001
ACME – CE	35	847976.4	<0.001
ACME – AC	35	847607.9	1

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE – ACMPE, where the first five letters tells us which of the variance parameters in criminal convictions that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 and e_o^2), and the five last letters tells us which of the cross-phenotype parameters that are included (i.e., r_A , r_C , r_M , r_P , and r_E). All of the variance parameters in maternal smoking during pregnancy are included in all models.

Appendix Table 4g

Likelihood ratio tests for smoking during pregnancy and violent criminal convictions

Model name	Number of estimated parameters	-2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE – ACMPE	39	624094.2	NA
AMPE – AMPE	37	624094.2	1
AME – AME	35	624098.1	0.142
AE – AE	33	624101.1	0.224
E –E	31	625980.3	<0.001
AE –E	32	625594.2	<0.001
AE – A	32	624101.1	0.975

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE – ACMPE, where the first five letters tells us which of the variance parameters in violent criminal convictions that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 , and e_o^2), and the five last letters tells us which of the cross-phenotype parameters that are included (i.e., r_A , r_C , r_M , r_P , and r_E). All of the variance parameters in maternal smoking during pregnancy are included in all models.

Appendix Table 4h

Likelihood ratio tests for smoking during pregnancy and drug/alcohol misuse

Model name	Number of estimated parameters	-2 log likelihood	P-value; test again previous model with more estimated parameters
ACMPE – ACMPE	39	573109.2	NA
ACME – ACME	37	573109.2	1
ACE – ACE	35	573115.3	0.049
AME – AME	35	573111.9	0.262
AE - AE	33	573112.3	0.827
AE – E	32	574303.7	<0.001
AE – A	32	573112.3	0.803

Abbreviations: NA, not applicable.

Note: “Best-fitting model” marked in bold letters. Each model is tested against previous model with more estimated parameters. The model name implies which parameters that are included, it is stated as ACMPE – ACMPE, where the first five letters tells us which of the variance parameters in drug/alcohol misuse that are included (i.e., a_o^2 , c_o^2 , m_o^2 , p_o^2 and e_o^2), and the five last letters tells us which of the cross-phenotype parameters that are included (i.e., r_A , r_C , r_M , r_P , and r_E). All of the variance parameters in maternal smoking during pregnancy are included in all models.

Appendix Table 5

Covariance between random effects, within and across phenotypes, for different relations as stated in terms of offspring

	Within subject		Full sibs		Half sibs		Mothers MZ twins		Mothers DZ twins		Mothers full sibs		Mothers maternal half sibs		Mothers paternal half sibs	
	A_{ijk}^{SDP}	A_{ijk}^{OUT}	$A_{ijk'}^{SDP}$	$A_{ijk'}^{OUT}$	$A_{ijk'}^{SDP}$	$A_{ijk'}^{OUT}$	$A_{ijj'}^{SDP}$	$A_{ijj'}^{OUT}$	$A_{ijj'}^{SDP}$	$A_{ijj'}^{OUT}$	$A_{ijj'}^{SDP}$	$A_{ijj'}^{OUT}$	$A_{ijj'}^{SDP}$	$A_{ijj'}^{OUT}$	$A_{ijj'}^{SDP}$	$A_{ijj'}^{OUT}$
A																
A_{ijk}^{SDP}	a_s^2	$\frac{1}{2}a_s a_o r_A$	a_s^2	$\frac{1}{2}a_s a_o r_A$	a_s^2	$\frac{1}{2}a_s a_o r_A$	a_s^2	$\frac{1}{2}a_s a_o r_A$	$\frac{1}{2}a_s^2$	$\frac{1}{4}a_s a_o r_A$	$\frac{1}{2}a_s^2$	$\frac{1}{4}a_s a_o r_A$	$\frac{1}{4}a_s^2$	$\frac{1}{8}a_s a_o r_A$	$\frac{1}{4}a_s^2$	$\frac{1}{8}a_s a_o r_A$
A_{ijk}^{OUT}	$\frac{1}{2}a_s a_o r_A$	a_o^2	$\frac{1}{2}a_s a_o r_A$	$\frac{1}{2}a_o^2$	$\frac{1}{2}a_s a_o r_A$	$\frac{1}{4}a_o^2$	$\frac{1}{2}a_s a_o r_A$	$\frac{1}{8}a_o^2$	$\frac{1}{4}a_s a_o r_A$	$\frac{1}{8}a_o^2$	$\frac{1}{4}a_s a_o r_A$	$\frac{1}{8}a_o^2$	$\frac{1}{8}a_s a_o r_A$	$\frac{1}{16}a_o^2$	$\frac{1}{8}a_s a_o r_A$	$\frac{1}{16}a_o^2$
C	C_{ijk}^{SDP}	C_{ijk}^{OUT}	$C_{ijk'}^{SDP}$	$C_{ijk'}^{OUT}$	$C_{ijk'}^{SDP}$	$C_{ijk'}^{OUT}$	$C_{ijj'}^{SDP}$	$C_{ijj'}^{OUT}$	$C_{ijj'}^{SDP}$	$C_{ijj'}^{OUT}$	$C_{ijj'}^{SDP}$	$C_{ijj'}^{OUT}$	$C_{ijj'}^{SDP}$	$C_{ijj'}^{OUT}$	$C_{ijj'}^{SDP}$	$C_{ijj'}^{OUT}$
C_{ijk}^{SDP}	c_s^2	$c_s c_o r_C$	c_s^2	$c_s c_o r_C$	c_s^2	$c_s c_o r_C$	0	0	0	0	0	0	0	0	0	0
C_{ijk}^{OUT}	$c_s c_o r_C$	c_o^2	$c_s c_o r_C$	c_o^2	$c_s c_o r_C$	c_o^2	0	0	0	0	0	0	0	0	0	0
M	M_{ijk}^{SDP}	M_{ijk}^{OUT}	$M_{ijk'}^{SDP}$	$M_{ijk'}^{OUT}$	$M_{ijk'}^{SDP}$	$M_{ijk'}^{OUT}$	$M_{ijj'}^{SDP}$	$M_{ijj'}^{OUT}$	$M_{ijj'}^{SDP}$	$M_{ijj'}^{OUT}$	$M_{ijj'}^{SDP}$	$M_{ijj'}^{OUT}$	$M_{ijj'}^{SDP}$	$M_{ijj'}^{OUT}$	$M_{ijj'}^{SDP}$	$M_{ijj'}^{OUT}$
M_{ijk}^{SDP}	m_s^2	$m_s m_o f_M$	m_s^2	$m_s m_o f_M$	m_s^2	$m_s m_o f_M$	m_s^2	$m_s m_o f_M$	m_s^2	$m_s m_o f_M$	m_s^2	$m_s m_o f_M$	m_s^2	$m_s m_o f_M$	0	0
M_{ijk}^{OUT}	$m_s m_o f_M$	m_o^2	$m_s m_o f_M$	m_o^2	$m_s m_o f_M$	m_o^2	$m_s m_o f_M$	m_o^2	$m_s m_o f_M$	m_o^2	$m_s m_o f_M$	m_o^2	$m_s m_o f_M$	m_o^2	0	0
P	P_{ijk}^{SDP}	P_{ijk}^{OUT}	$P_{ijk'}^{SDP}$	$P_{ijk'}^{OUT}$	$P_{ijk'}^{SDP}$	$P_{ijk'}^{OUT}$	$P_{ijj'}^{SDP}$	$P_{ijj'}^{OUT}$	$P_{ijj'}^{SDP}$	$P_{ijj'}^{OUT}$	$P_{ijj'}^{SDP}$	$P_{ijj'}^{OUT}$	$P_{ijj'}^{SDP}$	$P_{ijj'}^{OUT}$	$P_{ijj'}^{SDP}$	$P_{ijj'}^{OUT}$
P_{ijk}^{SDP}	p_s^2	$p_s p_o r_P$	p_s^2	$p_s p_o r_P$	0	0	0	0	0	0	0	0	0	0	0	0
P_{ijk}^{OUT}	$p_s p_o r_P$	p_o^2	$p_s p_o r_P$	p_o^2	0	0	0	0	0	0	0	0	0	0	0	0
E	E_{ijk}^{SDP}	E_{ijk}^{OUT}	$E_{ijk'}^{SDP}$	$E_{ijk'}^{OUT}$	$E_{ijk'}^{SDP}$	$E_{ijk'}^{OUT}$	$E_{ijj'}^{SDP}$	$E_{ijj'}^{OUT}$	$E_{ijj'}^{SDP}$	$E_{ijj'}^{OUT}$	$E_{ijj'}^{SDP}$	$E_{ijj'}^{OUT}$	$E_{ijj'}^{SDP}$	$E_{ijj'}^{OUT}$	$E_{ijj'}^{SDP}$	$E_{ijj'}^{OUT}$
E_{ijk}^{SDP}	e_s^2	$e_s e_o r_E$	0	0	0	0	0	0	0	0	0	0	0	0	0	0

	Within subject		Full sibs		Half sibs		Mothers MZ twins		Mothers DZ twins		Mothers full sibs		Mothers maternal half sibs		Mothers paternal half sibs	
	$e_i e_j^T E$	e_o^2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
E_{ijk}^{OUT}																

Abbreviations: SDP, smoking during pregnancy – the exposure. OUT, outcome. A, additive genetic effects. C, shared environment between siblings in offspring generation. M, shared environment between siblings in parental generation. P, paternal/spouse effect. E, unique environment in offspring generation. The K' and M' subscript are the compliments of K and M, respectively. The “.” is used to indicate any of possible values at subscript.

Appendix Table 6a

Observed means of birth weight in different exposure-combination groups

Birth weight				
SDP status		Mean birth weight in grams and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	3461	3625	1,360,988
0	Any value	3486	3651	1,129,312
1	Any value	3344	3498	231,674
Any value	0	3482	3654	1,173,284
Any value	1	3334	3443	187,702
0	0	3487	3654	1,098,770
1	0	3411	3643	74,514
0	1	3446	3516	30,542
1	1	3312	3429	157,160

Appendix Table 6b

Observed prevalences of pre-term birth in different exposure-combination groups

Pre-term birth				
SDP status		Prevalences and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	5.63%	3.61%	1,360,988
0	Any value	5.53%	3.41%	1,129,312
1	Any value	6.14%	4.62%	231,674
Any value	0	5.54%	3.39%	1,173,284
Any value	1	6.23%	4.99%	187,702
0	0	5.52%	3.38%	1,098,770
1	0	5.80%	3.56%	74,514
0	1	5.88%	4.33%	30,542
1	1	6.30%	5.12%	157,160

Appendix Table 6c

Observed prevalences of being born small for gestational age in different exposure-combination groups

Born small for gestational age				
SDP status		Prevalences and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	7.95%	4.40%	1,360,988
0	Any value	6.87%	3.62%	1,129,312
1	Any value	13.22%	8.18%	231,674
Any value	0	7.07%	3.60%	1,173,284
Any value	1	13.46%	9.37%	187,702
0	0	6.82%	3.52%	1,098,770
1	0	10.85%	4.75%	74,514
0	1	8.91%	7.16%	30,542
1	1	14.35%	9.80%	157,160

Appendix Table 6d

Observed prevalences of low academic achievement in different exposure-combination groups

Low academic achievement				
SDP status		Prevalences and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	7.80%	9.30%	453,806
0	Any value	5.73%	6.87%	341,492
1	Any value	14.08%	16.66%	112,314
Any value	0	5.76%	6.93%	356,552
Any value	1	15.26%	17.97%	97,254
0	0	5.44%	6.51%	327,628
1	0	9.38%	11.68%	28,924
0	1	12.58%	15.41%	13,864
1	1	15.71%	18.39%	83,390

Appendix Table 6e

Observed means of general cognitive ability in different exposure-combination groups

General cognitive ability				
SDP status		Means (on a nine-point scale) and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	5.44	5.08	31,614
0	Any value	5.59	5.22	23,836
1	Any value	4.99	4.64	7,778
Any value	0	5.58	5.21	25,064
Any value	1	4.94	4.59	6,550
0	0	5.62	5.25	22,928
1	0	5.17	4.80	2,136
0	1	5.05	4.68	908
1	1	4.92	4.57	5,642

Appendix Table 6f

Observed prevalences of criminal convictions in different exposure-combination groups

Crime				
SDP status		Prevalences and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	9.14%	10.20%	197,130
0	Any value	7.46%	8.37%	143,608
1	Any value	13.64%	15.10%	53,522
Any value	0	7.55%	8.51%	150,956
Any value	1	14.35%	15.74%	46,174
0	0	7.25%	8.16%	137,532
1	0	10.58%	12.02%	13,424
0	1	12.21%	13.17%	6,076
1	1	14.67%	16.13%	40,098

Appendix Table 6g

Observed prevalences of violent criminal convictions in different exposure-combination groups

Violent crime				
SDP status		Prevalences and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	1.76%	2.06%	196,726
0	Any value	1.17%	1.32%	143,370
1	Any value	3.36%	4.06%	53,356
Any value	0	1.20%	1.37%	150,704
Any value	1	3.59%	4.34%	46,022
0	0	1.09%	1.25%	137,310
1	0	2.33%	2.57%	13,394
0	1	2.84%	2.90%	6,060
1	1	3.71%	4.56%	39,962

Appendix Table 6h

Observed prevalences of drug/alcohol misuse in different exposure-combination groups

Drug/alcohol misuse				
SDP status		Prevalences and number of individuals		
First pregnancy	Second pregnancy	First pregnancy	Second pregnancy	N
Any value	Any value	4.69%	5.88%	94,470
0	Any value	3.61%	4.70%	68,242
1	Any value	7.50%	8.97%	26,228
Any value	0	3.69%	4.72%	71,848
Any value	1	7.88%	9.57%	22,622
0	0	3.49%	4.53%	65,386
1	0	5.66%	6.62%	6,462
0	1	6.37%	8.40%	2,856
1	1	8.09%	9.73%	19,766

Appendix Table 7

Expected/observed means or proportions of mothers concordant and discordant for smoking during pregnancy for each outcome

	Observed concordant not SDP	Observed concordant SDP	Observed discordant in SDP	Expected discordant SDP, additive ^a	Expected discordant SDP, multiplicative ^a
Birth weight	3571	3371	3514	3471	NA
Pre-term birth	4.45%	5.71%	4.80%	5.08%	5.04%
Born small for gestational age	5.17%	12.08%	7.87%	8.62%	7.96%
Low academic achievement	5.98%	17.05%	11.65%	11.51%	10.26%
General cognitive ability	5.43	4.75	4.95	5.09	NA
Criminal conviction	7.71%	15.40%	11.73%	11.55%	10.98%
Violent criminal conviction	1.17%	4.13%	2.58%	2.65%	2.21%
Drug/alcohol misuse	4.01%	8.91%	6.53%	6.46%	6.01 %

Abbreviation: NA, not applicable.

^a Expected discordant SDP refers to assuming that the effect of SDP has a linear effect on both siblings outcomes, i.e. discordant pairs have half the effect of the concordant smoking pairs effect relative to the concordant non-smoking pairs.

Appendix Table 8

Test of carry-over and contagion effects.

Outcome	Effect estimates (standard error)		Interaction effect; p-value
	SDP ₁ on OUT ₂	SDP ₂ on OUT ₁	
Birth-weight	−152.5 (1.7)	−148.4 (1.9)	0.110
Pre-term birth	0.32 (0.02)	0.13 (0.02)	<0.001
Born small for gestational age	0.86 (0.01)	0.72 (0.01)	<0.001
Low academic achievement	1.00 (0.02)	1.08 (0.02)	<0.001
General cognitive ability	−0.59 (0.03)	−0.64 (0.04)	0.282
Crime	0.67 (0.02)	0.72 (0.02)	0.098
Violent crime	1.15 (0.05)	1.12 (0.05)	0.624
Drug/alcohol misuse	0.69 (0.03)	0.80 (0.05)	0.064