Published in final edited form as:
JAMA Psychiatry. 2013 September ; 70(9): . doi:10.1001/jamapsychiatry.2013.127.

Maternal smoking during pregnancy and offspring conduct problems: Evidence from three independent genetically-sensitive research designs

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Abstract

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Conflict of interest/financial disclosure
None of the authors report any conflict of interests or financial disclosures

Data access and responsibility
Professor Gordon Harold takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had full access to all the data in the study.

Context—A number of studies report an association between maternal smoking during pregnancy and offspring conduct disorder. However, past research evidences difficulty disaggregating prenatal environmental from genetic and postnatal environmental influences.

Objective—To examine the relationship between maternal smoking during pregnancy and offspring conduct problems among children reared by genetically-related and genetically-unrelated mothers.

Design, Setting and Participants—Three studies employing distinct but complementary research designs were utilized: The Christchurch Health and Development Study (a longitudinal cohort study that includes biological and adopted children), the Early Growth and Development Study (a longitudinal adoption at birth study), and the Cardiff IVF Study (genetically-related and -unrelated families; an adoption at conception study). Maternal smoking during pregnancy was measured as the average number of cigarettes/day (0, 1–9 or 10+) smoked during pregnancy. A number of possible covariates (child gender, ethnicity, birth weight, breast feeding, maternal age at birth, maternal education, family SES, family breakdown, placement age, and parenting practices) were controlled in the analyses.

Main Outcome Measure—Child conduct problems (age 4–10 years) reported by parents and/or teachers using the Rutter and Conners behaviour scales, the Child Behavior Checklist and Children's Behavior Questionnaire, and the Strengths and Difficulties Questionnaire.

Results—A significant association between maternal smoking during pregnancy and child conduct problems was observed among children reared by genetically-related and genetically-unrelated mothers. Results from a meta-analysis affirmed this pattern of findings across pooled study samples.

Conclusions—Findings across the three studies using a complement of genetically-sensitive research designs suggest smoking during pregnancy is a prenatal risk factor for offspring conduct problems, when specific perinatal and postnatal confounding factors are controlled.

Introduction

Conduct disorder represents an issue of significant social, clinical and practice concern, with evidence highlighting increasing rates of child conduct problems internationally.[1, 2] Identifying risk factors and understanding mechanisms by which these risk factors influence conduct problems has important implications for future intervention and prevention efforts.

Maternal smoking during pregnancy is known to be a risk factor for offspring psychological problems, including attention deficits and conduct problems.[3, 4] Plausible biological mechanisms have been proposed to explain the prenatal effect of nicotine on neurodevelopmental processes in animals;[5–7] however, the underlying mechanisms specific to smoking in humans are not well understood.[3, 8] It has been suggested that anorexigenic, hypoxic, vascular and placental effects of nicotine may have direct teratogenic influences on the fetus and result in adverse physiological and psychological development.[9]

Longitudinal epidemiological studies have reported statistical associations between the extent of maternal smoking during pregnancy and subsequent offspring conduct disorder,[10–14] attention deficit hyperactivity disorder,[15, 16] and criminal behaviour.[17, 18] Some studies have provided evidence of a dose-response relationship between the amount of cigarettes smoked during pregnancy and the rate of subsequent conduct problems in offspring.[19]

However, it is important to note that the effect of maternal pregnancy smoking on offspring conduct problems can be confounded by a number of background factors, including low

socioeconomic status, early age of pregnancy, race, history of maternal psychopathology, and child-rearing environment.[11, 13, 20–23] For example, mothers who smoke during pregnancy are more likely to provide a child-rearing environment that promotes or at least condones externalizing behavior.[21] Therefore, the postnatal environment (independent of pregnancy smoking) may influence the development of conduct problems. A number of studies have found that the association between maternal smoking during pregnancy and offspring conduct problems persists after accounting for these possible confounders, while others have failed to demonstrate the association when confounders were considered.[21, 24]

Another problem with correlational family-based studies is the possibility of genetic risk factors and unmeasured environmental factors confounding the relationship between maternal smoking during pregnancy and offspring conduct problems.[25] Both maternal smoking during pregnancy[26] and conduct problems[27, 28] are influenced by genetic factors that have been shown to overlap.[29] Maternal smoking during pregnancy is associated with externalizing problems and forming partnerships with antisocial males.[21, 30, 31] Moreover, adults with a history of externalizing behavior tend to provide postnatal environments that foster the transmission of this behavior across generations.[32] Indeed, passive genotype-environment correlation (rGE) may be a factor in this association whereby genetic factors common to both the rearing environment (e.g., harsh parenting) and the specific phenotype considered (e.g., child conduct problems) underlie any observed association.[33] Thus, maternal smoking during pregnancy could be a marker of a genetic liability, rather than a direct cause of children's later conduct problems. Therefore, the association between maternal smoking during pregnancy and offspring conduct problems may be genetically, rather than environmentally, mediated.

Recent studies using genetically-sensitive designs have attempted to overcome this limitation of prior studies. Studies using sibling designs suggest that environmental variables influencing both pregnancy smoking and offspring conduct problems account for the observed associations.[34–37] The IVF study design, where children are either genetically-related or -unrelated to the mother undergoing the pregnancy,[38] and the children-of-twins study design,[39] also suggest that unmeasured confounders that are indexed by inherited influences contribute to the link.

Much of the existing evidence has been obtained from studying biological parents rearing their biological children, which does not allow the effects of genetic from prenatal and postnatal environmental factors to be clearly disentangled, or for the role of passive rGE to be disentangled from genetic and postnatal environmental (e.g., parenting behavior) associations.

The present study focuses on examining links between prenatal smoking and offspring conduct problems and the contribution of psychosocial and inherited factors using data from three independent studies: the Christchurch Health and Development Study (CHDS) in New Zealand, the Early Growth and Development Study (EGDS) in the United States, and the Cardiff IVF (C-IVF) Study in the United Kingdom. In these three studies, data on pregnancy smoking and the behavioral outcomes have been gathered from:

1. CHDS: 1088 children reared by genetically-related mothers and 36 children reared by genetically-unrelated adoptive mothers;
2. EGDS: 310 children reared by genetically-unrelated adoptive mothers;
3. C-IVF: 636 children reared by genetically-related mothers and 206 children reared by genetically-unrelated mothers.

This complement of genetically-sensitive research designs offers a number of advantages that allows advance of this important research question relative to past studies (see Table 1). First, it allows examination of associations between maternal smoking and conduct problems in children who are reared by genetically-related or genetically-unrelated mothers. Second, all the studies provide information on multiple covariates: child gender, ethnicity, maternal age at birth, maternal education, family SES, family breakdown, breast feeding, birth weight, placement age, and parenting practices. Third, results obtained from individual studies can be pooled using a meta-analytic approach to allow examination of the magnitude of common effects generated across studies. Finally, two of the studies employed allow examination of the contribution of prenatal and possible postnatal passive genotype-environment correlation influences on derived associations.

Methods

Sample

Study 1: The Christchurch Health and Development Study (CHDS)—The CHDS is a longitudinal study of a birth cohort of 1265 children born in the Christchurch (New Zealand) urban region in 1977. Of this cohort 1124 (89%) were assessed on maternal smoking during pregnancy and child behavior to age 7. This group comprised 1088 children reared by biological mothers and 36 children reared by non-relative adoptive mothers. The median child age at placement for adoption was three weeks (range 2–12 weeks). A detailed description of the study is available elsewhere.[40]

Study 2: Early Growth and Development Study (EGDS)—The EGDS is an ongoing, longitudinal, multisite study of linked sets of adopted children, adoptive parents, and birth parents.[41] The EGDS drew its sample from adoption agencies from four regions in the United States: the Northwest, Southwest, Midwest, and Mid-Atlantic. The EGDS has two cohorts, but only data from Cohort I were used in this paper because Cohort II does not have data at these ages yet. Cohort I included children who were born in 2003–2006 (n = 361) and were placed in non-relative adoptive homes within 90 days of birth (median age of placement = 2 days). Birth parent data were used to assess maternal smoking and adoptive family data were considered to evaluate the child-rearing environment (n = 311). A detailed description of the study is available elsewhere.[41]

Study 3: Cardiff IVF Study (C-IVF)—Children conceived via assisted reproductive technologies[42] may be genetically related to parents (homologous IVF), mother only (sperm donation), father only (egg donation), or to neither parent (embryo donation). Families who had a live birth between 1994 and 2002 following successful artificial reproductive treatment from any of the four conception groups were recruited from 18 UK clinics and 1 US clinic.[43, 44] The study design required that all donors were unrelated to either rearing parent. The number of families in each conception group in the full sample is: 444 homologous IVF, 210 IVF with sperm donation, 175 IVF with egg donation, and 36 IVF with embryo donation. Comparisons between the present sample, UK national norms, and an age matched twin sample suggest minimal differences in mean levels of behavior.[45] Further, no appreciable differences were noted between the IVF subgroups for mother- or father-rated adjustment problems. For the purpose of the present study, we focused on comparing mothers and children who were genetically related (homologous IVF and sperm donation) (n = 636) and those who were genetically unrelated (egg and embryo donation) (n = 206) who provided information on smoking status during pregnancy and child behavior outcomes.

Measures

Offspring conduct problems—In Study 1 (CHDS), mothers and teachers reported on children's conduct problems at ages 6 and 7 years using selected items from the Rutter and Conners behaviour rating scales.[46] Standardised maternal and teacher derived scores were summed for each year and then averaged over the two assessments to derive an overall measure of childhood conduct problems. The internal consistency of the measure was α = .76. In Study 2 (EGDS), adoptive mothers and fathers reported on children's conduct problems at age 4.5 and 6 years using the externalizing subscale of the Child Behavior Checklist (CBCL)[47] and the impulsivity scale of the Children's Behavior Questionnaire Short Form.[48] Similar to the CHDS, the two scales were standardized and averaged at each age, and then averaged over the two assessments to derive an overall measure of childhood conduct problems. The internal consistency of the measure was α = .69. In study 3 (C-IVF), mothers and fathers reported on children's conduct problems at age 4–10 years (mean age = 5.50 years, SD = .37) using the Strengths and Difficulties Questionnaire.[49] Internal consistency was acceptable (mothers: α = .67; fathers: α = .66). In each study, the behavior reports have been scaled to a mean of 100 and standard deviation of 10 within cohort to facilitate comparisons across studies.

Maternal smoking during pregnancy—Pregnancy smoking was reported retrospectively by mothers in all three studies: within 1–3 days of giving birth (CHDS), 4-months postpartum using a life history calendar method to facilitate recall (EGDS), and maternal retrospective recall and antenatal records (C-IVF), with reports provided by mothers during initial assessment (children aged 4 years+). In Studies 1 (CHDS) and 2 (EGDS), birth mothers reported on the average number of cigarettes smoked per day in each trimester of pregnancy. In Study 3 (C-IVF), mothers answered questions about whether they smoked 0, 1–9, or 10+ cigarettes per day during pregnancy. Because the number of cigarettes smoked per day across the trimesters was highly correlated (EGDS: $r = .89 – .95$; CHDS: $r = .86 – .94$) and to make the measures comparable across the three studies, the maternal reports on smoking during pregnancy in Studies 1 and 2 were first averaged across the trimesters and then classified into three levels: 0, 1–9, or 10+ cigarettes per day, thereby matching measurement of smoking in Study 3.

Covariates—To control for perinatal factors and specific characteristics of the postnatal child-rearing environment a number of covariates were included in the models: child gender and ethnicity, birth weight, maternal age at birth, maternal education, family SES, family breakdown, breast feeding, placement age, and parenting practices.

Parenting practices: In Study 1 (CHDS), the maternal emotional responsiveness and avoidance of restriction and punishment subscales of the HOME inventory[50] assessed at ages 3–5 years were used to measure parenting practices. The reliability of each of these scales was α = .68. In Studies 2 (EGDS) and 3 (C-IVF), the Hostility Subscale of the Iowa Youth and Families Project Family Interaction Rating Scales[51] assessed parents' negative behaviors expressed toward their child. In Study 2, the 5-item hostility subscale was completed by adoptive mothers and fathers when children were 27 months old and 4.5 years old and a mean score was used across both parents at both time points. In Study 3, the 4-item hostility subscale was administered when children were 4–10 years old. Sample items include: "Shout or yell at him/her because you were mad at him/her"; "Criticize him/her or his/her ideas"; and "Hit, push, shove, or grab him/her." Internal consistency estimates were acceptable for Study 2 and Study 3, respectively (α = .74; α = .81).

Data analysis

The following steps were employed to test whether the association between maternal smoking during pregnancy and child conduct problems was evident and still present after considering all theoretical covariates in both genetically-related and genetically-unrelated mother-child dyads. First, we compared the mean scores of conduct problems in children with mothers who did not smoke during pregnancy, who smoked 1 to 9 cigarettes per day, or who smoked 10 or more cigarettes per day (Step 1). Second, we used ordinary least squares regression analysis to test for a significant dose-response association between maternal smoking during pregnancy and child conduct problems in each of the three studies. We first fitted a model containing only the maternal smoking variable as a predictor (Step 2), and then assessed the potential confounding effects of child covariates including gender, ethnicity, birth weight and breast feeding (Step 3); and also the confounding effect of maternal characteristics/postnatal environment: maternal age at birth, maternal education, family SES, family breakdown, placement age, and parenting practices (Step 4). Steps 1 and 2 test the extent to which the association between maternal smoking during pregnancy and child conduct problems are related for cohorts of children reared by genetically-related and genetically-unrelated mothers. Steps 3 and 4 control for potentially important confounders that may underlie associations across studies.

Finally, to increase the statistical power of our analyses, the regression coefficients for the genetically-related samples and the genetically-unrelated samples (adoption at birth) were pooled across studies using standard meta-analytic methods and assuming a random-effects model for the calculation of the pooled standard error.[52] A Stata (Version 11.0) *metan* command was applied to estimate the between studies component of variance in the pooled regression analyses.

Results

Maternal smoking during pregnancy in the three studies

The prevalence of maternal smoking during pregnancy varied across the three studies. In the CHDS, the prevalence of pregnancy smoking was 50% in children who were reared by genetically-unrelated mothers, and 32.7% in children who were reared by genetically-related mothers. This prevalence was similar to that in the EGDS sample, with 41% of children having a biological mother who smoked during pregnancy. The lowest prevalence of pregnancy smoking was observed in the C-IVF Study: 6% of children who were reared by genetically-related mothers and 4% of children who were reared by genetically-unrelated mothers.

Offspring conduct problems and maternal smoking during pregnancy

Table 2 shows the mean scores of conduct problems in the groups of children with different rates of maternal smoking during pregnancy (0, 1–9, or 10+ cigarettes/day) across the three studies. The mean scores of conduct problems were significantly different across rates of maternal smoking among children reared by genetically-related mothers (CHDS: $p < .001$, CIVF: $p = .005$) and among children reared by genetically-unrelated mothers (adoption at birth) (EGDS: $p = .007$, CHDS: $p = .04$), but not among children reared by genetically-unrelated mothers (adoption at conception) (C-IVF: $p = .98$).

Across all the studies, for children reared by genetically-related mothers and children reared by genetically-unrelated mothers (adoption at birth), higher mean scores of conduct problems were observed for those whose mother smoked during pregnancy in comparison to those whose mother did not smoke during pregnancy. Further, children whose mothers smoked 10 or more cigarettes/day had the highest mean scores of conduct problems.

Because the sample size of the C-IVF genetically-unrelated mothers who smoked during pregnancy was very small (n = 8), we did not include this subgroup in further analyses due to limitations pertinent to statistical power. The correlation between the amount of smoking during pregnancy and child conduct problems varied across the samples from r = .11, p = .005 (C-IVF genetically-related) to r = .34, p = .04 (CHDS genetically-unrelated).

Association between maternal smoking during pregnancy and child conduct problems

Table 3 shows the results derived from analysis of maternal smoking during pregnancy and child conduct problems using linear regression models (Models 1–3). The unadjusted models (Model 1), with maternal smoking during pregnancy as a predictor and child conduct problems score as an outcome, showed a significant association between pregnancy smoking and child conduct problems in the genetically-related mother-child pairs (CHDS: b=2.61, 95% CI=1.88–3.33, p<.001; and C-IVF: b=3.07, 95% CI=0.95–5.18, p=.005), as well as in the genetically-unrelated rearing mother-child pairs (adoption at birth) (EGDS: b=2.08, 95% CI=0.57–3.59, p=.007; and CHDS: b=4.51, 95% CI=0.32–8.70, p=.04).

Results of the analysis using an unadjusted model with the maximum sample size were similar to those in the samples with complete information on covariates (data available upon request). The comparisons between the maximum samples and those with the full information on all covariates showed that they were not different in terms of frequency of pregnancy smoking or means of child conduct problems.

In the model adjusted for child gender, ethnicity, and birth weight (Model 2), the associations remained similar to those in the unadjusted model. The final model was adjusted for all child covariates and also maternal characteristics and postnatal environment (maternal age at birth, maternal education, family SES, family breakdown, breast feeding, placement age, and parenting practices) (Model 3). In this fully adjusted model the association between maternal smoking during pregnancy and child conduct problems was attenuated but remained statistically significant in the genetically-related mother-child pairs (CHDS: b=0.82, 95% CI=0.08–1.56, p=.03, and C-IVF: b=2.15, 95% CI=0.11–4.18, p=.04). In the genetically-unrelated rearing mother-child pairs, the association remained statistically significant in the EGDS (b=1.99, 95% CI=0.48–3.90, p=.011), but was attenuated in the CHDS (b=4.27, 95% CI=−0.90–9.44, p=.12).

Results of the meta-analysis using the effect estimate and standard error from each study are also presented in Table 3. These results provide further evidence for a statistical dose-specific relationship between maternal smoking during pregnancy and offspring conduct problems in both the genetically related mother-child pairs (Unadjusted model: b=2.66, 95% CI=1.97- 3.34, (SE=0.35), p<.001; Fully adjusted model: b=1.13, 95% CI=0.02–2.24, (SE=0.56), p=.04) and the genetically-unrelated rearing mother-child pairs (Unadjusted model: b=2.48, 95% CI=0.72–4.23, (SE=0.90), p=.006; Fully adjusted model: b=2.17, 95% CI=0.72–3.62, (SE=0.74), p=.003).

Discussion

Results derived from the present study showed that maternal smoking during pregnancy was associated with offspring conduct problems. This association was observed for children reared by both genetically-related and genetically-unrelated mothers. In the genetically-unrelated (adoption at birth) mother-child pairs, characteristics of an adoptive mother and the child-rearing environment are distinct from the presence or absence of pregnancy smoking. Therefore, our results suggest that the association between maternal smoking during pregnancy and offspring conduct problems was not confounded by maternal characteristics or the child-rearing environment, specifically parenting practices. Moreover,

this association was observed when possible passive genotype–postnatal environment correlation was removed utilizing the attributes of the adoption-at-birth (EGDS and CHDS adoptees) design.

Our findings add to evidence highlighting the adverse effects of smoking during pregnancy as a risk factor for offspring conduct problems. First, prior sibling design studies suggest that siblings who differed in their exposure to pregnancy smoking did not differ in terms of conduct problems across childhood and adolescence.[34–36] However, these studies were not able to control for passive genotype-environment correlations, whereas our study included an adoption at birth design and could therefore demonstrate that having a postnatal environment free from genetic confounding did not explain the association between maternal smoking during pregnancy and offspring conduct problems. Second, prenatal exposure to smoking might represent an inherited rather than a true environmental risk factor underlying offspring conduct problems.[38, 39] It is possible that pre-existing genetically-based differences in the propensity to engage in externalizing behavior may confound the relationship between maternal smoking during pregnancy and offspring conduct problems.[53] For example, a previous study by Rice *et al.* (2009) using data from the C-IVF study showed that the association between prenatal smoking and child antisocial behavior was observed in genetically-related but not in genetically-unrelated mother-child pairs, suggesting that the association represents an inherited rather than truly causal effect.[38]

The results from previous studies using the IVF design[38] and a children-of-twins design[39, 54] suggest that passive genotype-environment correlation may contribute to the link between maternal smoking during pregnancy and offspring conduct problems. Combined with existing research, findings from the present study demonstrate that the underlying mechanisms for the association between maternal pregnancy smoking and offspring conduct problems are present during the prenatal period. These may involve common genetic factors that may interact with pregnancy smoking. Results of recent molecular-genetic studies revealed that offspring with a particular genetic profile are more sensitive to the negative effect of maternal smoking during pregnancy than those without.[55–58] For example, a gene-environment interaction between *COMT* and *MAOA* genes and maternal smoking during pregnancy on offspring aggressive behaviour has been reported.[56, 57] Importantly, the interaction between *COMT* and pregnancy smoking might be explained at the epigenetic level as the association of nicotine exposure with methylation of the gene promoter has recently been demonstrated.[59] In order to further our knowledge of effects of maternal smoking during pregnancy on offspring conduct problems, genetically-sensitive designs incorporating information on genetic and epigenetic markers are needed in future studies.

Strengths and limitations

Findings provided in the present study were obtained by using comparable measures of maternal smoking during pregnancy across the three studies. There is a possibility that the results are affected by historical smoking trends, specifically in relation to the CHDS study. However, any bias due to cohort effects is likely to be minimal as results are consistent across studies. Multi-informant reports (from a mother and a father or a mother and a teacher) were used to measure child conduct problems. These measures are not identical, yet the pattern of findings is consistent across independent samples of mother-child pairs, derived from distinct geographical and social backgrounds while controlling for a wide range of possible covariates. In addition, we confirmed the substantive finding in the pooled datasets using meta-analysis. Given that each design has its own set of strengths and weaknesses, different designs were employed. Indeed, as Rutter et al. (2007) outline, greater confidence is achieved when there is convergence of findings across studies using a complement of research designs.[60]

Strengths notwithstanding, several limitations should be noted. First, the number of smokers in the genetically-unrelated group in Study 3 (C-IVF) was very small ($n = 8$), thereby precluding incorporation of this group in the regression analysis and meta-analysis. Second, the prevalence of maternal smoking during pregnancy in the C-IVF genetically-related sample was significantly lower than that in the CHDS (6% versus 33%). However, the magnitude of association between maternal smoking during pregnancy and conduct problems was similar in these two distinct sample groups before adjustment for potential confounders (CHDS: b=2.61; C-IVF: b=3.07). Third, exposure to other substances (drugs, alcohol) during pregnancy, and postnatal smoking exposure (passive smoking) following birth, may be important risk factors for child development and need to be considered in future studies. As an additional test, we examined the role of passive smoking or environmental tobacco smoke, where this measure was available (CHDS). Results remained unchanged when we incorporated this measure into the analysis (available on request). Finally, our study, like most in the field, predominantly relied on maternal self-report of smoking. Although such methods have shown to have excellent agreement with antenatal records,[35, 46] biological measures may provide more accurate quantitative data concerning the true levels of nicotine that the foetus was exposed to during pregnancy. Also, future studies may need to explore a time-specific effect of exposure to pregnancy smoking.

Conclusions

Using a complement of genetically sensitive research designs, the present study examined the relationship between maternal smoking during pregnancy and offspring conduct problems among children reared by genetically-related and genetically-unrelated mothers, when specific perinatal and postnatal factors were controlled. Our findings suggest that there is an association between pregnancy smoking and child conduct problems that is unlikely to be fully explained by postnatal environmental factors (i.e., parenting practices), even when postnatal passive genotype-environment correlation has been removed. The causal explanation for the association between smoking in pregnancy and offspring conduct problems is not known, but may include genetic factors as well as other prenatal environmental hazards, including smoking itself. Research designs that allow disaggregation of genetic and environmental pathways underlying intergenerational transmission of psychopathology are critical for understanding the role of maternal smoking during pregnancy and could have important implications for future intervention and prevention programmes aimed at remediating child conduct problems.

Acknowledgments

We are very grateful to all the families who participated in these studies. We thank Xiaojia Ge, John Reid, Rand Conger, Laura Scaramella, Jody Ganiban, and Brandon Gibson for scientific and data analytic contributions to the EGDS; Dr. Frances Rice, Professor Dale Hay, Professor Jacky Boivin, Dr. Marianne van den Bree, Allyson Lewis, Valerie Russell, and the late Professor Xiaojia Ge for assistance in the Cardiff IVF study. We particularly thank Professor Anita Thapar for very helpful comments provided on earlier versions of this manuscript.

Acknowledgements of funding support

The CHDS was supported by grants from the Health Research Council of New Zealand, the Canterbury Medical Research Foundation, the Child Health Research Foundation (Cure Kids) and the New Zealand Lottery Grants Board.

The Early Growth and Development Study was supported by grant R01 HD042608 from NICHD, NIDA, and OBSSR, NIH, U.S. PHS (PIs: Reiss and Leve), by grant R01 DA020585 from NIDA, NIMH, and OBSSR, NIH, U.S. PHS (PI: Neiderhiser), by grant R01 MH092118 from NIMH, NIH, U.S. PHS (PIs: Neiderhiser and Leve). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development or the National Institutes of Health.

The Cardiff IVF Study was supported by a Wellcome Trust showcase award and a Wellcome Trust Project grant along with a project grant award from the Nuffield Foundation.

The funding bodies had no further role in the study design, the collection, analysis and interpretation of data, manuscript preparation, or in the decision to submit the paper for publication.

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Table 1

Summary of genetically-sensitive designs of three longitudinal studies: Christchurch Health and Development Study (CHDS), Early Growth and Development Study (EGDS) and Cardiff IVF Study

Design	Study	Features	Can/Cannot
Children reared by genetically-related mothers	Christchurch Health and Development Study (CHDS) Cardiff IVF Study	Mothers provide genetic, prenatal and postnatal environmental factors to children	Can control for a number of postnatal environmental factors / Cannot disentangle the effects of genetic from prenatal and postnatal environmental factors on children
Children reared by geneticallyunrelated mothers (adoption at birth)	Early Growth and Development Study (EGDS) Christchurch Health and Development Study (CHDS)	Adoptive mothers provide only postnatal environmental factors, but not genetic or prenatal environmental factors to children	Can test whether the effect of prenatal factors is confounded by postnatal environmental factors / Cannot remove passive genotype-environment correlation with prenatal environment influences on children
Children reared by genetically-unrelated mothers (adoption at conception)	Cardiff IVF Study	Adoptive mothers provide both prenatal and postnatal environmental factors but not genetic factors to children	Can test whether the effect of prenatal factors is confounded by genetic factors / Cannot disentangle the effects of prenatal and postnatal environmental influences on children

Table 2

Mean childhood conduct problem scores (combined reports) by rates of pregnancy smoking among children reared by genetically-related and genetically-unrelated mothers; subgroup numbers shown in brackets

		Pregnancy Smoking (Avg Cigs/Day)				
Design	**Study**	**0**	**1–9**	**10+**	**r**	***p***
Children reared by genetically-related mothers	CHDS *n*	98.63 (730)	100.80 (160)	103.96 (196)	.21	<.001
	Cardiff IVF *n*	99.20 (600)	103.59 (20)	104.54 (16)	.11	.005
Children reared by genetically-unrelated mothers (adoption at birth)	EGDS *n*	98.66 (184)	101.79 (82)	102.23 (45)	.15	.007
	CHDS *n*	97.07 (18)	107.81 (7)	105.45 (11)	.34	.04
Children reared by genetically-unrelated mothers (adoption at conception)	Cardiff IVF *n*	101.43 (198)	99.04 (5)	103.59 (3)	.00	.98

Table 3

Estimated effects of pregnancy smoking on child conduct problems (combined reports) for genetically-related and genetically-unrelated rearing mothers (adoption at birth) before and after adjustment for covariates, by individual study and pooled over studies

Design and Study	Model 1: Unadjusted			Model 2: Adjusted for child covariates			Model 3: Fully adjusted		
	b	95%CI	*p*	b	95%CI	*p*	b	95%CI	*p*
Children reared by genetically-related mothers									
CHDS	2.61	1.88; 3.33	<.001	2.36	1.59; 3.08	<.001	0.82	0.08; 1.56	.03
Cardiff IVF	3.07	0.95; 5.18	.005	3.00	0.86; 5.15	.006	2.15	0.11; 4.18	.04
Pooled	**2.66**	**1.97; 3.34**	**<.001**	**2.58**	**1.33; 3.82**	**<.001**	**1.13**	**0.02; 2.24**	**.04**
Children reared by genetically-unrelated mothers (adoption at birth)									
EGDS	2.08	0.57; 3.59	.007	2.20	0.57; 3.83	0.008	1.99	0.48; 3.90	.01
CHDS	4.51	0.32; 8.70	.04	4.17	−0.22, 8.56	0.07	4.27	−0.90, 9.44	.12
Pooled	**2.48**	**0.72; 4.23**	**.006**	**2.44**	**0.91, 3.96**	**.002**	**2.17**	**0.72, 3.62**	**.003**