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Maternal smoking during pregnancy and anger temperament among adult offspring

Tianli Liu, PhD^{1,2}, Constantine A. Gatsonis, PhD², Ana Baylin, MD, DrPH^{2,3}, Laura D. Kubzansky, PhD⁴, Eric B. Loucks, PhD², and Stephen L. Buka, ScD²

¹Institute of Population Research, Peking University, Beijing, P.R.China, 100871

²Department of Community Health, Brown University, Providence, Rhode Island, 02912

³Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, 48109

⁴Department of Society, Human Development, and Health, Harvard School of Public Health, Boston, Massachusetts, 02115

Abstract

Maternal smoking during pregnancy has been consistently associated with aggressive behaviors among offspring across the life course. We posit that anger, as a precedent of aggression, may have mediated the association. The current study examines the relation between maternal smoking during pregnancy and anger proneness among the adult offspring. Participants were 611 adult offspring (ages 38 – 48 years) of mothers enrolled in the Collaborative Perinatal Project between 1959 and 1966 in Boston and Providence. Information on maternal smoking during pregnancy was collected during prenatal visits. Spielberger's trait anger scale was used to measure anger proneness which has two components: anger temperament and angry reaction. Results from the full sample analyses showed that offspring whose mother smoked one pack or more per day on average scored 1.7 higher in anger temperament T scores in comparison to offspring whose mother never smoked during pregnancy ($\beta=1.7$, 95% Confidence Interval (CI): 0.1, 3.2). The fixed effects analyses among siblings that accounted for more confounding found a greater effect of around one standard deviation increase in anger temperament T scores corresponding to maternal smoking of one pack or more ($\beta=7.4$, 95% CI: 0.5, 14.4). We did not observe an association of maternal smoking during pregnancy with offspring angry reaction or other negative emotions including anxiety and depression. We concluded that prenatal exposure to heavy cigarette smoke was associated with an increased level of anger temperament, a stable personality trait that may carry the influence of prenatal smoking through the life course.

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CORRESPONDING AUTHORS: Tianli Liu, Institute of Population Research, Peking University, No. 5 YiHeYuan Road, HaiDian District, Beijing 100871, P.R.China, Tel: 86-10-62745841, Fax: 86-10-62751976, tianli.liu@gmail.com. Stephen L. Buka, Department of Community Health, Brown University, 121 South Main St, 2nd Floor, Providence RI 02912, Tel: 1-401-8636224, Fax: 1-401-8633713, stephen_buka@brown.edu.

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Keywords

Maternal smoking during pregnancy; prenatal exposure to cigarette smoke; anger proneness; anger temperament; angry reaction; aggression

BACKGROUND

Maternal smoking during pregnancy has been consistently linked to a range of mild to severe aggressive behaviors among offspring across the life course. (Brennan, Grekin, & Mednick, 1999; Ernst, Moolchan, & Robinson, 2001; Fergusson, Woodward, & Horwood, 1998; Rasanen et al., 1999; Tremblay et al., 2004; Wakschlag et al., 1997; Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002) It has been proposed that exposure to cigarette smoke toxins during the prenatal period may cause deficits in the developmental fetal brain that subsequently lead to disruptive behaviors, (Ernst et al., 2001; Slotkin, 2004) although the precise pathway remains unclear.

Cigarette smoke contains many known toxicants, some of which, such as nicotine and carbon monoxide, have been suggested as the key neurobehavioral teratogens. (Richardson & Tizabi, 1994; Singh, 1986) They could pass the placenta to influence the normal development of the fetal brain through (1) teratologic effects on the developing fetal nervous system, and (2) hypoxic effects on the fetal-placental unit that reduce the fetal blood circulation. (DiFranza, Aligne, & Weitzman, 2004; Wakschlag et al., 2002) Reduced thickness of the orbital prefrontal cortex had been found among adolescents exposed to maternal smoking during the prenatal period. (Toro et al., 2008) Patients with lesions in the orbital prefrontal cortex and adjacent regions showed explosive bursts of anger, impulsive aggression and violent behaviors. (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Blair & Cipolotti, 2000) In addition, evidence for the impact of exposure to cigarette smoke during the prenatal period on neural substrates of disruptive behaviors had also been provided in functional MRI neuroimaging, (Bennett et al., 2009) genotype (Wakschlag et al., 2010) and phenotype (Wakschlag et al., 2011) studies.

Temperament as a stable personality trait has long been suggested as having a neurobiological basis. (Whittle, Allen, Lubman, & Yucel, 2006) For instance, the orbital prefrontal cortex region had been proposed as a key region associated with a fundamental dimension of temperament – restraint. (Whittle et al., 2006) In normal individuals, activation of certain brain regions including the orbital prefrontal cortex that occur during anger arousal constrains the impulsive expression of emotion and the presence of aggressive behaviors. (Davidson, Putnam, & Larson, 2000)

Previous studies had shown that infants and school aged children who were exposed to maternal smoking during the prenatal period were more likely to have difficult temperament, for example low positive/high negative mood, in comparison to their unexposed counterparts. (Martin, Dombrowski, Mullis, Wisenbaker, & Huttunen, 2006; Pickett, Wood, Adamson, D'Souza, & Wakschlag, 2008) Temperament reflects prepositions to behavior patterns as it underlies and drives behavioral manifestations. (Dadds & Salmon, 2003) Among a diverse set of temperamental traits, we consider that anger temperament might be particularly relevant to impulsive aggressive behaviors. Anger as a negative affect has been identified as a fundamental cause or pre-condition for impulsive aggression. It reduces inhibitions against and sometimes justifies and energizes aggressive behaviors towards others. (Anderson & Bushman, 2002)

Spielberger's trait anger scale (Spielberger, 1999) that had been widely used to measure anger proneness consists two components (1) Anger temperament that refers to a person's propensity to outbursts of anger with minimum provocation; and (2) angry reaction that denotes the tendency to become angry when treated unfairly by others. In the current study, we examine the relation between maternal smoking during pregnancy and anger temperament, angry reaction as well as trait anger among the adult offspring. We posit that the frequently-noted link between maternal smoking during pregnancy and subsequent aggressive behaviors may be mediated through offspring anger temperament. In addition, because a high level of anger temperament may co-occur with other negative affect such as anxiety and depression, we further assess their relation with maternal smoking during pregnancy to test the specificity of the study finding.

METHODS

Study sample

As shown in Figure 1, participants were offspring of pregnant women enrolled in the Collaborative Perinatal Project (CPP) between 1959 and 1966. (Niswander, 1972) The Collaborative Perinatal Project was a multi-site prospective cohort study designed to investigate developmental consequences of pregnancy and delivery complications. Comprehensive data on expectant mothers' health, behavior and demographic characteristics were recorded at the time of registration (usually at their first visit for prenatal care). Information on offspring birth outcomes and subsequent growth and development was obtained periodically during their first year of life, and again at ages 4 and 7 years.

Building on the Collaborative Perinatal Project, the New England Family Study (NEFS) was established in 2001 to locate and interview the adult Collaborative Perinatal Project offspring at the Providence, Rhode Island and Boston, Massachusetts sites (N=17,921). From then on several studies have derived their samples from the New England Family Study. (Almeida et al., 2010; Buka, Shenassa, & Niaura, 2003; Gilman et al., 2008; Graham et al., 2008; Paradis, Fitzmaurice, Koenen, & Buka, 2010) One of the follow up studies had assessed 1625 adult offspring to investigate nicotine dependence and health outcomes across the lifespan and across generations. Additional funds were later obtained for a new study of the association between educational attainment and subsequent health status; funds were available to study approximately 900 of the 1625 previously assessed participants. All non-white subjects (predominantly African American: n=219) were first selected to maximize power for race/ethnic comparisons. Second, to best adjust for confounding due to family-level factors, all siblings who were discordant for attained level of education (N=396) were selected. The remaining were 299 individuals who were selected to balance the sample by race, attained education, and predicted level of education. In total 914 adult offspring were selected to participate, among them 16 were determined to be deceased or were otherwise ineligible for follow-up assessments (e.g., incarcerated). From the 898 eligible individuals, 618 were successfully located and interviewed (67.6%). They participated in a three hour in-person interview that collected extensive information on education, socioeconomic status, psychological and cognitive status, as well as health behaviors. (Almeida et al., 2010) In comparison with the non-respondents (N= 280), the respondents (N=618) were more likely to be white ($p<0.001$) and highly educated ($p<0.001$), and their mothers reported more years of education ($p<0.01$), less cigarette smoking during pregnancy ($p=0.02$), and less mental illness ($p=0.04$).

Participants with missing data for anger proneness (N=6) or for maternal smoking during pregnancy (N=1) were excluded from the analyses, resulting in a final analytic sample of 611 individuals, included 340 singletons, 104 sibling pairs, 17 sibling trios, and 3 sibling quartets.

The institutional review boards of Brown and Harvard Universities approved the follow-up studies; written informed consent was obtained from participants.

Study variables and measures

Maternal smoking during pregnancy—At the first prenatal visit, mothers reported whether they currently smoked and, if so, the number of cigarettes they smoked per day. Questions on smoking were repeated at each subsequent prenatal visit until the time of delivery. From these repeated measurements, the maximum number of cigarettes smoked at any point during pregnancy was used as the measure of maternal smoking during pregnancy in this study. The accuracy of these maternal reports of smoking during pregnancy has been validated by serum cotinine assays. (Klebanoff, Levine, Clemens, DerSimonian, & Wilkins, 1998)

Anger proneness of the offspring—The Spielberger's 10-item trait anger scale (Appendix 1) (Spielberger, 1999) was administered to the adult offspring to assess their anger proneness as a stable trait. This measure has two subscales labeled angry temperament (4 items) and angry reaction (4 items). An example item in the angry temperament subscale is 'I am a hotheaded person', and an example item in the angry reaction subscale is 'I feel annoyed when I am not given recognition for doing good work'. Participants rated themselves on each item as '1= almost never', '2 = sometimes', '3 = often', or '4 = almost always'. The item scores were summed to obtain the subscale and total scale raw scores. The raw scores were transformed into t scores according to information provided by Spielberger and colleagues. (Spielberger, 1999) Psychometric properties of the trait anger scale as well as the two subscales have been supported by validation studies. (Forgays, Forgays, & Spielberger, 1997; Spielberger, 1999) The Cronbach's alphas for trait anger, angry temperament, and angry reaction scales are 0.86, 0.89 and 0.71, respectively in our data.

Anxiety of the offspring—The anxiety scale contained in the Minnesota Multiphasic Personality Inventory -2 (MMPI-2) (Butcher, 1992) was used to measure anxiety of the adult offspring. The scale consists of 23 items, an example item is "I worry quite a bit over possible misfortunes". Participants rated themselves on each item with a 4 point scale, '1=rarely or none of the time', '2=some or little of the time', '3=often or a moderate amount of time', '4=most or all of the time'. The items scores were summed to obtain the scale total score, a higher score indicating a higher level of anxiety. The Cronbach's alpha for the anxiety scale is 0.93 in our data.

Depression of the offspring—Depression of the offspring was assessed by the short version of the Center for Epidemiological Studies Depression Scale (CES-D) (Andresen, Malmgren, Carter, & Patrick, 1994) that was developed to identify depressive symptomatology related to major or clinical depression in adults or adolescence. The short version scale consists of 10 items, an example item is "I felt depressed." Items were rated for the previous month on a 4-point scale '1=rarely or none of the time', '2=some or little of the time', '3=often or a moderate amount of time', '4=most or all of the time'. A summary score was calculated. Higher scores indicate greater symptoms. The Cronbach's alpha for the depression scale is 0.89 in our data.

Potential confounders—Information on mother's age at pregnancy and years of education were recorded during prenatal visits. Parental mental illness was assessed by interviewing the mothers during their pregnancy and 7 years after the delivery. Mothers and fathers were separately categorized as having a history of mental health problems if the mother reported psychiatric hospitalization or outpatient treatment for a mental health issue

or substance abuse. Data on adult offspring characteristics including age, gender, race, education, and smoking status were collected during the offspring follow-up interview.

Analytic approach

We conducted two sets of linear regression analyses to examine the relation between prenatal exposure to cigarette smoke and offspring anger proneness (trait anger, anger temperament and angry reaction). The first was linear regression analysis among the full sample adjusted for offspring and parental characteristics including offspring age, race, education, current smoking, maternal age at pregnancy, mother education, mother mental illness, and father mental illness. Generalized Estimating Equations (GEE) were used to adjust variance estimates for the non-independence of multiple siblings per family. The second analysis was fixed effects (Allison, 2005) linear regression with the sibling sample. The basic principle of this analysis is to stratify the sibling sample by mothers, and compare siblings of the same mother who may smoke differently across pregnancies to estimate the effect of maternal smoking on offspring anger proneness. Due to the fact that siblings were typically born and raised in the same family, this analysis accounts for the confounding factors such as genetic factors and parenting that shared by siblings. (Gilman et al., 2008) Only factors differed among siblings including offspring age, education and current smoking status were adjusted for in these models. In addition, we repeated the above two sets of analyses with offspring anxiety and depression as dependent variables.

All statistical analyses were conducted by SAS 9.2 software. (SAS Institute, Inc., Cary, North Carolina)

RESULTS

Participants (N=611) were 38 to 48 years old at the time of interview. The majority were female (61%), white (77%), and more than half had a college or higher education (57%). Their mothers were on average 25.3 (Standard Deviation (SD) = 5.5) years old at pregnancy. Around 55% of the mothers reported smoking during pregnancy; and 32% of the mothers had smoked one pack or more per day during pregnancy. There were 124 sibling sets (104 sibling pairs, 17 sibling trios, and 3 sibling quartets) in the sample. There were 38 sibling sets where the mothers smoked different amounts across her pregnancies, and for 8 sets, the difference in maternal smoking was 20 cigarettes or more. Characteristics of the participants who had one or more siblings enrolled in the study (N=271) were very similar as those who did not have a sibling enrolled (N=340), except for a higher proportion of white individuals in the sibling sample (83%) than in the non sib sample (72%).

Table 1 compares characteristics of the participants by categories of maternal smoking during pregnancy. Participants who were exposed to maternal smoking of one pack or more per day during the prenatal period reported a lower educational attainment than participants who were exposed to lighter or no maternal smoking during the prenatal period. The mothers who had smoked one pack or more per day during pregnancy were more likely to have mental illness as well as low education attainment than the mothers who never smoked or smoked less than one pack per day during pregnancy. We observed an increasing trend in levels of trait anger and anger temperament, but not angry reaction, anxiety or depression among participants corresponding to increases in levels of maternal smoking during pregnancy.

Table 2 shows results from the analyses among the full sample and among the sibling sample on the associations between maternal smoking during pregnancy and offspring anger proneness. Results from the full sample analysis suggested that in comparison to offspring whose mother never smoked during pregnancy, offspring whose mother smoked one pack or

more per day during pregnancy had scored significantly higher in anger temperament T scores ($\beta = 1.7$, 95% Confidence Interval (CI): 0.1, 3.2), whereas we did not observe significant difference in their angry reaction ($\beta = -0.7$, 95% CI: -2.9, 1.5) as well as trait anger total ($\beta = 1.1$, 95% CI: -1.1, 3.3) T scores.

A greater effect size was observed in the fixed effects analysis that accounted for more confounding than the full sample analyses. We found that in comparison with siblings who were not exposed to cigarette smoking during the prenatal period, siblings exposed to maternal smoking of one pack or more on any pregnancy day scored 7.4 higher in anger temperament T scores ($\beta = 7.4$, 95% CI: 0.5, 14.4) and there was a non-significant increase in angry reaction T scores ($\beta = 4.0$, 95% CI: -5.8, 13.8). In addition, the increase in trait anger total scale score corresponding to heavy maternal smoking reached statistical significance ($\beta = 10.0$, 95% CI: 0.2, 19.9) here, largely due to a greater increase in both the anger temperament and angry reaction subscales scores than in the full sample analysis.

Table 3 shows results from the analyses on the relation between maternal smoking during pregnancy and offspring anxiety and depression. Neither the full sample analysis nor the fixed effects analysis found an association of maternal smoking during pregnancy with offspring anxiety or depression.

DISCUSSION

To the best of our knowledge, this is the first study to examine the association between prenatal exposure to cigarette smoke and anger proneness in human adults. Results from the analyses suggested that in comparison with offspring whose mother never smoked during pregnancy, offspring whose mother smoked heavily (one pack or more per day) during pregnancy scored higher on anger temperament but not on anger in reaction to unfair treatment. Anger temperament is an aspect of personality, an enduring component of anger proneness that persists across the life span and social contexts, (Spielberger, 1983; Williams, Nieto, Sanford, & Tyroler, 2001) whereas the component of angry reaction that refers to angry experiences following certain social provocations (e.g. criticized in front of others), might be influenced by a person's immediate social environment. If this distinction is appropriate, it is plausible that the impact of a prenatal factor on a person's anger proneness is more likely to be maintained through to adulthood by anger temperament than by angry reaction. In addition, maternal smoking during pregnancy was specifically associated with anger temperament, but not with other negative affect including anxiety and depression.

As anger is primarily regulated by the central nervous system, we propose that the increased level of anger temperament among adult offspring may be attributable to neurodevelopmental deficits in the brain of the exposed offspring. Nicotine contained in cigarette smoke is a known neural toxicant readily transferred to the fetal compartment throughout pregnancy. (Ernst et al., 2001; Luck, Nau, Hansen, & Steldinger, 1985) It primarily acts through activation of nicotinic acetylcholine receptors (nAChRs). Acetylcholine is a neurotransmitter that plays a critical tropic role in brain cell replication and differentiation, synaptic outgrowth, and architecture modeling during the prenatal period. (Slotkin, 2004) Stimulation of nAChRs by nicotine may disrupt tropic signaling elicited by acetylcholine, subsequently lead to profound and permanent abnormalities to the central nervous system. (Ernst et al., 2001; Slotkin, 1998; 2004) Altered brain development may also result from intrauterine hypoxia due to either nicotine that reduces blood flow to the fetus or possibly carbon monoxide, another known toxin contained in cigarette smoke, which produces increased level of carboxyhemoglobin in maternal and fetal blood. (DiFranza et al., 2004) In addition, fetus exposed to prenatal smoking had an increased risk of low birth weight and intrauterine growth retardation. (Horta, Victora, Menezes, Halpern,

& Barros, 1997; Windham, Hopkins, Fenster, & Swan, 2000) A higher rate of brain dysfunction had been observed in the low birth weight population than their normal birth weight counterparts. (Hack, Klein, & Taylor, 1995)

We consider that dysfunction of the central serotonin system might be particularly relevant. Although such a notion is purely speculative, experimental studies have implicated that prenatal exposure to cigarette smoke disturbs the normal development of the serotonin system. (Muneoka et al., 1997; Xu, Seidler, Ali, Slikker, & Slotkin, 2001) The serotonin system in regions of the prefrontal cortex exerts an inhibitor role over anger, impulses, and impulsive aggression. (Davidson et al., 2000) Reduced central serotonin function has been linked to increased irritability (defined as “readiness to explode with negative affect at the slightest provocation”) (Coccaro et al., 1989) and lack of impulse control. (Coccaro, 1992) These characteristics are consistent with Spielberger’s description of a high anger temperament person: ‘hot headed, quick tempered, have a fiery temper, and fly off the handle’. (Spielberger, 1999)

Genetic influence could also contribute to individual differences in anger temperament. (Saudino, 2005) The observed association between maternal smoking during pregnancy and offspring anger temperament may partially reflect the operation of underlying genetic factors. It is possible that offspring with high levels of anger temperament were born to mothers who were also high in this dimension and who smoked heavily because of her frequent and intense angry experiences. (Jamner, Shapiro, & Jarvik, 1999) In fact, smoking has been widely used as a coping strategy for negative emotions. (Kassel, Stroud, & Paronis, 2003) However, anger temperament is not determined by heredity alone. (Saudino, 2005) Our fixed effects analyses showed that being born to the same mother did not make siblings resemble each other in anger temperament when mother’s smoking behavior changed across the pregnancies. The sibling exposed to heavy maternal smoking during the prenatal period had a much higher level of anger temperament than the sibling not exposed, despite fixed maternal genetic factors. In addition, smoking is not only more prevalent among high anger mothers, but also among mothers with other negative emotions such as anxiety and depression that also have strong genetic bases. (Hammen & Brennan, 2003; McClure, Brennan, Hammen, & Le Brocque, 2001) However, no association between maternal smoking and offspring anxiety and depression was observed.

The major strength of this study is that maternal smoking during pregnancy was prospectively measured at the prenatal visits, and the validity of the measure has been supported by comparisons with serum cotinine assays. Hence, recall bias, which is a concern of most studies of the same nature, has been greatly minimized. Our study also has limitations. The study participants reported a higher socioeconomic status than that of the non respondents. This limits the generalizability of the results to a relatively higher socioeconomic status population. Although presumably the sibling fixed effects analyses could account for unmeasured and unknown familial confounding factors (such as genetic factors, parenting style and family environment etc.), its effect estimates were based on a small number of siblings discordant for maternal smoking. Further, a mother’s smoking during one pregnancy, but not another, may be associated with complex individual and family stress and circumstances that affect the development of the anger traits among offspring, (Graham, Hawkins, & Law, 2010; Morales, Marks, & Kumar, 1997; Pickett, Wilkinson, & Wakschlag, 2009) hence there might be some residue confounding due to change in maternal and family psychosocial factors across pregnancies. Future studies among a large size sibling sample with detail measures on the family psychosocial environment are necessary.

In sum, we report a positive association between prenatal exposure to heavy maternal smoking and an increased level of anger temperament that causes frequent and intense angry experience. As a precedent of aggression, prolonged and intense anger has been linked to a wide range of aggressive behaviors. (Boyle & Vivian, 1996; Deffenbacher, Deffenbacher, Lynch, & Richards, 2003; Justice, 2000; Rodriguez & Green, 1997) Future study of the relation among maternal smoking during pregnancy, offspring anger temperament and impulsive aggressive behaviors may shed a light on one of the potential mechanisms underlying the consistent association between maternal smoking during pregnancy and offspring aberrant behaviors.

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References

- Allison, P. Fixed effects regression methods for longitudinal data using SAS. Cary, NC: SAS Institute Inc; 2005.
- Almeida ND, Loucks EB, Kubzansky L, Pruessner J, Maselko J, Meaney MJ, Buka SL. Quality of parental emotional care and calculated risk for coronary heart disease. *Psychosom Med*. 2010; 72:148–55. [PubMed: 20064905]
- Anderson CA, Bushman BJ. Human aggression. *Annu Rev Psychol*. 2002; 53:27–51. [PubMed: 11752478]
- Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat Neurosci*. 1999; 2:1032–7. [PubMed: 10526345]
- Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med*. 1994; 10:77–84. [PubMed: 8037935]
- Bennett DS, Mohamed FB, Carmody DP, Bendersky M, Patel S, Khorrami M, Faro SH, Lewis M. Response inhibition among early adolescents prenatally exposed to tobacco: an fMRI study. *Neurotoxicol Teratol*. 2009; 31:283–90. [PubMed: 19351556]
- Blair RJ, Cipolotti L. Impaired social response reversal. A case of ‘acquired sociopathy’. *Brain*. 2000; 123 (Pt 6):1122–41. [PubMed: 10825352]
- Boyle DJ, Vivian D. Generalized versus spouse-specific anger/hostility and men’s violence against intimates. *Violence Vict*. 1996; 11:293–317. [PubMed: 9210274]
- Brennan PA, Grekin ER, Mednick SA. Maternal smoking during pregnancy and adult male criminal outcomes. *Arch Gen Psychiatry*. 1999; 56:215–9. [PubMed: 10078497]
- Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry*. 2003; 160:1978–84. [PubMed: 14594744]

- Butcher, JN.; Williams, CL.; Graham, JR.; Archer, RP.; Tellegen, A.; Ben-Porath, YS.; Kaemmer, B. Minnesota Multiphasic Personality Inventory-Adolescent Version(MMPI-A): Manual for administration, scoring and interpretation. Minneapolis, MN: University of Minnesota Press; 1992.
- Coccaro EF. Impulsive aggression and central serotonergic system function in humans: an example of a dimensional brain-behavior relationship. *Int Clin Psychopharmacol*. 1992; 7:3–12. [PubMed: 1624755]
- Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL. Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. *Arch Gen Psychiatry*. 1989; 46:587–99. [PubMed: 2735812]
- Dadds MR, Salmon K. Punishment insensitivity and parenting: temperament and learning as interacting risks for antisocial behavior. *Clin Child Fam Psychol Rev*. 2003; 6:69–86. [PubMed: 12836578]
- Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence. *Science*. 2000; 289:591–4. [PubMed: 10915615]
- Deffenbacher JL, Deffenbacher DM, Lynch RS, Richards TL. Anger, aggression and risky behavior: A comparison of high and low anger drivers. *Behaviour Research and Therapy*. 2003; 41:701–718. [PubMed: 12732377]
- DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics*. 2004; 113:1007–15. [PubMed: 15060193]
- Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. *J Am Acad Child Adolesc Psychiatry*. 2001; 40:630–41. [PubMed: 11392340]
- Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry*. 1998; 55:721–7. [PubMed: 9707383]
- Forgays DG, Forgays DK, Spielberger CD. Factor structure of the State-Trait Anger Expression Inventory. *J Pers Assess*. 1997; 69:497–507. [PubMed: 9501480]
- Gilman SE, Martin LT, Abrams DB, Kawachi I, Kubzansky L, Loucks EB, Rende R, Buka SL. Educational attainment and cigarette smoking: a causal association? *Int J Epidemiol*. 2008; 37:615–24. [PubMed: 18180240]
- Graham AL, Papandonatos GD, DePue JD, Pinto BM, Borrelli B, Neighbors CJ, Niaura R, Buka SL, Abrams DB. Lifetime characteristics of participants and non-participants in a smoking cessation trial: implications for external validity and public health impact. *Ann Behav Med*. 2008; 35:295–307. [PubMed: 18414962]
- Graham H, Hawkins SS, Law C. Lifecourse influences on women's smoking before, during and after pregnancy. *Soc Sci Med*. 2010; 70:582–7. [PubMed: 19932931]
- Hack M, Klein NK, Taylor HG. Long-term developmental outcomes of low birth weight infants. *Future Child*. 1995; 5:176–96. [PubMed: 7543353]
- Hammen C, Brennan PA. Severity, chronicity, and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Arch Gen Psychiatry*. 2003; 60:253–8. [PubMed: 12622658]
- Horta BL, Victora CG, Menezes AM, Halpern R, Barros FC. Low birthweight, preterm births and intrauterine growth retardation in relation to maternal smoking. *Paediatr Perinat Epidemiol*. 1997; 11:140–51. [PubMed: 9131707]
- Jamner LD, Shapiro D, Jarvik ME. Nicotine reduces the frequency of anger reports in smokers and nonsmokers with high but not low hostility: an ambulatory study. *Exp Clin Psychopharmacol*. 1999; 7:454–63. [PubMed: 10609980]
- Justice, U. S. D. o. U. d. o. Justice. Crime in the United States 2000: Uniform Crime Reports. 2000.
- Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. *Psychol Bull*. 2003; 129:270–304. [PubMed: 12696841]
- Klebanoff MA, Levine RJ, Clemens JD, DerSimonian R, Wilkins DG. Serum cotinine concentration and self-reported smoking during pregnancy. *Am J Epidemiol*. 1998; 148:259–62. [PubMed: 9690362]
- Luck W, Nau H, Hansen R, Steldinger R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev Pharmacol Ther*. 1985; 8:384–95. [PubMed: 4075937]

- Martin RP, Dombrowski SC, Mullis C, Wisenbaker J, Huttunen MO. Smoking during pregnancy: association with childhood temperament, behavior, and academic performance. *J Pediatr Psychol*. 2006; 31:490–500. [PubMed: 16002482]
- McClure EB, Brennan PA, Hammen C, Le Brocque RM. Parental anxiety disorders, child anxiety disorders, and the perceived parent-child relationship in an Australian high-risk sample. *J Abnorm Child Psychol*. 2001; 29:1–10. [PubMed: 11316331]
- Morales AW, Marks MN, Kumar R. Smoking in pregnancy: a study of psychosocial and reproductive risk factors. *J Psychosom Obstet Gynaecol*. 1997; 18:247–54. [PubMed: 9443133]
- Muneoka K, Ogawa T, Kamei K, Muraoka S, Tomiyoshi R, Mimura Y, Kato H, Suzuki MR, Takigawa M. Prenatal nicotine exposure affects the development of the central serotonergic system as well as the dopaminergic system in rat offspring: involvement of route of drug administrations. *Brain Res Dev Brain Res*. 1997; 102:117–26.
- Niswander, KR.; Gordon, M. *The Women and Their Pregnancies: the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke*. Washington, DC: National Institutes of Health; 1972.
- Paradis AD, Fitzmaurice GM, Koenen KC, Buka SL. Maternal smoking during pregnancy and criminal offending among adult offspring. *J Epidemiol Community Health*. 2010
- Pickett KE, Wilkinson RG, Wakschlag LS. The psychosocial context of pregnancy smoking and quitting in the Millennium Cohort Study. *J Epidemiol Community Health*. 2009; 63:474–80. [PubMed: 19258350]
- Pickett KE, Wood C, Adamson J, D'Souza L, Wakschlag LS. Meaningful differences in maternal smoking behaviour during pregnancy: implications for infant behavioural vulnerability. *J Epidemiol Community Health*. 2008; 62:318–24. [PubMed: 18339824]
- Rasanen P, Hakko H, Isohanni M, Hodgins S, Jarvelin MR, Tiihonen J. Maternal smoking during pregnancy and risk of criminal behavior among adult male offspring in the Northern Finland 1966 Birth Cohort. *Am J Psychiatry*. 1999; 156:857–62. [PubMed: 10360123]
- Richardson SA, Tizabi Y. Hyperactivity in the offspring of nicotine-treated rats: role of the mesolimbic and nigrostriatal dopaminergic pathways. *Pharmacol Biochem Behav*. 1994; 47:331–7. [PubMed: 8146225]
- Rodriguez CM, Green AJ. Parenting stress and anger expression as predictors of child abuse potential. *Child Abuse & Neglect*. 1997; 21:367–377. [PubMed: 9134265]
- Saudino KJ. Behavioral genetics and child temperament. *J Dev Behav Pediatr*. 2005; 26:214–23. [PubMed: 15956873]
- Singh J. Early behavioral alterations in mice following prenatal carbon monoxide exposure. *Neurotoxicology*. 1986; 7:475–81. [PubMed: 3785762]
- Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? *J Pharmacol Exp Ther*. 1998; 285:931–45. [PubMed: 9618392]
- Slotkin TA. Cholinergic systems in brain development and disruption by neurotoxicants: nicotine, environmental tobacco smoke, organophosphates. *Toxicol Appl Pharmacol*. 2004; 198:132–51. [PubMed: 15236950]
- Spielberger, CD. STAXI-2: State–Trait Anger Expression Inventory—2. Professional manual. Odessa, FL: Psychological Assessment Resources; 1999.
- Spielberger, CD.; Jacobs, G.; Russell, S.; Crane, RS. Assessment of anger: the State-Trait anger scale. In: Butcher, SCJN., editor. *Advances in personality assessment*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1983. p. 161-89.
- Toro R, Leonard G, Lerner JV, Lerner RM, Perron M, Pike GB, Richer L, Veillette S, Pausova Z, Paus T. Prenatal exposure to maternal cigarette smoking and the adolescent cerebral cortex. *Neuropsychopharmacology*. 2008; 33:1019–27. [PubMed: 17609681]
- Tremblay RE, Nagin DS, Seguin JR, Zoccolillo M, Zelazo PD, Boivin M, Perusse D, Japel C. Physical aggression during early childhood: trajectories and predictors. *Pediatrics*. 2004; 114:e43–50. [PubMed: 15231972]
- Wakschlag LS, Henry DB, Blair RJ, Dukic V, Burns J, Pickett KE. Unpacking the association: Individual differences in the relation of prenatal exposure to cigarettes and disruptive behavior phenotypes. *Neurotoxicol Teratol*. 2011; 33:145–54. [PubMed: 21256429]

- Wakschlag LS, Kistner EO, Pine DS, Biesecker G, Pickett KE, Skol AD, Dukic V, Blair RJ, Leventhal BL, Cox NJ, Burns JL, Kasza KE, Wright RJ, Cook EH Jr. Interaction of prenatal exposure to cigarettes and MAOA genotype in pathways to youth antisocial behavior. *Mol Psychiatry*. 2010; 15:928–37. [PubMed: 19255579]
- Wakschlag LS, Lahey BB, Loeber R, Green SM, Gordon RA, Leventhal BL. Maternal smoking during pregnancy and the risk of conduct disorder in boys. *Archives of General Psychiatry*. 1997; 54:670–676. [PubMed: 9236551]
- 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]
- Whittle S, Allen NB, Lubman DI, Yucel M. The neurobiological basis of temperament: towards a better understanding of psychopathology. *Neurosci Biobehav Rev*. 2006; 30:511–25. [PubMed: 16289282]
- Williams JE, Nieto FJ, Sanford CP, Tyroler HA. Effects of an angry temperament on coronary heart disease risk: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2001; 154:230–5. [PubMed: 11479187]
- Windham GC, Hopkins B, Fenster L, Swan SH. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. *Epidemiology*. 2000; 11:427–33. [PubMed: 10874550]
- Xu Z, Seidler FJ, Ali SF, Slikker W Jr, Slotkin TA. Fetal and adolescent nicotine administration: effects on CNS serotonergic systems. *Brain Res*. 2001; 914:166–78. [PubMed: 11578609]

Appendix 1: Spielberger's Trait Anger Scale items

1. I have a fiery temper
2. I am quick-tempered
3. I am a hot-headed person
4. I fly off the handle
5. When I get mad, I say nasty things
6. When I get frustrated, I feel like hitting someone
7. I feel infuriated when I do a good job and get a poor evaluation
8. It makes me furious when I am criticized in front of others
9. I feel annoyed when I am not given recognition for doing good work
10. I get angry when I am slowed down by other's mistakes

Items 1 to 4 belong to the angry temperament subscale, and items 7 to 10 belong to the angry reaction subscale.

Figure 1.
Flow chart for study sampling

Characteristics of offspring in the Providence and Boston cohorts of the Collaborative Perinatal Project (N=611), by maternal smoking during pregnancy.

Table 1

	Maternal Smoking During Pregnancy (cigarettes per day)			
	None (N=272)	Less than one pack (N=141)	One pack or more (N=198)	p value ^a
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	<u>Mean (SD)</u>	
Age (yrs) ^d	42.5 (1.9)	42.5 (1.8)	42.4 (1.8)	0.87
Maternal age at pregnancy (yrs)	25.9 (5.8)	24.6 (5.5)	25.1 (5.1)	0.05
Trait anger - raw score ^b	15.7 (4.8)	16.3 (5.1)	17.0 (5.7)	0.04
Anger temperament - raw score ^b	5.6 (2.2)	6.1 (2.8)	6.5 (3.1)	<0.01
Angry reaction - raw score ^b	7.5 (2.6)	7.4 (2.4)	7.5 (2.6)	0.08
Trait anger - T score ^c	42.9 (10.9)	44.3 (11.1)	45.5 (11.9)	0.05
Anger temperament - T score ^c	50.2 (7.2)	51.9 (8.6)	52.9 (9.2)	<0.01
Angry reaction - T score ^c	43.2 (10.8)	42.9 (9.9)	43.2 (10.5)	0.96
Anxiety	38.4 (11.7)	39.1 (11.5)	39.8 (12.3)	0.43
Depression	15.6 (5.6)	16.3 (5.4)	16.2 (5.8)	0.35
	<u>N(%)</u>	<u>N(%)</u>	<u>N(%)</u>	
Female	158 (58.1)	87 (61.7)	125 (63.1)	0.52
Non white ^d	69 (25.6)	34 (24.1)	38 (19.5)	0.3
Education				
Less than high school or GED	14 (5.2)	16 (11.4)	37 (18.7)	
High school plus additional training	91 (33.5)	50 (35.5)	56 (28.3)	
College or higher	167 (61.4)	75 (53.2)	105 (53.0)	<0.01
Current smoking (cigarettes per day) ^d				
0	201 (77.0)	93 (69.4)	126 (67.4)	
1-19	35 (13.4)	28 (20.9)	29 (15.5)	
20+	25 (9.6)	13 (9.7)	32 (17.1)	0.03
Mother mental illness - Yes ^d	11 (4.1)	5 (3.6)	21 (10.8)	<0.01
Father mental illness - Yes ^d	5 (1.9)	4 (2.8)	9 (4.6)	0.22
Mother education ^d				

	Maternal Smoking During Pregnancy (cigarettes per day)			<i>p</i> value ^a
	None (N=272)	Less than one pack (N=141)	One pack or more (N=198)	
	<u>Mean (SD)</u>	<u>Mean (SD)</u>	<u>Mean (SD)</u>	
Less than 10 years	49 (18.7)	31 (22.0)	63 (32.5)	
10 or more years	213 (81.3)	110 (78.0)	131 (67.5)	<0.01

^aFor continuous variables, *p* values were derived from ANOVA tests; for categorical variables, *p* values were calculated by chi square tests.

^bRaw score for trait anger scale ranges from 10 to 40; and raw scores for angry temperament and angry reaction subscales range from 4 to 16, they were the sums of the relevant items scores.

^cThe raw scores were transferred into normalized T scores that have a mean of 50 and standard deviation of 10 in the normative sample.

^dMissing data counts: 4 for age, 5 for race, 29 for current smoking, 4 for mother mental illness, 4 for father mental illness, and 14 for maternal education.

SD: standard deviation.

Table 2
Relation between maternal smoking during pregnancy and offspring trait anger, anger temperament, and angry reaction.

	Trait anger				Anger temperament				Angry reaction			
	N	Mean (SD)	β	95% CI	Mean (SD)	β	95% CI	Mean (SD)	β	95% CI		
<u>Linear regression models</u> ^a :												
Maternal smoking during pregnancy												
None	250	42.9 (11.0)	0		50.1 (7.2)	0		43.2 (10.9)	0			
Less than one pack per day	132	44.4 (11.2)	0.7	(-1.6, 3.1)	52.0 (8.7)	1.2	(-0.6, 3.0)	43.0 (10.0)	-0.4	(-2.6, 1.7)		
One pack or more per day	178	45.5 (12.0)	1.1	(-1.1, 3.3)	52.8 (9.2)	1.7*	(0.1, 3.2)	43.3 (10.7)	-0.7	(-2.9, 1.5)		
<u>Fixed effects models</u> ^b :												
Maternal smoking during pregnancy												
None	127	42.0 (11.0)			49.7 (7.2)			42.4 (10.8)				
Less than one pack per day	52	43.6 (12.1)	3.2	(-4.9, 11.2)	52.0 (9.0)	4.4	(-1.3, 10.0)	42.2 (11.0)	-1.1	(-9.2, 6.9)		
One pack or more per day	77	45.7 (11.7)	10.0*	(0.2, 19.9)	52.4 (8.1)	7.4*	(0.5, 14.4)	43.7 (10.8)	4.0	(-5.8, 13.8)		

* p<0.05

^a Linear regression models examined relation between maternal smoking during pregnancy and offspring trait anger, anger temperament and angry reaction, respectively. Generalized Estimating Equation (GEE) was employed to account for correlation due to multiple offspring per mother. Confounders adjusted in the models included offspring age, race, education, current smoking, maternal age at pregnancy, mother education, mother mental illness, and father mental illness. Gender was not included in the models since the anger T scores were calculated separately by gender. Study sample with complete data for the covariates were included in the models.

^b Fixed effects linear models fitted among siblings to examine relation between maternal smoking during pregnancy and offspring trait anger, anger temperament and angry reaction, respectively. The basic principle of the analyses was to stratify the sibling sample by mothers, and compare siblings of the same mother to estimate the effect of maternal smoking on anger proneness. As confounding factors shared by siblings such as certain genetic factors and parenting style have minimum variation within each stratum (among siblings of the same mother), the fixed effects analysis, by its nature, controls these confounding factors, either measured or unmeasured, known or unknown. Confounding factors adjusted in the fixed effects models were those not shared by siblings including offspring age, education and current smoking status.

Table 3
Relation between maternal smoking during pregnancy and offspring anxiety and depression.

		Anxiety			Depression		
	N	Mean (SD)	β	95% CI	Mean (SD)	β	95% CI
Linear regression models ^a:							
Maternal smoking during pregnancy							
None	242	38.4 (11.9)			15.7 (5.8)		
Less than one pack per day	130	39.3 (11.7)	0	(-2.5, 2.5)	16.3 (5.5)	0.2	(-1.0, 1.4)
One pack or more per day	173	39.6 (12.5)	-0.5	(-2.7, 1.8)	16.2 (5.9)	-0.2	(-1.3, 0.9)
Fixed effects models ^b:							
Maternal smoking during pregnancy							
None	120	39.7 (13.4)			16.2 (6.6)		
Less than one pack per day	50	40.7 (12.4)	1.3	(-11.2, 13.7)	16.8 (5.7)	1.5	(-4.5, 7.5)
One pack or more per day	75	39.4 (13.0)	-3.2	(-13.5, 7.2)	16.1 (6.2)	-1.7	(-6.7, 3.3)

^a Adjusted for offspring age, gender, race, education, current smoking, maternal age at pregnancy, mother education, mother mental illness, and father mental illness.

^b Adjusted for offspring age, gender, education and current smoking status.