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Maternal smoking during pregnancy and child outcomes: Real or spurious effect?

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Abstract

Maternal smoking during pregnancy (MSDP) is a major public health concern with clearly established consequences to both mother and newborn (e.g., low birth weight, altered cardiorespiratory responses). MSDP has also been associated with higher rates of a variety of poor cognitive and behavioral outcomes in children, including ADHD, conduct disorder, impaired learning and memory, and cognitive dysfunction. However, the evidence suggesting causal effects of MSDP for these outcomes is muddied in the existing literature due to the frequent inability to separate prenatal exposure effects from other confounding environmental and genetic factors. Carefully designed studies using genetically sensitive strategies can build upon current evidence and begin to elucidate the likely complex factors contributing to associations between MSDP and child outcomes.

Introduction

Maternal smoking during pregnancy (MSDP) is a major public health concern with nearly half of all women who smoke continuing to do so throughout their pregnancies (Centers for Disease Control (CDC), 2002, 2004; Ebrahim, Floyd, Merrit, Decoufle, & Holtzman, 2000). As a result, more than half a million infants per year are prenatally exposed to maternal smoking (CDC, 2004; Smith, Martin, & Ventura, 1999). Offspring of women who smoke during pregnancy show low birth weight (e.g., Ricketts, Murray, & Schwalberg, 2005), increased risk of stillbirth (e.g., Salihu et al., 2008), altered cardiorespiratory responses (e.g., Huang et al., 2006; Neff, Simmens, Evans & Mendelowicz, 2004), and increased asthma and wheezing (e.g., Gilliland, Li, & Peters, 2001; Janson, 2004; Stocks & Dezateux, 2003) as well as behavioral abnormalities, including increased evidence of attentional deficits, impaired learning and memory, lowered IQ, and cognitive dysfunction (DiFranza & Lew, 1995; Levin & Slotkin, 1998; Naeye & Peters, 1984; Rantakallio & Koiranen, 1987; Roy, Seidler & Slotkin, 2002; Wakschlag, Lahey, Loeber, Green, Gordon & Leventhal, 1997). Despite this large literature suggesting undesirable outcomes in children exposed to MSDP, the underlying biological processes in humans are not well understood. Moreover, the evidence suggesting causal effects of MSDP for these childhood outcomes is muddied in the existing literature due to the frequent inability to separate prenatal tobacco exposure effects from other confounding environmental and genetic factors. Specifically, the vast majority of existing studies provide only limited control for the fact that prenatal exposures may be correlated with parental behaviors that could act as more proximal risk factors that are in turn transmitted to their offspring. Failure to control for such (possibly heritable) confounding factors may account for a large part of the suggested associations between

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MSDP and offspring outcomes. For example, if mothers with ADHD more commonly smoke during pregnancy, and also confer increased child risk of ADHD via genetic transmission, the observed correlation between MSDP and childhood ADHD would be largely spurious, with limited etiological relevance. Genetically-sensitive study designs can begin to elucidate the likely complex factors contributing to the association between MSDP and child outcomes.

The outcomes associated with MSDP cover broad cognitive and behavioral domains such that a comprehensive review is beyond the scope of this report. Thus, a brief overview of the pertinent literature is provided below and will draw on two bodies of work: (i) animal models of prenatal nicotine, and (ii) human studies of maternal smoking during pregnancy (see Tables 1 and 2). The final section will focus on a review of the few genetically informative studies of MSDP. These will be presented within the context of descriptions of a number of different behavior genetic designs that can be used to study the influence of genetic and environmental factors associated with specific measures of the environment.

Animal models: the role and mode of action of prenatal nicotine

Animal models tend to show the most consistent support of the effects, as well as the mode of action, of prenatal nicotine, which is just one toxic component of cigarettes. Importantly, animal studies do pinpoint nicotine, which partially mimics the actions of acetylcholine, as a neuroteratogen (Slikker, Xu, Levin & Slotkin, 2005). The major outcome variables examined in prenatally exposed animals include birth weight, locomotor activity, and cognitive performance.

Birth weight

Similar to results in humans (e.g., Eskenazi, Prehn, & Christianson, 1995; Ricketts et al., 2005), findings in rats consistently show lower birth weight in offspring exposed to prenatal nicotine when compared with nonexposed offspring (see Ernst, Moolchan & Robinson, 2001 for review). Although prenatally exposed mice do not exhibit significantly lower birth weight, pups born to nicotine-administered dams show a significantly slower rate in postnatal weight gain (Ajarem & Ahmad, 1998). These findings are of importance since, in humans, low birth weight has been shown to be associated with long-term cognitive deficits and ADHD (e.g., Botting, Powls, Cooke & Marlow, 1997; Bresleau & Chilcoat, 2000).

Locomotor activity and cognitive function

In general, animal studies tend to show increased locomotor activity in offspring who have been exposed to nicotine prenatally (see Ernst et al., 2001 for review). Studies in rats and mice have reported cognitive impairment, such as attention and memory deficits in various maze tasks, associated with prenatal nicotine exposure (Levin, Briggs, Christopher & Rose, 1993; Liang, Poytress, Chen, Leslie, Weinberger & Metherate, 2006; Martin & Becker, 1971; Paz, Barsness, Martenson, Tanner & Allen., 2006; Peters & Ngan, 1982; Sorenson, Raskin & Suh, 1991; Yanai, Pick, Rogel-Fuchs, Zahalka, 1992). Mild deficits in learning have also been reported in rats (e.g., Liang et al., 2006; Martin & Becker, 1971), mice (e.g., Paz et al., 2006) and guinea pigs (e.g., Johns, Louis, Becker & Means, 1982; Johns, Walters & Zimmerman, 1993). These impairments in attention, memory, and learning are consistent with the cognitive deficits found in children diagnosed with, for example, ADHD (Ernst et al., 2001). It has also been hypothesized that the observed deficits in operant learning found in animals, might translate to, and be associated with, dysfunction in reward or motivational processes, which could also predispose to substance abuse (Ernst et al., 2001).

Hypothesized mode of action (for more detail see Ernst et al., 2001; Slikker et al., 2005; Shea & Steiner, 2008)

Prenatal exposure to nicotine evokes a spectrum of effects by discoordinating the timing of trophic events linked to a subset of cholinergic receptors, specifically nicotinic cholinergic receptors (nAChRs), present very early in the developing brain of rodents (embryonic day 10) and humans (4–5 weeks of gestation) (Hellstrom-Lindahl, Seiger, Kjaeldgaard & Nordberg, 2001; Levin & Slotkin, 1998; Slikker et al., 2005; Slotkin, 1998; Slotkin, 1999; Slotkin, McCook, Lappi & Seidler, 1992; Slotkin, Orband-Miller & Queen, 1987). Once nicotine enters the fetal bloodstream it binds to nAChRs, which are found in the central and peripheral nervous system and can be found both postsynaptically (e.g., acetylcholine neurotransmission) and presynaptically influencing the release of other neurotransmitters (Dani, 2001).

nAChRs are ligand-gated channels including five subunits, usually made of two alpha (a) and three beta (B) subunits. Several nAChR subtypes (or combinations of subunits) exist, each of which has a specific pharmacology, physiology, and anatomical distribution (Pakkanen, Jokitalo & Tuominen, 2005). The two most abundant subtypes in vertebrate brain are: (i) α4, β2 combination, and (ii) α7. The different subtypes have important functional implications, particularly during development, as their relative distribution in the brain varies with developmental stage and age (Ernst et al., 2001). nAChRs are significantly involved in brain development via promotion of cell division during gastrulation and subsequent promotion of the switch from cell replication to cell differentiation in terminal neuronal differentiation (Shea & Steiner, 2008). The presence of these receptors in early embryogenesis (Hagino & Lee, 1985) suggests that nicotinic signaling may be an important part of neural development. Reported changes in receptor density during normal development (e.g., high levels found at early gestation) might also imply windows of vulnerability to exogenous nicotine. In humans, periods of high density have been found in the frontal cortex, hippocampus, cerebellum, and brainstem during mid-gestation and neonatal periods (Hellstrom-Lindahl, Gorbounova, Seiger, Mousavi & Nordberg., 1998; Hellstrom-Lindahl et al, 2001; Huizink & Mulder, 2006).

In the rat (e.g., Slotkin et al., 1987), and to a lesser extent in the mouse (Van de Kamp & Collins, 1994), binding to the nAChR during development, whether during prenatal or early postnatal stages, is a necessary and key step leading to the adverse effects of nicotine. Several studies indicate that chronic prenatal nicotine exposure in rats and mice results in increased receptor density of fetal and neonatal cerebral nAChRs (for example, Slotkin, 1998; Van de Kamp & Collins, 1994). Upregulation of the nAChRs during development is conclusive evidence that the cell has experienced chronic nicotinic stimulation. The long-term effects of this up-regulation remain unclear (Ernst et al., 2001); although the proposed mode of action suggests that this stimulation results in premature onset of cell differentiation, at the expense of replication, leading to (i) brain cell death, (ii) structural changes in regional brain areas, and (iii) altered neurotransmitter systems (i.e., acetylcholine, norephinephrine, epinephrine, dopamine, serotonin, as well as glutamate and gamma-aminobutyric acid; Shea & Steiner, 2008; Slikker et al., 2005). Such alterations could translate to physical deficits, such as impaired cardiac function associated with hypoxia, as well as deficits in later learning, memory, behavior, and development. Differences in developmental profiles of receptor binding between species and strains suggest that genetic factors regulate the maturation of the nicotinic receptor (Van de Kamp & Collins, 1994). These genetic factors may explain interindividual differences in sensitivity to the effects of in utero exposure to nicotine (Ernst et al., 2001).

There is no question that animal work is vital to the study of human problems; however the rat brain, for example, is obviously different from the human brain. Effects of MSDP in

humans, for example, often show up in higher-level cognitive (executive) function, which are controlled by the prefrontal cortex. Functional and structural differences in the region of rat brain traditionally considered homologous to the dorsolateral prefrontal cortex in primates suggest that the rat may not have an equivalent region (Preuss, 1995). Moreover, in humans, MSDP results in fetal exposure not only to nicotine, but to a large amount of other toxic components, such as carbon monoxide, ammonia, nitrogen oxide, lead, and other metals (Huizink & Mulder, 2006). Thus, one should not limit the effects of MSDP in humans to nicotine alone. Importantly, while we can use the evidence of negative effects of prenatal nicotine exposure that we garner from animal work as a guide to narrow our focus on potential effects in humans, we cannot directly extrapolate from animal findings to the complex human condition.

Maternal smoking during pregnancy: A more complicated story

As suggested earlier, the evidence for deleterious effects of MSDP on behavior and cognition later in life in human studies is muddied in the existing literature due to the inability to separate these effects from other confounding environmental and genetic factors. In a methodological review of the literature on effects of MSDP, Ramsay and Reynolds (2000) suggest that women who smoke during pregnancy may possess a constellation of personality traits that distinguishes them from other women. They focus on traits such as (i) increased depression and thus decreased motivation to quit smoking during pregnancy (Depression-Compulsivity model), (ii) elevated antisocial traits and thus reduced awareness of their consequences of MSDP as well as reduced concern for others (Antisocial model), and (iii) reduced attention to her own and, by extension, her infant's nutrition and general well-being (Self-Care model). Thus, the personality of pregnant smokers may reflect a familial vulnerability for later disorders. Ernst and colleagues (2001) go on to outline numerous potential confounds, which include those suggested by Ramsay and Reynolds (2000), as well as others: (1) parental characteristics: including IQ, psychiatric history (e.g., ADHD, antisocial personality disorder, substance abuse) and parenting; (2) maternal characteristics (e.g. health, height and weight (affecting metabolism of tobacco by-products)); and (3) smoking characteristics: intensity, gestational age at consumption (Ernst et al., 2001). Importantly, a number of these confounds can be controlled for via alternative genetically sensitive designs. However, there is a surprising lack of comprehensive examination of the effects of MSDP within a genetically-informative framework. Specifically, the joint roles of environmental factors (e.g., MSDP) and genetic transmission in the risk for deficits, such as behavioral, learning, and cognitive dysfunction, are downplayed and there is a lack of control for differences between women who smoke during pregnancy and those who do not.

Neurobehavioral and cognitive effects of MSDP in humans

The offspring outcomes associated with MSDP cover broad cognitive and behavioral domains and are outlined thoroughly in several well laid-out and comprehensive reviews of the effects of MSDP (see Cnattingius, 2004; Ernst et al., 2001; Huizink & Mulder, 2006; Linnet et al., 2003; Shea & Steiner, 2008). These reviews are presented primarily from the phenotypic association point of view and say very little about how genetic factors may influence the reported associations between MSDP and offspring outcome. The main points of these reviews are presented briefly in this section, along with results from a few recent studies. The scope of results concerning the negative impact of MSDP, both suggestive and inconclusive, are presented. What is clear from these reviews is the need for more comprehensive study design as well as the lack of genetically informed studies on MSDP. The few studies that have considered genetic effects are reviewed in the final section of this report.

Pregnancy and birth outcomes

Epidemiological evidence from prospective and case-control studies show relatively high consistency for the association of adverse pregnancy outcomes (i.e., fetal growth restriction, hypoxia and placental effects, stillbirth, sudden infant death syndrome, etc) with MSDP (see Cnattingius, 2004 for detailed review ; Ernst et al., 2001); however, neurobehavioral outcomes have shown less consistency, indicating the potential need for more sensitive sampling designs and strategies.

MSDP is reported to increase rates of spontaneous abortion, stillbirth, sudden infant death syndrome, cleft palate, and most relevant to long-term neurobehavioral effects, preterm birth and low birth weight (Bada et al., 2005; Conter, Cortinovis, Rogari & Riva, 1995; DiFranza & Lew, 1985; D'Onofrio et al, 2003; Ernst et al., 2001; Knopik et al., 2005; Kyrklund-Blomberg, Granath & Cnattinguis, 2005; Levin & Slotkin, 1998; Meyer, Williams, Hernandez-Diaz & Cnattinguis, 2004; Salihu, Aliyu & Kirby, 2006; Salihu et al., 2008; Sastry, 1991). Recent evidence also suggests that offspring of nonsmokers who used nicotine substitutes during pregnancy are at increased risk for congenital malformations (Morales-Suarez-Varela, Bille, Christiansen & Olson, 2006).

These outcomes reported to be associated with prenatal exposure may be indirect or direct toxic consequences of MSDP. Nicotine produces anorexigenic, hypoxic, vascular, and placental effects that can adversely affect fetal development (Cnattingius, 2004; Ernst et al., 2001). Existing theories focus on (i) maternal and fetal undernutrition due to the acute anorexigen effects of tobacco smoking (Davies & Abernethy, 1976; Perkins, Sexton, DiMarco & Fonte, 1994); (ii) intrauterine hypoxia secondary to increased carbon monoxide and dioxide, reduced blood flow, and inhibition of respiratory enzymes (Abel, 1980, 1984; Byrd & Howard, 1995); (iii) disruption of the function of the placenta (Huizink & Mulder, 2006; Naeye, 1978; Sastry, 1991; Suzuki, Minei & Johnson, 1980) via nicotinic activation of placental cholinergic systems which depresses transplacental amino acid transport, which may contribute to intrauterine growth retardation (Cnattingius, 2004; Ernst et al., 2001). Thus, prenatal exposure may have direct teratogenic effects on the fetus leading to more readily observed adverse phenotypes; however, these effects most likely depend on the specific outcome measure of interest (D'Onofrio et al., 2003).

Infant and Toddler outcomes

The evidence for effects of MSDP on infant and toddler outcomes has been overall, inconsistent, perhaps due to the possibility that a certain level of brain maturation needs to be achieved before deficits become detectable (Ernst et al., 2001; Huizink & Mulder, 2006). The inconsistency may also be due to less sensitive assessment tools for this age group. Data showing negative effects of MSDP suggest deficits in speech processing ability (Key, Ferguson, Molfese, Peach, Lehman & Molfese, 2006), decreased scores in motor ability and verbal comprehension (Gusella & Fried, 1984), reduced auditory acuity (Saxton, 1978), increased hypotonicity, heightened tremors and startles (Fried & Makin, 1987), and negative affect (Brook, Brook & Whiteman, 2000) among infants who were prenatally exposed to nicotine. Since it has been shown that adverse birth outcome, such as preterm birth, is related to neurologic and developmental disabilities during the first two years of life (Marlow, Wolke, Bracewell, Samara & EPI Cure Study Group, 2005), a recent study (Law, Stroud, LaGasse, Niaura, Liu & Lester, 2003) adjusted their findings for factors relating to birth outcome and still found that newborns exposed to MSDP were more excitable and hypotonic and showed more stress/abstinence signs on a standard neurobehavioral assessment. Not all studies have found significantly negative relationships however. For instance, Obel, Henriksen, Hedegaard, Secher, and Ostergaard (1998) found mixed results when comparing babbling abilities in prenatally exposed 8-month olds to controls. When

comparing nonbabblers to di- and polysyllable babblers, a trend toward a dose-response effect of MSDP was found, with those children exposed to more cigarettes per day showing less babbling ability. However, this trend was nonsignificant when comparing nonpolysyllable babblers to polysyllable babblers. Baghurst, Tong, Woodward, and McMichael (1992) also found no evidence for differences in verbal, perceptual, and motor scores due to prenatal exposure once adjusting for social class, home environment, and mother's intelligence. Together, these findings suggest the *possibility* that MSDP is associated with motor, sensory, and cognitive deficits in infants and toddlers, which may indicate a pervasive toxic effect on early neurodevelopment.

Childhood outcomes

Findings in children also seem to support a negative influence of in utero exposure to smoking on behavior and cognitive function; however, there are again some inconsistencies. MSDP has been associated with a significant increase in externalizing (e.g., oppositional, aggressive, overactive) scores but not internalizing behavior (Brook, Zhang, Rosenberg & Brook, 2006; Day, Richardson, Goldschmidt & Cornelius, 2000; Orlebeke, Knol, & Verhulst 1999). Cognitive function has also been shown to be negatively affected by MSDP, with deficits in sustained attention (Fried, O'Connell & Watkinson., 1992a), response inhibition, memory, and impulsivity, overall cognitive function, receptive language (Fried, Watkinson & Gray, 1992b), verbal learning and design memory (Cornelius, Ryan, Day, Goldschmidt & Willford, 2001), problem solving (Cornelius et al., 2001), speech and language (Makin, Fried, & Watkinson, 1991), school performance (Lambe, Hultman, Torrang, MacCabe & Cnattinguis, 2006), and auditory processing (McCartney, Fried & Watkinson, 1994). Dose-response relationships, in which the smoking-related relative risk increases with amount smoked, have also been reported for general cognitive ability (Sexton, Fox & Hebel, 1990), arithmetic, and spelling (Batstra, Hadders-Algra & Neeleman, 2003), suggesting the presence of vulnerable periods during fetal development (Ernst et al., 2001).

As with infant and toddler outcomes however, some negative findings are also reported. For example, Bauman, Flewelling and LaPrelle (1991) reported that scores on receptive language and matrices tasks of more than 3000 9–11 yr olds exposed to MSDP but whose mothers quit afterwards, were similar to those of children not exposed to MSDP; however, both of these groups performed better than children exposed to *both* MSDP and smoking after pregnancy, suggesting the importance of also considering postnatal environment. No clear relationship was observed for MSDP and receptive language scores at 5 yrs or at 15–17 yrs. Eskanazi and Trupin (1995) also found no dose-response relationship of MSDP during the third trimester and cognitive performance in 5 yr olds. Moreover, despite findings of adverse effects of MSDP on school performance using a between family analysis (Lambe et al., 2006), a within-sibling comparison of siblings exposed to differential amounts of MSDP (an example of a case-crossover design which is detailed below) indicated that if a mother had smoked during either pregnancy, both siblings were at increased risk of poor school performance (Lambe et al., 2006); results suggesting that observed associations between MSDP and poor cognitive performance might not be causal.

In one of the most comprehensive analyses to date, D'Onofrio and colleagues (2008) analyzed data from the National Longitudinal Survey of Youth (NLSY), with particular attention to controlling for differences between women who do and do not smoke during pregnancy. They focused their efforts on the association between MSDP and offspring externalizing behavior [conduct (CP), oppositional defiant (ODP), attention deficit hyperactivity (ADHP) problems]. Their comparisons of unrelated children were consistent with the results of previous studies (Wakschlag, Pickett, Cook, Benowitz & Leventhal, 2002) in several respects: (a) CP, ODP, and ADHP were significantly associated with

MSDP; (b) each association followed a dose-response relationship; (c) the number of CP demonstrated by children exposed to MSDP was higher for males; and (d) each association remained significant after statistically controlling for associated maternal characteristics. In addition to the use of statistical covariates used in previous studies, D'Onofrio et al. (2008) utilized the clustered nature of NLSY data to account for unmeasured confounds. The hypothesis was that if MSDP caused higher externalizing, the relation would have been evident both when comparing related (e.g. within mothers) and unrelated children (e.g., Rodgers, Cleveland, van den Oord & Rowe, 2000). However, similar to Lambe et al. (2006), when siblings who differed in exposure to MSDP (i.e., none/some vs. more exposure, *a broad definition of discordance for MSDP*) were compared, the offspring did not differ significantly with respect to CP or ODP. These results suggest that previous studies found a relationship between MSDP and offspring CP not because MSDP causes increased risk for CP or ODP, but because environmental influences that vary between families confound associations between MSDP and offspring externalizing (D'Onofrio et al., 2008). This finding is consistent with studies that have included more precise measurement of adult characteristics that may confound the relation, such as maternal *and* paternal antisocial characteristics (Maughan, Taylor, Caspi, & Moffitt, 2004) and maternal delinquency during adolescence (Silberg et al., 2003). It is also generally supportive of a recent children-of-twins study of maternal alcohol use disorder, MSDP and ADHD (Knopik et al., 2006; detailed below).

Adolescent and adult outcomes

Overall, it seems that behavioral and cognitive deficits associated with MSDP continue into late childhood and early adolescence and lead to increased risk for ADHD and Conduct Disorder (CD). MSDP has been associated with ADHD, CD, criminality and substance use (particularly smoking) in adolescence (Ernst et al., 2001). Milberger and colleagues (1996, 1997, 1998) investigated MSDP as a risk factor for ADHD and found that 22% of children with ADHD had a history of MSDP, compared with 8% of controls. Significantly lower IQ scores were also found in children exposed to MSDP versus those who were not exposed (Milberger, Biederman, Faraone & Jones 1998). Wakschlag and colleagues (1997, 2001, 2002) have consistently shown that MSDP is a robust, independent risk-factor for CD in males. Weissman, Warner, Wickramaratne and Kandel (1999) report similar findings reporting 4-fold increases in CD rates and 5-fold increases in adolescent drug abuse in children exposed to MSDP. Cornelius, Leech, Goldschmidt and Day (2000) and Buka, Shenassa and Niaura (2003) found increased risk for early tobacco experimentation and nicotine dependence, respectively, in children exposed to MSDP. Fergusson, Woodward and Horwood (1998) also suggested that MSDP contributes to children's risk of later externalizing problems. Children exposed to MSDP had higher psychiatric symptom rate for CD, alcohol abuse, substance abuse, and depression compared with unexposed children. These childhood associations also appear to carry into adulthood. For example, Brennan, Grekin and Mednick (1999) and Rasanen et al. (1999) found relationships between MSDP and later criminality in male offspring up to age 28 and Mortensen, Michaelsen, Sanders and Reinisch (2005) reported a dose-response relationship between MSDP and adult intelligence.

Summary of MSDP in humans—MSDP is associated with offspring behavioral abnormalities, including increased evidence of attentional deficits, impaired learning and memory, lowered IQ, cognitive dysfunction, later childhood conduct problems, substance use, and early adult criminality; however, not all studies have reported a significantly negative relationship between MSDP and offspring outcomes.

What is clear from these reviews, however, is the need for more comprehensive study design in the study of MSDP. In short, there are a paucity of studies investigating gene-environment interplay in the proposed associations between MSDP and subsequent child outcomes. A key approach is to use a combination of strategies, such as twin, children-of-twin, and sibling-control designs, emphasizing both behavioral and molecular genetic methods, to elucidate the likely complex factors contributing to the association between MSDP and child outcomes. Preliminary findings from this work in the area of child externalizing problems (Maughan et al., 2004; Knopik et al., 2006; D'Onofrio et al, 2008) indicate that, once genetic and environmental effects are accounted for, MSDP accounts for a much smaller effect than proposed by existing literature; however, while the effects were smaller, MSDP continued to be significantly linked to childhood behavior. Such results suggest that MSDP is unlikely to be a unique cause of early childhood behavior problems and illustrate the need for comprehensive study design.

Comprehensive study design – things to consider

The idea of joint roles of genetic and environmental factors can be referred to as gene-environment interplay. This is a broad term that encompasses several different concepts with different meanings and interpretations (see Rutter, Moffitt & Caspi, 2006 for detailed review). While a thorough and comprehensive review of gene-environment interplay is beyond the scope of this report, we will focus briefly on gene-environment interaction (G×E) and gene by environment correlation (rGE). G×E occurs when the effect of environmental exposure is conditional on a person's genotype (Moffitt, Caspi & Rutter, 2005). An example of G×E is phenylketonuria (PKU), a genetic disorder characterized by deficiency of the enzyme phenylalanine hydroxylase. Children who are homozygous (carry two copies) for a certain form of the phenylalanine hydrolylase gene are deficient in phenylalanine hydroxylase and cannot metabolize phenylalanine in food. Thus, phenylalanine accumulates and damages the developing brain. Phenylalanine has no harmful effects on other children who do not carry this particular genotype. However, PKU is one of the few genetic diseases that can be controlled by diet (an example of an environmental influence). A diet low in phenylalanine can be very effective treatment, yet this low phenylalanine diet has no harmful or beneficial effect on other children. Perhaps the most well-known example of G×E in the development of psychiatric disorders was reported by Caspi et al. (2002) who found that a functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) was found to moderate the effect of maltreatment, such that maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems. These findings provided the basis for a growing literature suggesting that genotypes can moderate children's sensitivity to environmental insults.

rGE can be thought of as genetic control of exposure to the environment or, in other words, an individuals genotype influences the probability of exposure to certain environments (Caspi & Moffit, 2006; D'Onofrio et al., 2003; Jaffee & Price, 2007; Kendler & Eaves, 1986). rGE has been described as passive, active or evocative (see Jaffee & Price, 2007, for a full review). (i) *Passive* gene-environment correlation refers to the association between the genotype a child inherits from her parents and the environment in which the child is raised. Parents create a home environment that is influenced by their own heritable characteristics. (ii) *Evocative* (or reactive) gene-environment correlation happens when individuals are reacted to based on their genetic propensities or, in other words, an individual's (heritable) behavior evokes an environmental response (see Burt, 2008). (iii) *Active* gene-environment correlation occurs when an individual seeks out or creates certain environments based on their genetic propensity. rGE results in "the contamination of measures of environmental

exposure with genetic variation and thus clouds interpretation of results" (Caspi & Moffitt, 2006, p.587).

One of the main limitations of studying familial and environmental influence and child development is that the parents are providing both the environment and the genes to their offspring (D'Onofrio et al., 2003). In addition to prenatal environment, separate consideration should also be given to environmental exposure to second-hand smoke (see Eskenazi & Castorina, 1999 for review) since children born to smoking mothers are more likely to be exposed to environmental tobacco smoke (Key et al., 2006), which could increase risk of developmental deficits (Yolton, Dietrich, Auinger, Lanphear & Hornung, 2005). Most studies that have considered prenatal nicotine exposure have considered latent genetic variables or have examined the presence of measured G×E by focusing on the dopaminergic system and genes involved in the metabolism of tobacco by-products. These few studies are included in the review below.

Adoption studies

At the time of this report, there have been no adoption studies that have specifically considered maternal smoking during pregnancy; however, two studies outlined in this section have considered prenatal drug exposure more generally (Crea, Barth, Guo & Brooks, 2008; Neiderhiser et al., 2007). The lack of adoption studies in this arena does not preclude the potential importance of this design for MSDP. Adoption designs provide a direct way to disentangle genetic and environmental sources of variation. Adoption creates pairs of genetically related individuals who do not share a common family environment (and/or prenatal environment; i.e., biological siblings adopted apart and raised in different homes) and also creates family members who share family environment but who are not genetically related (i.e., non-biologically related children adopted into the same adoptive home). In both situations, any resemblance estimates the contributions of the family environment. A strong suit of the adoption design is the ability to study gene by environment interaction and additional processes through which gene-environment correlation creates the covariance between parents and children (D'Onofrio et al., 2003). However, the adoption design does suffer from certain limitations. First, due to highly selective placement ensuring that the adoptive environment is excellent, there is an inherent difficulty in obtaining samples of children who are exposed to high-risk environments. Moreover, an assumption of this design is that there are no negative consequences of being adopted and that environmental processes operate similarly in adoptive and nonadoptive families (D'Onofrio et al., 2003). Such an assumption is not needed in other genetically sensitive designs.

Crea et al (2008) did not focus on disentangling genetic and environmental influences on behavior per se, but rather examined behavioral trajectories for substance exposed adopted children, fourteen years after adoption. They found that prenatal exposure predicted elevated behavior problems but only slightly higher than those of nonexposed adopted counterparts. The overall rate of change in behavioral problems did not differ between exposed and nonexposed groups. This finding contradicts the argument that substance exposure alone is responsible for triggering a cascade of negative sequelae and encourages the investigation of protective familial environmental factors (e.g., positive rearing environment) that buffer the impact of this exposure (Crea et al., 2008).

In a recent analysis of a sample from the Early Growth and Development Study (Leve et al., 2007), Neiderhiser et al. (2007) examined 350 'yoked' birth mothers, adopted children and adopted parents and 104 birth fathers. The focus was on toddler temperament and behavior problems at 18 months. The authors reported preliminary results suggesting that high levels of prenatal drug use significantly contributed to suppressed toddler affect and effects of genetic risk operated only via prenatal drug exposure (Neiderhiser et al., 2007). Future

planned work to extend these analyses in order to facilitate the disaggregation of prenatal exposure, genes (via DNA collection), as well as postnatal rearing environment will lend considerable and potentially important information to the effort to elucidate these complex relationships (Leve et al., 2007).

Twin studies and their extensions

The twin method compares the similarity between identical (monozygotic or MZ) twins and fraternal (dizygotic or DZ) twins (see Plomin, DeFries, McClearn & McGuffin, 2008 for details). If a trait is genetically influenced, MZ twins will be more similar than DZ twins; however, it is also possible that this greater similarity is due to environmental rather than genetic factors. This design can offer considerable knowledge in the genetic etiology of, not only outcomes of interest (e.g., ADHD or cognitive ability), but also risk factors (e.g., MSDP; see Agrawal et al., 2008 for genetic etiology of MSDP; D'Onofrio et al, 2003, 2008;). It can also determine whether genetic effects differ in two environments; however, the models may only partially control for genetic factors since they assume that the specified environments represent 'true' or 'pure' environmental risk factors which are free from genetic influences (i.e., that there is no gene-environment correlation; Caspi, Taylor, Moffitt & Plomin, 2000; D'Onofrio et al., 2003; Purcell & Koenen, 2005). Classical twin studies, even those that add explicit measures of the environment, are also not able to delineate the processes involved in intergenerational processes (D'Onofrio et al., 2003).

Four recent studies have tested the association between MSDP and ADHD or conduct problems/antisocial behavior within a twin design (Button, Thapar & McGuffin, 2005; Knopik et al., 2005; Maughan et al., 2004; Thapar et al., 2003). As discussed in this section, using a twin design allows the genetic effects that contribute to the outcomes in children to be estimated (see Purcell & Koenen, 2005 for details on limitations involving environmental mediation in the classical twin study). In an examination of conduct problems in 5–7 year old twins, Maughan et al. (2004) report that, once genetic and environmental risks were controlled for, the effects of MSDP were substantially reduced. Thapar et al (2003) found that, in addition to substantial genetic influences on ADHD symptoms, MSDP explains additional variance above and beyond genetic effects. Button et al. (2005) report similar results when considering the covariation between antisocial behavior and ADHD stating that MSDP contributes small but significant amounts to the variance of both phenotypes. Knopik et al. (2005) suggest that prenatal and parental risk factors (e.g., maternal and paternal psychopathology) combine additively with the important genetic risk of developing ADHD, rather than interactively (i.e., no significant findings for G×E interaction). Thus, in summary it appears that, while genetic influences on these ADHD phenotypes are important, MSDP also has an independent effect on ADHD.

An extension of the classical twin study is the bivariate twin study that investigates the relationship between an environmental risk factor (considered as a phenotype) and an outcome of interest. A limitation of this extension is that the bivariate design cannot study all of the possible environmental risk factors that are involved in developmental psychology because the model can only include environments for which twins can differ (i.e., individual-specific environment; Purcell & Koenen, 2005). Thus, in the case of exposure to smoking during pregnancy (i.e., an obligatory shared environment in twin offspring exposed prenatally; Purcell & Koenen, 2005), this is a design that cannot be used. However, if one is considering the etiology of the behavior of smoking during pregnancy (i.e., twin mothers who can differ in their smoking behaviors), this design can be used to determine the covariation of MSDP and another outcome of interest. For example, Agrawal et al (2008) considered the genetic covariation of maternal smoking during pregnancy and nicotine dependence. Results indicated that women who smoked during an entire pregnancy reported heavier dependence and more unsuccessful quit attempts, compared with a community

sample of mothers and with women who smoked during only part of a pregnancy. Educational attainment, weekly church attendance, spousal current smoking, and nicotine dependence also were associated with MSDP. The authors also found that heritable influences, even after adjustment for the above-stated significant psychiatric and sociodemographic covariates, explain nearly half of the variation in MSDP, with the remainder of the variance being due to environmental factors not shared by members of a twin pair. A large proportion of the genetic influences on MSDP were shared with nicotine dependence. These results, though not focused on childhood outcomes of MSDP, do have strong implications for treatment and intervention, in that a lifetime history of difficulty with smoking cessation, in conjunction with social background and psychiatric comorbidity, especially during pregnancy, needs to be considered by treatment providers when counseling expectant mothers about the potential risks of MSDP.

Another expansion of the classical twin study incorporates assessment of the twins' parents. This design has the ability to estimate environmental effects while controlling for genetic effects on both parents and children (D'Onofrio et al., 2003; Rutter et al., 1997). Limitations exist, as outlined in Rutter, Pickles, Murray, and Eaves (2001). Specifically, the twin-family design requires identical measures for parents and children and also assumes that the same genetic and environmental structure influences both generations (D'Onofrio et al., 2003).

Children-of-twins

The Children-of-Twins (COT) design can begin to elucidate the role that specific environments (such as prenatal exposure) play in the etiology of psychological and behavioral phenomena (D'Onofrio et al., 2003), while studying intergenerational associations with fewer assumptions than the twin-family design. In the case of prenatal exposure, it allows one to begin to disentangle genetic, prenatal exposure, and other environmental effects on offspring outcomes. It also offers the additional advantage of including offspring sibling pairs that may differ in their amounts and/or timing of prenatal exposure (an obligatory shared environment in classical twin studies).

There are several approaches within this design: (i) children of discordant twins, which essentially involves (a) a comparison between the children of affected and unaffected MZ twins, and (b) a subsequent comparison of the rates of the disorder in children of the unaffected MZ and DZ cotwins; (ii) the MZ half-sib design (Nance, 1976; Nance & Corey, 1976; Nance, Corey, & Boughman, 1978) which is a nested analysis of variance approach to the study of offspring of MZ twin pairs; (iii) a structural equation model fitting approach as outlined in D'Onofrio et al. (2003) which is a variation on the twin-family study and examines (a) within-generation, (b) cross-generation, same-family, and (c) cross-generation, cross-family correlations; and (iv) inferring genetic and environmental risk on offspring outcome from the co-twin's (parental) history of the phenotype of interest (Jacob et al., 2003; Knopik et al., 2006).

The COT design (see Jacob et al., 2003 for general discussion of the method) has been used less often in behavioral genetic studies, and has just recently been expanded to not only assess the potentially complex relationship between parental psychopathology (such as substance dependence) and child behavior, but to also consider the role of prenatal exposure in intergenerational associations (D'Onofrio et al., 2003; Knopik et al., 2006). For example, in an attempt to understand the underlying processes associated with MSDP, D'Onofrio et al (2003) used the structural equation model approach within a COT sample to move beyond the straight phenotypic association between MSDP and birth weight. Their results suggested that MSDP appears to have a specific environmental association with offspring birth weight with no apparent confounding by genetic factors, common environment, or other measured covariates (D'Onofrio et al., 2003).

Given evidence that mothers who abuse alcohol, who are alcohol dependent, or who have an alcohol dependent partner are more likely to smoke or drink during pregnancy (e.g., Knopik et al., 2005), Knopik et al (2006) used the COT design to examine the relationship between maternal psychopathology (specifically alcohol use disorder, AUD), MSDP, and child ADHD. This approach provides a powerful pseudo-adoption design in which genetic and environmental risk status is inferred from the co-twin's history of, in this case, AUD. Importantly, children raised by an AUD monozygotic (MZ) or dizygotic (DZ) twin parent are at high risk for psychiatric disorders (e.g., ADHD) and other health problems because of high genetic and high environmental risk. In contrast, children raised by a non-AUD twin of an AUD MZ co-twin are at reduced environmental risk because they have not grown up with a mother with AUD, but these children are at the same (high) genetic risk as children raised by an AUD twin because the mothers have identical genotypes. In turn, children raised by the non-AUD twin of an AUD DZ co-twin are also at reduced (low) environmental risk but at only intermediate genetic risk because DZ twin pairs share on average 50% of their genes.

Thus, in the absence of any environmental effect of maternal AUD, after controlling statistically for psychopathology in the biological parents, the child of an AUD mother should be no more likely to develop ADHD than the child of a non-AUD parent who is the MZ co-twin of an AUD individual. Excess rates of ADHD in children of AUD mothers, after controlling for comorbid psychiatric disorders and pertinent variables, would imply an environmental impact of maternal AUD. Therefore, the COT design is a powerful design to disentangle the genetic and environmental effects on the association between maternal (or paternal) psychopathology and offspring outcome, while also estimating direct effects of measured environmental variables, such as prenatal exposure.

These data (Knopik et al., 2006) yielded a pattern of results consistent with a genetic contribution to the association between maternal AUD and increased offspring risk of ADHD, but also reaffirmed the potential importance of MSDP. Compared to controls, rates of offspring ADHD were significantly elevated not only in families where the mother had a history of AUD, but also in families where the mother had no history of AUD, but had a monozygotic twin sister with AUD. In addition, rates of maternal regular smoking, and maternal regular smoking during pregnancy, were significantly elevated in those mothers who had a history of AUD, and in mothers who were unaffected, but had an affected monozygotic cotwin. This is consistent with a strong genetic correlation between alcoholism and smoking that has been found in other research, and implies a potential confounding of MSDP and genetic risk of alcoholism. Thus, genetic transmission and effects of MSDP are partially confounded. Models predicting ADHD outcome from family risk (of AUD) status, as well as other maternal and paternal psychopathology, indicated that even when maternal genetic risk of AUD and maternal regular smoking were controlled for, heavy MSDP remained a significant and strong predictor of offspring ADHD risk. Thus, while MSDP is likely contributing to the association between maternal AUD and offspring ADHD, the evidence for a significant genetic correlation suggests: (i) pleiotropic genetic effects, with some genes that influence risk of AUD also influencing vulnerability to ADHD; or (ii) ADHD is a direct risk-factor for AUD (Knopik et al., 2006). Thus, these results from the COT design (D'Onofrio et al., 2003; Knopik et al., 2006) yielded a pattern of results consistent MSDP having an independent effect on offspring outcomes even after controlling for potential confounders (e.g., genetic transmission, other environmental factors, and other covariates). The ability to begin to disentangle genetic and environmental intergenerational transmission in the domain of MSDP is critical for understanding the magnitude of risk that MSDP carries as this can have real implications for future research, intervention, and prevention efforts.

Cotwin-control

The cotwin-control design is a modification of the traditional case-control design where data is considered from twin pairs that are discordant for (i) the outcome of interest (e.g., ADHD), (ii) a variable related to the outcome of interest (e.g., schizophrenia in a model examining cognitive ability, see Kremen et al., 2006; early cannabis use in a model examining drug use as in Lynskey et al., 2003), or (iii) a environmental measure. The design controls for effects of age, gestational influences, and genetic factors (D'Onofrio et al., 2003). It can also control for many environmental factors; however, similar to twin studies and as pointed out in D'Onofrio et al. (2003), it is limited by methodological problems that prohibit the examination of many environmental risk factors that are commonly examined in epidemiological studies such as divorce, parenting practices, parental psychopathology, and MSDP (see D'Onofrio et al., 2003 for detail). The difficulties also lie in finding large enough samples of twins that are discordant for salient environmental factors that are under consideration. Thus, there is typically not enough power to draw definitive and meaningful conclusions (D'Onofrio et al., 2003; Kendler & Gardner, 2001).

Case-crossover design

A variation on the cotwin-control study is the case-crossover design (or within-mother between-pregnancy design) which examines siblings discordant for prenatal exposure to MSDP. A form of this design was used in two studies discussed earlier in this report which compared siblings exposed to a broad definition of differential amounts of prenatal smoking (more vs less; D'Onofrio et al., 2008; Lambe et al., 2006). Meyer et al (2004) also used a case-crossover approach to examine the effects of MSDP on risk of oral cleft; however, their cases were those with cleft lip with or without cleft palate rather than defined by exposure to MSDP. More recently, Salihu et al. (2008) examined MSDP and risk of stillbirth using case-control and case-crossover designs. Similar to Meyer et al (2004), case status was not defined by MSDP but rather as a stillbirth with controls being defined as live births (Salihu et al., 2008).

In general, this method provides statistical control for confounding factors (e.g., heritable and sociodemographic characteristics of the mother that predict increased probability of MSDP) that might otherwise artifactually create, or alternatively mask, an association between MSDP and child outcomes. Moreover, this design, in combination with molecular genetic information (see examples below), could offer substantial information to the delineation of genetic and environmental factors in the relationship between MSDP and child outcomes. There are potential limitations of this case-crossover design, e.g., (i) mothers who are able to quit in one pregnancy but not all, may be, on average, less nicotine dependent and therefore smoke less than mothers who are unable to quit; (ii) smoking during pregnancy may be secondary to other life stressors that were present during pregnancy and these life events may not be readily captured during assessment (particularly if retrospective reporting is used); (iii) there may be a selection bias if more women give up rather than initiate smoking during the reproductive years (Meyer et al., 2004); (iv) MSDP tends to be highly correlated in sequential pregnancies introducing possible bias due to autocorrelation (Levy, Lumley, Sheppard, Kaufman, & Checkoway, 2001; Mittleman, Maclure, & Robins, 1995); and (v) the prevalence of smoking during pregnancy has, in general, declined over time (CDC, 2004) which could affect results. Some of these limitations can be overcome with the use of bi-directional case-crossover designs, where controls (nonexposed siblings) are chosen from both sides of the exposed pregnancy (e.g., Lumley & Levy, 2000; Meyer et al., 2004). To control for exposure trends, a case-time-control design can also be used in conjunction with the case-crossover design (see Meyer et al., 2004). The case-time-control design estimates an exposure trend by explicitly matching cases with controls. This exposure trend is then used to adjust the case-crossover estimates

by the trend estimate. There is also the issue of identifying such samples and acquiring large enough samples to make meaningful conclusions. Despite these limitations, this case-crossover design in combination with molecular genetic information holds promise in the study of adverse effects of MSDP.

Molecular genetic studies

Earlier it was suggested that prenatal exposure may have direct teratogenic effects on the fetus leading to more readily observed adverse phenotypes; however, these effects most likely depend on the specific outcome measure of interest. In fact, the effect of MSDP on the fetus may also interact with other factors, such as genetic factors. In an investigation of gene-environment interaction (G×E), Wang and colleagues (2002) investigated the modifying role of two maternal xenobiotic [i.e., corresponding to a chemical compound (such as a drug, pesticide, or carcinogen) that is foreign to a living organism] metabolism genes (CYP1A1 and GSTT1) in the association between MSDP and infant birth weight. Their research was prompted by the fact that tobacco smoke contains approximately 4000 compounds (Brunnemann & Hoffmann, 1991); the most important carcinogens in tobacco smoke are polycyclic aromatic hydrocarbons (PAHs), arylmines, and N-nitrosamines (Bartsch et al, 2000). The ability of an individual to convert toxic metabolites of cigarette smoke to less harmful ones is important for minimizing other adverse health effects. As outlined in Wang et al. (2002), the metabolic processing of PAH (for example) in humans occurs in two phases. The phase 1 metabolism is an activation process, in which the inhaled, hydrophobic PAHs are converted mainly through aryl hydrocarbon hydroxylase activity into hydrophilic, reactive, electrophilic intermediates that can bind covalently to macromolecules, especially DNA (National Research Council, 1983). These intermediates may be more toxic than the original form. Aryl hydrocarbon hydroxylase, encoded by the CYP1A1 gene, is a phase 1 enzyme and is particularly relevant to the metabolism of cigarette smoke. The phase 2 metabolism is a detoxification process, in which these metabolic intermediates are detoxified by enzymes such as glutathione S-transferases (GSTs) or uridine diphosphate (UDP)-glucuronosyltransferase through transformation into conjugated forms that are sufficiently polar to be excreted from the body (Timbrell, 1991). GSTT1, encoded by the GSTT1 gene, is a major phase 2 enzyme. Both CYP1A1 and GSTT1 are highly polymorphic (Ishibe et al., 1997; Nelson et al., 1995; Xu, Kelsey, Wiencke, Wain & Christiani, 1996) and their polymorphisms have been associated with their encoded enzyme activities (Kawaijiri et al., 1990; Wiencke, Pemble, Ketterer & Kelsey, 1995). Wang et al. (2002) found that, when considering the CYP1A1 genotype (i.e., the combination of alleles for the CYP1A1 gene), increased reduction in infant birth weight was seen in children born to mothers with the Aa/aa genotype (OR=3.2, 95% CI=1.6–6.4). When the GSTT1 genotype was considered, there was increased reduction in birth weight (OR=3.5, 95% CI=1.5–8.3) in children born to mothers with the absent genotype group. When both CYP1A1 and GSTT1 genotypes were considered, the greatest reduction in birth weight was found among smoking mothers with the CYP1A1 Aa/aa and GSTT1 absent genotypes (−1285g). These results suggest an interaction between maternal metabolic genes and MSDP with regard to infant birth weight.

More recently, Tsai et al. (2008) observed a significant joint association of maternal smoking, CYP1A1 (Aa/aa) and GSTT1 (absent) genotypes with gestational age and with preterm delivery. Such joint association was particularly strong in certain preterm subgroups, including spontaneous preterm delivery, preterm delivery < 32 weeks, and preterm delivery accompanied by intrauterine infection/inflammation. Taken together, maternal smoking significantly increased the risk of preterm delivery among women with high-risk CYP1A1 and GSTT1 genotypes. Findings were strongest among preterm delivery accompanied by intrauterine infection/inflammation suggesting that intrauterine infection/

inflammation may be a potential pathogenic pathway by which MSDP affects preterm delivery. Specifically, the gene-MSDP interactions may exert their effects synergistically on preterm delivery through maternal and fetal inflammatory responses and raise the possibility of identifying women at high risk for certain pregnancy outcomes by accounting for environmental exposures and genetic polymorphisms (Tsai et al., 2008).

Infante-Rivard, Weinberg, and Guiguet (2006) studied CYP1A1, GSTT1, as well as a set of 'repair' genes (XRCC1, XRCC3, and XPD), due to the fact that cigarette smoke can generate reactive oxygen species, which are capable of inducing double-strand breaks in DNA. These 'repair' genes can maintain the integrity of the genetic code. The authors investigated these genetic polymorphisms and their interaction with MSDP in the role of small-for-gestational-age births (birth weight below the 10^{th} percentile according to gestational age and gender). Results indicated that certain genetic variants (maternal CYP1A1, maternal XRCC3, and newborn GSTT1) increased the risk of small-for-gestational-age birth and modified the effects of MSDP by increasing or decreasing its risk (Infante-Rivard et al., 2006). Of particular interest here is the fact that not only are maternal genotypes involved, but also newborn genotypes which emphasizes the importance of obtaining DNA from mother, child, and father if available and conducting family-based studies to further examine the roles of these genes.

There are also a few studies that have focused on, and claim evidence for gene-environment interactions (dopaminergic pathway genes and prenatal smoking) on externalizing behavior in children (Kahn, Khoury, Nichols & Lanphear, 2003; Neuman et al., 2007). However, these causal relationships need to be considered carefully. These studies, to the best of my knowledge, do not control for the fact that prenatal smoking may be correlated with parental behaviors that could act as more proximal risk factors that are in turn transmitted to their offspring. In brief, Kahn et al. (2003) found that children with the DAT1 480/480 homozygous genotype who were exposed to prenatal smoking had significantly elevated hyperactive-impulsive and oppositional scores on the Conners' Parent Rating Scale Revised-Long Version. The most striking association was with oppositional defiant behavior. Consistent with Kahn et al. (2003), Becker, El-Faddagh, Schmidt, Esser and Laught (2008) also reported evidence of an environmentally moderated risk for ADHD behaviors, suggesting that effects of MSDP were dependent on genetic susceptibility (as reflected by individuals' DAT1 genotypes) and thus operating via G×E interaction. Specifically, males who were exposed to MSDP and who were homozygous for the DAT1 480 allele had higher hyperactivity-impulsivity than males in other groups. This G×E effect was not evident in females. Recently, Neuman et al (2007) also reported that the risk of diagnosis for any DSM-IV ADHD was greatest for children exposed to MSDP and whose genotype contained either the DAT1 440 allele [in contrast to Kahn et al (2003) and Becker et al (2008)] or the DRD4 exon 3 7-repeat allele. In summary, these results suggest an interaction between dopaminergic genes (in offspring) and MSDP with regard to child externalizing behavior; however, the conflicting nature of reported findings also stress the need for highly refined phenotypes, the measurement of other potential confounding factors (such as the fact that MSDP might only be a marker for maternal ADHD or other important genes transmitted to the child), and the measurement of other gene variants that might be in linkage disequilibrium (non-randomly associated) with the dopaminergic genes investigated (Becker et al., 2008). Futher, the multifactorial nature of many child outcomes underscores the importance of studying both genetic and environmental factors and their interaction (Becker et al., 2008).

Summary of genetically-informative studies

The few genetically-informed studies that have considered MSDP suggest that, for certain outcomes, MSDP does have a specific environmental effect that is not confounded with

genetic factors, common environmental factors, and other covariates. GxE (measured gene) studies also indicate that there is suggestive evidence that certain genetic polymorphisms (both maternal and offspring) do moderate the teratogenic effects of prenatal smoking exposure on infant birth weight, preterm delivery, and externalizing behavior. Taken as a group, these results highlight the importance of including genetic and environmental variables in the study of the association between MSDP and offspring outcomes.

A note on prospective vs retrospective studies

Ideally, studies assessing effects of MSDP would recruit participants while pregnant, with continued follow-up of offspring to investigate outcomes associated with MSDP and its correlates (e.g., maternal/paternal psychopathology, home environment, exposure to second-hand smoke, etc). This, however, is not always possible. Many studies must rely on retrospective report of smoking during pregnancy. There has been some question of the reliability of retrospective reporting, in that such reporting could result in underreporting due to social desirability or greater measurement error which could cause the importance of prenatal exposure to be underestimated. Petitti, Friedman, and Kahn (1981) state that the reliability of retrospective reports is similar to the recall of other substance use. More recent reports also indicate high reliability and stability of maternal reporting about their pregnancies, including smoking (Heath et al., 2003; Patrick et al., 1994; Reich, Todd, Joyner, Neuman & Heath, 2003; Tomeo et al., 1999;). Moreover, there is a high correlation between self-reported smoking and serum cotinine measures (Klebanoff, Levine, Clemens, DerSimonian & Wilkins, 1998; McDonald, Perkins, & Walker, 2005).

Despite advances in interview assessment and procedures, the use of retrospective reports of the prenatal and postnatal environment should be used with caution. Retrospective recall of environmental exposures are likely to give rise to artefactual gene-environment associations arising from behavioral ‘contamination’ of the reported events (Jaffee & Price, 2007). Specifically, such reports may be influenced by individual differences in personality, mood, or mental health, or may reflect the degree to which past environments were elicited by an individuals behavior (Kendler, 1996; Jaffee & Price, 2007).

Summary

It is unlikely, given methodological limitations and the risk factor under consideration (MSDP which, in twin offspring, will not differ), that a single design will provide the answers to the complicated nature of the association between MSDP and subsequent outcomes. Over the past three decades, behavioral geneticists have begun to use designs that combine many of the methods outlined in this report in order to bring more power to bear on analyses. For example, a necessary first step in mapping complex traits to genetic loci is to establish the amount of genetic variation that underlies the phenotypic variation of the trait (i.e., heritability). This is accomplished via twin studies. If phenotypic variation in a trait is found to be caused in part by genetic sources (i.e., the trait is heritable), linkage and/or association studies can be conducted in order to characterize the effects of specific genes on phenotypic variation (Posthuma & Boomsma, 2000). But, if the trait of interest is not found to be heritable, the search for the measured genetic effects (i.e., direct main effects or interactive effects of, for example, dopaminergic genes) will most likely not be initiated. Researchers need to not only (i) use the knowledge that we can gain from the designs presented here as well as the information that animal models of MSDP provide (i.e., the teratogenic effect of nicotine on the fetus), but also (ii) to consider pooling resources in order to conduct studies that are powerful enough to make meaningful conclusions. Only then will we gain insight into the underlying processes involved in MSDP.

The ultimate goal of future research in prenatal tobacco exposure is to attempt to derive a relatively unbiased estimate of the magnitude of the association between exposure and outcome – to determine a real vs. statistically spurious effect. Indeed, the fully unbiased estimate is an elusive concept that is never achieved but hopefully more closely realized through increasingly rigorous and comprehensive methods. Future research in this domain should attempt to achieve as accurate as possible an assessment of the magnitude of the association between MSDP and neuropsychological as well as other more physical outcomes. There is strong reason to believe that the established estimates of MSDP-risk on outcome in the literature are upwardly biased due to lack of control for heritable and other confounding factors. A comprehensive approach incorporating genetically-informed samples is of critical importance to obtain a more refined estimate of these associations. Indeed, the more refined effect size may be smaller than what is currently accepted. This, in and of itself, is of great public health significance, not because it will identify a new putative causal agent, but because it will more accurately assess the upper limit of the potential causal association between MSDP and outcomes important for public health, such as low birth weight, cardiorespiratory illness, and ADHD. This should not diminish concern regarding MSDP, but rather could help clarify what are and are not potential causes of ADHD, other neuropsychological, and physical deficits seen in children across the developmental spectrum. Thus, not only is there the potential that findings could provide yet one more incentive for pregnant women to overcome tobacco dependence and quit, but findings can also guide treatment providers to think more comprehensively about smoking during pregnancy and the potential correlates of said behavior. In other words, treatment providers may not only treat, or be concerned with, MSDP, but also correlated behaviors (e.g., maternal psychopathology, detrimental rearing environment, secondhand exposure to smoking) that might also increase risk of certain offspring outcomes. This more informed approach to treatment or general cessation efforts could, in theory, have significant effects on the major public health concern that is smoking during pregnancy and thus result in something that is of substantial value to the field of public health.

Admittedly getting a pregnant woman to stop smoking is perhaps the most straightforward intervention; however, we have ignored other potential confounding factors for far too long. The reality is that, in humans, we do not understand how much of the association between MSDP and offspring outcomes can be attributed to either nicotine or other smoking by-products. By putting more realistic boundaries on the impact of MSDP and not continuing to ignore confounding factors, we open the door for other avenues of treatment, intervention, and prevention – opportunities that heretofore have been missed. The first step around this hurdle – and elucidating real vs. statistically spurious effects of MSDP -- are genetically informed designs.

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Table 1

Selected review of animal models of prenatal nicotine exposure

Authors and Publication date	Prospective or Retrospective	Populations species and size	Measures	Brief results
Animal Models				
Ajarem & Ahmad, (1998)	Daily 0.1 ml subcutaneous injection of nicotine during pregnancy	Swiss-Webster strain mice	Post-natal body weight, latency to eye-opening, latency to the appearance of body hair, and sensory motor reflexes	Exposure resulted in reduced weight gain and delays in development. Exposure also resulted in increased motor activity into early adulthood.
Hagino & Lee (1985)	175 ug/0.9 ul/hr for 7 days using minipumps	Sprague Dawley rats	H^{+3} nicotine binding	Exposure resulted in increased Bmax values for H^{+3} nicotine binding
Johns et al., (1982)	Nicotine 3mg/kg twice daily throughout pregnancy	Duncan –Hartley "English short hair" guinea pigs n = 10 nicotine treated and 10 saline treated	Spontaneous alternation, response to novel alley, black-white discrimination, and reversal beginning	Nicotine exposure resulted in impaired alternating, novel alley entry, and discrimination, and reversal.
Johns et al., (1993)	Twice daily doses of 0.5, 1.5, or 2.5 mg/kg nicotine throughout gestation	Duncan –Hartley "English short hair" guinea pigs n = 15 in each group	Spontaneous alternation, response to novel alley	Prenatal nicotine treatment resulted in deficits in learned and innate behaviors
Levin et al., (1993)	3.4 mg/day of nicotine for 3 weeks and then one week of withdrawal before assessment	Young adult male Sprague Dawley rats	Radial arm maze	Evidence of nicotine-induced cognitive facilitation at least 4 weeks after withdrawal that is not dependent on state dependent learning, nicotinic or muscarinic responsivity
Liang et al., (2006)	0.7 mg/kg nicotine	Sprague-Dawley rat pups	Adult cortical function and auditory learning	Nicotine exposure impairs nicotine regulation of cortical function and auditory learning
Martin et al., (1971)	3.0 mg/kg twice daily or hypoxic episodes	Female rats derived from HOT: Holtzman stock	Appetitive schedules	Nicotine exposed and hypoxic offspring performed more poorly on fixed ratio, variable interval discrimination, and discrimination reversal schedules
Paz et al., (2006)	Free choice of nicotine/ saccharin or pure water (controls had free choice of saccharin or pure water)	Offspring of C57BL/6J dams	Spontaneous locomotion, fear associated learning, addictive and depression related behaviors	Nicotine exposure associated with increased spontaneous locomotion, preference for cocaine-associated place, and latency to escape in a learned helplessness paradigm
Peters & Ngan, (1982)	1.5 and 3 mg/kg/day of nicotine	Fischer rats	Maternal weight gain, birth weight, righting reflex, temperature regulation, adherence to screen, organ/body weight ratios, maze testing, brain protein content	Nicotine treatment led to deficits in maternal weight gain, birth weight, righting reflex, temperature regulation, adherence to screen, organ/body weight ratios, maze testing, brain protein content
Slotkin et al., (1987)	3 mg/kg twice daily	Sprague Dawley rats	H^{+3} nicotine binding	Exposure resulted in elevated binding on gestational day 18

Authors and Publication date	**Prospective or Retrospective**	**Populations species and size**	**Measures**	**Brief results**
Slotkin et al., (1992)	6 mg/kg/day throughout gestation by minipump	Sprague Dawley rats	Adenylate cyclase activity in brain	Nicotine exposure alters adenylate cyclase activity differently by brain region and neurotransmitter systems
Sorenson et al., (1991)	Exposure to 6.0 mg/kg/day of nicotine in drinking water	Sprague Dawley rats n = 12 mothers	Radial arm maze performance	Nicotine exposure resulted in poorer performance on radial arm maze
Van de Kamp & Collins, (1994)	Exposure to saline or 2.0 mg/kg/h nicotine during last half of pregnancy	Offspring of C3H/21bg crosses and C57BL crosses	H^{+3} nicotine binding	Increased maternal nicotine binding sites but not alpha-I^{125} bungarotoxin binding sites
Yanai et al., (1992)	Exposure to 1.5mg/kg nicotine twice daily on gestation days 9–18 (PreN) or daily SC injections on postnatal days 2–21 (NeoN)	HS/Ibg mice PreN = 12 NeoN = 8 Controls = 18	8-Arm maze, Morris water maze, Muscarinic receptor binding	Early or neonatal nicotine exposure decreased performance on the behavioral tasks and increased the number of muscarinic receptors in the hippocampus

Table 2

Selected human models of maternal smoking during pregnancy (MSDP).

Authors and Publication date	Prospective or Retrospective	Populations species and size	Measures	Brief results
Pregnancy and Birth Outcomes				
Bada et al., (2005)	Prospective – maternal smoking data collected "during pregnancy"	Dyads recruited from the NICHD Neonatal Research Network n = 9637 mother-infant dyads	Birth weight, intrauterine growth restriction	Maternal smoking associated with lower birth weight and intrauterine growth restriction
Conter et al., (1995)	Retrospective – maternal smoking data collected the 3rd or 4th day after delivery	Nationwide multicenter obstetric/pediatric survey in Italy n = 12,987 babies	Birth weight	Maternal smoking associated with lower birth weight in dose response relationship
Davies & Abernethy, (1976)	Prospective – maternal smoking data collected at 36 weeks	Mother giving birth in one of two South Wales towns n = 1159 mothers	Maternal weight gain, fetal growth	Maternal smoking associated in a dose-response fashion with lower maternal weight gain, and lower birth weights, length, and head circumference
D'Onofrio et al., (2003)	Unclear – presumably retrospective	Children of twins from two twin samples	Birth weight	Smoking during pregnancy covaries with offspring birth weight through a direct environmental pathway rather than genetic or shared environmental factors.
Knopik et al., (2005)	Retrospective – maternal smoking data collected in mothers of twins aged 11–19 years	Adolescent female twins pairs n = 1936 twin pairs	DSM-IV ADHD, low birth weight	No evidence for maternal smoking effects on ADHD status when covariates included. Maternal smoking associated with low birth weight.
Kyrklund-Blomberg et al., (2005)	Prospective – maternal smoking data collected at first antenatal visit (usually before week 15)	All singleton births in two Swedish hospitals were examined for very preterm birth n = 295	Very preterm births (between 22 and 32 weeks)	Dose dependent association between maternal smoking and very preterm birth.
Meyer et al., (2004)	Prospective – maternal smoking data collected at first antenatal visit (typically weeks 8–12)	All cases in Swedish Medical Birth Registry between 1983 and 1997 with cleft palate or cleft lip excluding multiple births, immigrants, those with missing smoking data and recurrent cleft births and controls n = 872 with cleft palate, 678 with isolated cleft palate, 1456 with cleft lip and 1175 with isolated cleft lip	Cleft lip and cleft palate	Cleft palate associated with MSDP using multiple designs, cleft lip associated with MSDP only with case-control design

Authors and Publication date	Prospective or Retrospective	Populations species and size	Measures	Brief results
		10% of 128,688 noncleft births used as controls		
Morales-Suarez-Varela et al., (2006)	Prospective – Maternal smoking data collected at 11–25 weeks of gestation	Mothers and offspring from Danish National Cohort n = 76,768 births	Congenital malformations using EUROCAT criteria	No association of congenital malformations with maternal smoking, children born to nonsmokers using nicotine substitutes had increased congenital malformations (especially musculoskeletal malformations)
Naeye, (1978)	Prospective-"during pregnancy"	Participants in the Collaborative Perinatal Project n = 53,518 pregnancies at 12 hospitals in the United States	Birth weight, placental health, and length of pregnancy	Maternal smoking associated with lower birth weight, poorer placental health, and shorter pregnancies
Suzuki et al., (1980)	Prospective-100ug/kg body weight over 20 minutes during pregnancy	8 pregnant rhesus monkeys near term	Uterine arterial blood flow	Nicotine decreases uterine arterial blood flow
Infant and Toddler Outcomes				
Baghurst et al., (1992)	Prospective –maternal smoking data collected at first antenatal visit, 32nd week of gestation, and after birth	Offspring of women enrolled in the Port Pirie Cohort Study n = 548 children followed from birth to 4 years	Bayley Scales of Infant Development at 2 years and McCarthy Scales of Children's Abilities at 4 years	No significant association between maternal smoking and neuropsychological development
Brook et al., (2000)	Retrospective – maternal smoking data collected to mother's of 2 year olds	Community sample of 99 toddlers and mothers. 52 smoked during pregnancy, 47 did not smoke during pregnancy	Negativity as measured by impulsivity, risk taking, and rebelliousness	Maternal smoking during pregnancy was associated with negativity
Fried and Makin, (1987)	Prospective – maternal smoking data collected in each trimester	Children aged 2–8 days that had participated in the Ottawa Prenatal Prospective Study n = 250 babies	Brazelton Neonatal Behavioral Assessment Scale	Maternal smoking associated with increased tremors and poorer auditory habituation
Gusella and Fried, (1984)	Prospective – maternal smoking data collected in each trimester	Children aged 13 months days that had participated in the Ottawa Prenatal Prospective Study n = 84 offspring	Bayley Mental and Motor Scales	Maternal smoking associated with decreased motor scores, poorer verbal comprehension, and poorer fine motor skills
Key et al., (2006)	Unclear- maternal smoking data collected within 48 hours of birth	Smoking exposed neonates and controls taken from a larger study on early language development n = 8 exposed and 8 unexposed neonates	Newborn speech discrimination ability measured by event-related potentials	Infants of smoking mothers discriminated fewer syllables and began the discrimination process 150 ms later than matched controls.

Authors and Publication date	Prospective or Retrospective	Populations species and size	Measures	Brief results
Law et al., (2003)	Prospective –self report and biomarkers used during pregnancy	27 nicotine exposed and 29 unexposed infants n = 56 mother offspring pairs	NICU Network Neurobehavioral Scale within 48 hours of birth	Offspring of mothers who smoked were excitable, showed greater asymmetrical reflexes and more hypertonia than unexposed infants. Exposed infants also had higher scores on the stress abstinence scale in a dose response fashion.
Obel et al., (1998)	Prospective – Maternal smoking behavior reported at 16 weeks gestation	Singleton infants without disability n = 1871	Babbling abilities at home visit lasting 1–1.5 hours	Trend of dose response relationship between maternal smoking during pregnancy and the likelihood of being a nonbabbling infant was found.
Saxton, (1978)	Unclear when assessed	15 smokers and 17 nonsmokers	Brazelton Neonatal Behavioural Assessment Scale	Prenatally exposed children exhibited decrements to bell, and deficits in inanimate orientation (auditory), animate orientation (auditory), and consolability
Childhood outcomes				
Batstra et al., (2003)	Prospective – maternal smoking data collected during pregnancy	Subsamples of the Groningen Perinatal Project were identified and re-examined at age 5.5 – 11 years n = 1186 singleton births	Reading spelling and arithmetic and parent and teacher ratings of attention and level of internalizing/ externalizing	Children of mothers who smoked showed increased attention problems, externalizing behavior, and did worse on arithmetic and spelling tasks
Bauman et al., (1991)	Prospective – maternal smoking data collected “during pregnancy”	9–11-year old children who participated in the Child Health and Development Studies n = varies between 1745 and 3260 by longitudinal timepoint	Peabody Picture Vocabulary Test, Raven Coloured Progressive Matrices Test, Goodenough-Jarrios Drawing Test, and Quick test	Offspring of mothers who smoked during pregnancy but quit afterwards did not differ on language and matrices tasks from offspring not exposed to smoking during pregnancy. However, children exposed to *both* MSDP and smoking after pregnancy scored lower than either group.
Brook et al., (2000)	Retrospective – maternal smoking data collected to mother’s of 2 year olds	Community sample of 99 toddlers and mothers. 52 smoked during pregnancy, 47 did not smoke during pregnancy	Negativity as measured by impulsivity, risk taking, and rebelliousness	Maternal smoking during pregnancy was associated with negativity
Cornelius et al., (2001)	Prospective – maternal smoking data collected from fourth prenatal month	10 year old children n = 593 mother/ offspring pairs	Wide Range Assessment of Memory and Learning Screening, Wisconsin Card Sorting Task, Stroop and Trail making Tasks, Pediatric Assessment of Cognitive Efficiency, Grooved Pegboard.	Maternal smoking associated with deficits in verbal learning, design memory, eye hand coordination, flexible problem solving, and increases in impulsivity
D’Onofrio et al., (2008)	Mixed- mothers were initially assessed on smoking during	Females from the National	Behavioral Problem Index	Although smoking during pregnancy was associated

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	pregnancy 4 years after entry into the study; mothers who had a child within these four years would be retrospective whereas those giving birth later would be prospective	Longitudinal Survey on Youth and their children n = 11, 192 children form 4886 mothers		in a dose response fashion with offspring conduct problems, oppositional defiant problems or attention deficit hyperactivity problems (especially in males), the relationship between conduct problems and oppositional defiant problems were not found when examined in siblings that differed in exposure to prenatal nicotine suggesting the possibility of environmental effects that vary between families confound this relationship.
Eskanazi & Trupin, (1995)	Prospective – maternal smoking data collected “during pregnancy”	5-year old children who participated in the Child Health and Development Studies n = 2,124	Peabody Picture Vocabulary Test, Raven Coloured Progressive Matrices Test and a behavioral rating scale	Maternal smoking during pregnancy was not significantly associated with differences on the neurobehavioral assessment
Fried et al., (1992a)	Prospective – maternal smoking data collected in each trimester	Children aged 6 years that had been followed in the Ottawa Prenatal Prospective Study n = 135 60-month old children and 137 72-month old children	McCarthy Scales of Children’s Abilities and Home Observation for Measurement of the Environment (only a subset)	Maternal smoking associated with impaired cognitive and receptive language scores at both 60 and 72 months
Fried et al., (1992b)	Prospective – maternal smoking data collected in each trimester	Children aged 6 years that had been followed in the Ottawa Prenatal Prospective Study n = 126 children	The Gordon Diagnostic System, sustained attention, The Sentence Memory Test, McCarthy Scales of Children’s Abilities, Target Test and Conners Parent Rating Scale	Maternal smoking was associated with poorer performance on memory tasks (in particular those with verbal recall)
Knopik et al., (2006)	Retrospective – maternal smoking data collected when offspring were 13–21 years old.	Australian female twin pairs where at least one twin had a history of alcohol abuse or dependence (DSM-IV) and at least one twin had children between ages of 13–21 n = 536 twin mothers (268 pairs) and 922 children	Child ADHD assessed with items from Diagnostic Interview for Children and Adolescents and Semi-Structured Assessment of the Genetics of Alcoholism	MSDP associated with offspring ADHD but children-of-twin design suggests genetic transmission of risk for ADHD is not fully explained by MSDP
Lambe et al., (2006)	Prospective – maternal smoking data collection begun at first antenatal visit	15 year old males and females n = 400,000	Educational achievement: grade point summary score	Maternal smoking associated with increased risk of poor scholastic achievement OR = 1.59 for 1–9 cigarettes daily, OR =1.92 for 10+ cigarettes daily. However, within mother comparisons suggested that siblings *not* exposed to MSDP also at

Authors and Publication date	Prospective or Retrospective	Populations species and size	Measures	Brief results
				increased risk for poor school performance.
Makin et al., (1991)	Prospective – maternal smoking data collected in each trimester	Children between the ages of 6 and 9 years that had been followed in the Ottawa Prenatal Prospective Study N = 91 children	Test battery including Sound blending, Pegboard test, Conners parent Questionnaire, Developmental Drawings test. Peabody Picture Vocabulary Test, Wide Range, Achievement Test, and Hand Dominance	Maternal smoking associated with poorer performance on tests of speech and language skills, intelligence, visual/spatial abilities, and maternal rating of behavior
Maughan et al., (2004)	Retrospective-maternal smoking data collected one year after twins' birth	High risk twin pairs at age 5 with 18-month follow-up n = 1116 twin pairs	Conduct problems on Achenbach instruments	Prenatal smoking associated with children conduct problems at age 5 and 7 years with dose response relationship for light, moderate and heavy smokers. However, once antisocial behavior in both parents, maternal depression, familial disadvantage, and genetic influences were controlled for, the effects of MSDP were substantially reduced.
McCartney et al., (1994)	Prospective – assessed in each trimester	Children aged 6–11 years that had participated in the Ottawa Prenatal Prospective Study n = 110 children	Central auditory processing task (SCAN)	Prenatal exposure associated with poorer performance on SCAN
Orlebeke et al, (1999)	Retrospective-maternal smoking data collected shortly after birth	2–3 year old twin pairs from the Netherlands Twin Register n = 377 twin pairs	Child Behavior Checklist	Association of MSDP with externalizing (especially aggression) but not internalizing behaviors
Sexton et al., (1990)	Prospective-maternal smoking data collected to gain entry into smoking cessation study	3 year old offspring of mothers who smoked during pregnancy n = 366 offspring	McCarthy Scales of Children's Abilities and Minnesota Child Development Inventory (MCDI)	Offspring of mothers who quit smoking showed higher scores on the General Cognitive Index of the McCarthy Scales and MCDI scores compared with offspring of mothers who did not quit smoking
Silberg et al., (2003)	Retrospective – maternal smoking data collected when offspring were aged 8–16 years	Twins from the Virginia Twin Study of Adolescent Behavioral Development n = 1413 families	Conduct disturbance and smoking behavior form the Child and Adolescent Psychiatric assessment	Conduct disorder related to some other variable than smoking during pregnancy
Adolescent & Adult Outcomes				
Brennan et al., (1999)	Prospective – mother reported smoking behavior in third trimester	Birth cohort of 4169 males at age 34 years	Adult criminal outcomes	Dose response relationship between maternal smoking behavior and arrests for nonviolent and violent crimes (especially persistent criminal behavior.

Authors and Publication date	Prospective or Retrospective	Populations species and size	Measures	Brief results
Buka et al., (2003)	Prospective – maternal smoking behavior assessed at each prenatal visit	Offspring from the National Collaborative Perinatal Project n = 1248	DSM III nicotine and marijuana dependence	Offspring of mothers who smoked during pregnancy were more likely to develop nicotine but not marijuana dependence compared with unexposed offspring
Cornelius et al., (2000)	Prospective – maternal smoking data collected at fourth and seventh prenatal visit and at delivery	Low-SES birth cohort randomly sampled from an urban prenatal clinic n = 589 10-year olds	Questions about use of tobacco, alcohol and marijuana	Association of MSDP and early tobacco experimentation in preadolescence
Fergusson et al (1998)	Retrospective – maternal smoking data collected at birth	18 year old offspring followed in a longitudinal study n = 1022 children	Mental health problems measured with Composite International Diagnostic Interview at age 18	Offspring of mothers who smoked were more likely to have higher psychiatric symptom rates for conduct disorder, alcohol and substance abuse and depression
Milberger et al., (1996)	Retrospective – maternal smoking data collected at 4-year follow-up	Siblings of ADHD and non-ADHD probands n = 266	DSM III- R	Maternal smoking associated with ADHD,
Milberger et al., (1997)	Retrospective – maternal smoking data collected at 4-year follow-up	Siblings of ADHD and non-ADHD probands n = 266	DSM III- R	Maternal smoking associated with ADHD, CD, Major Depression and drug abuse
Milberger et al., (1998)	Retrospective- Maternal smoking data collected from mothers of ADHD probands and non-ADHD comparison probands (mean age of 13)	High risk-siblings ascertained through probands of ADHD and non-ADHD controls n = 174 siblings of ADHD probands and 129 siblings of non-ADHD probands	DSM III-R diagnosis of ADHD	Association of MSDP and ADHD. Association also found after controlling for SES, parental IQ, and parental ADHD status
Mortensen et al., (2005)	Mixed - maternal smoking data collected during and in first few days after pregnancy	Assessment at mean age of 18.7 n = 3044 singleton males	Intelligence assessed by Børge Priens Prøve.	Negative association of maternal smoking with intelligence in a dose-response relationship for five levels of maternal smoking.
Rasanen et al., (1999)	Unclear – appears to be prospective	Men from a general population cohort n = 5636	Criminal records	Maternal smoking associated with violent and persistent (but not nonviolent) offenses.
Wakschlag et al., (1997)	Retrospective – maternal smoking data collected when offspring were aged 7–12 years	A longitudinal study of boys referred to one of two university outpatient clinics n = 177 boys	DSM-III-R using the Diagnostic Interview Schedule	Maternal smoking associated with conduct disorder
Wakschlag et al., (2001)	Retrospective-maternal smoking data collected when offspring were 2.5–5.5 years old	Preschoolers referred to Preschool Behavior Problems Clinic and controls n = 79 referred to clinic and 52 controls recruited	DSM-IV symptoms of ODD and CD assessed using K-SADS	Disruptive behavior disorder symptoms were associated with prenatal exposure to cigarettes

Authors and Publication date	Prospective or Retrospective	Populations species and size	Measures	Brief results
		from a general pediatric clinic		
Weissman et al., (1999)	Retrospective – maternal smoking data collected when offspring were between 6 and 23 years old	Mother offspring pairs selected for presence or absence of lifetime history of major depression in parents N = 147 offspring whose mothers reported either never smoking during pregnancy (97) or 10+ cigarettes daily during pregnancy (50)	Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-LA) and Peabody Picture Vocabulary Test (PPVT)	Male offspring of mothers who smoked during pregnancy had more than a 3-fold increased lifetime risk of conduct disorder, female offspring of mothers who smoked during pregnancy had a more than 5-fold increased risk of drug abuse/dependence