Published in final edited form as:

Early Hum Dev. 2007 November ; 83(11): 727–732.

The relationship of maternal smoking to psychological problems in the offspring

Tanya Maria May Button, Ph.D.,

Institute for Behavioral Genetics, University of Colorado, Boulder, Colorado, United States of America

Barbara Maughan, Ph.D., and

MRC Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

Peter McGuffin, MB Ph.D FRCP FRCPsych FMedSci

MRC Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

Abstract

There is strong evidence for an association between maternal smoking in pregnancy and psychological problems in offspring. The problems most frequently associated are attention problems, hyperactivity, and conduct problems, although there is some evidence for an association with substance use problems as well. The nature of this association is unclear, but it is likely the result of a number of different mechanisms. Animal studies provide evidence for a causal relationship, in which exposure to nicotine has detrimental effects on foetal development. Other studies suggest that factors that correlate with maternal prenatal smoking may be the real risk factors for behavioural problems, although evidence that the associations remain after controlling for such risks goes some way to dispel this as the only explanation. Finally, maternal prenatal smoking may index underlying psychological problems in the mother that are inherited by the offspring. In all likelihood, a combination of these mechanisms may contribute to observed relationships between prenatal smoking and offspring psychological problems. Now that the association is well established, future research needs to focus more strongly on disentangling underlying mechanisms. Although animal studies demonstrate a causal relationship, it appears from other research that this may not be the whole story in human samples. Furthermore, the relationship may only exist under certain conditions (i.e. against a certain genetic background), and this possibility warrants further examination, particularly in relation to other genetic risks, and outcomes other than ADHD. Application of the children-of-twins design may also cast further light on the processes involved.

Keywords

Prenatal Smoking; ADHD; antisocial behaviour; substance use; genes

Address: Institute for Behavioral Genetics, 447 University of Colorado, Boulder, CO 80309-0447, USA. **Telephone:** 303-735-3152 **Fax:** 303-492-8063 **Email:** Tanya.Button@colorado.edu. **Address:** MRC Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, 16 DeCrespigny Park, London SE5 8AF, U.K. **Telephone:** +44 (0)20 7848 0470 **Fax:** +44 (0)20 7848 0866 **Email:** b.maughan@iop.kcl.ac.uk. **Address:** MRC Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, 16 DeCrespigny Park, London SE5 8AF, U.K. **Telephone:** +44 (0)20 7848 0871 **Fax:** +44 (0)20 7848 0866 **Email:** p.mcguiffin@iop.kcl.ac.uk.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Recent years have seen a massive growth in studies describing associations between fetal exposure to prenatal smoking and aspects of children's psychological development. At this stage, the meaning of these associations, and the mechanisms that may underlie them, are unclear. In time, however, a better understanding of the nature of these associations should aid the development of successful interventions and prevention policies.

In this review we outline the evidence for an association between maternal prenatal smoking and psychological problems in offspring, focusing in particular on attention deficit hyperactivity disorder and associated problems (e.g. hyperactivity, inattention), antisocial behaviours (e.g. delinquency, conduct problems, criminality), and substance use problems. There has been very little evidence for an association of maternal smoking with emotional disorders (e.g. anxiety, depression), and that which has been published is largely limited to animal studies; consequently, emotional disorders are not considered in this review. Next, we describe mechanisms whereby maternal smoking might directly impact on offspring behaviour, and the evidence in support of causal mechanisms of this kind. Finally, we discuss some of the confounding and compounding factors that may impact on - or even account for - the association between maternal prenatal smoking and children's psychological outcomes, and offer some possible alternative explanations for the relationship.

A. Evidence for an association between maternal prenatal smoking and psychological problems

B. Attention, hyperactivity, and related problems

Attention and hyperactivity-related problems encompass a variety of symptoms: inattention (where children are easily distracted and unable to keep their mind on a single task for extended periods of time); hyperactivity (often indicated by a child's constant restlessness); and impulsivity, indicated by a lack of control or restraint. For the purpose of research, these phenotypes are often defined operationally in terms of counts of the numbers of symptoms the child has exhibited over a period of time, either for the individual phenotypes or for a composite attention-hyperactivity-impulsivity score. In addition, classification may be by clinical diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM based criteria) or Hyperkinetic Disorder (ICD-10 based criteria). Consistent associations have been reported between attention/hyperactivity problems and maternal prenatal smoking, that seem robust to variations in methods of analysis, measures of child outcomes, or measures of maternal smoking (e.g. any versus none; numbers of cigarettes smoked; or smoking in specific trimesters of pregnancy). Linnet et al¹ provide a comprehensive review of studies in this area. The strength of the association does differ slightly across studies, although generally it appears that the children of smokers are approximately 3 times more likely to have clinical diagnoses of ADHD than the children of non-smokers, with an increase in risk of between 2 and 4 times commonly reported. For example, one research group demonstrated that the mothers of ADHD probands were twice as likely to smoke more than 20 cigarettes per day for at least 3 months of their pregnancy as the mothers of control children;² and a second research group showed that not only were children of smokers at greater risk of ADHD than the children of non-smokers,³ but that the siblings of ADHD probands were also four times more likely to have ADHD when their mothers smoked during pregnancy.⁴ A similar association was demonstrated for diagnoses of Hyperkinetic Disorder in 2 to 8 years olds.⁵ In this study⁵ children of prenatal smokers were 3 times more likely to have hyperkinetic disorder than the children of mothers who refrained from smoking, an association that remained significant even after controlling for potentially confounding factors such as family psychiatric history, parental schooling, employment, income, and co-habitation status (although inclusion of these controls did result in a reduction of the risk estimate to two-fold).

In addition to associations with clinical diagnoses, research has also demonstrated that a range of ADHD symptoms found within a general population, as well as the more common inattention and hyperactivity phenotypes, are also associated with maternal prenatal smoking. For example, a community twin sample demonstrated that maternal prenatal smoking explains a small (2%) but significant proportion of the variance of scores from an ADHD rating scale.⁶ At first glance it may seem confusing that prenatal exposure to maternal smoking might result in an increased risk of 2 to 4 times for ADHD, but only contribute 2% to the phenotypic variance. However, the contribution to the phenotypic variance reflects the extent to which smoking during pregnancy contributes to the variance of ADHD in the measured population. Given that ADHD is a complex disorder, many factors may each contribute slightly to the population variance. Results from this study⁶ also demonstrated an increase in the ADHD score with increasing cigarette smoking during pregnancy, with a dose dependent relationship described.

B. Antisocial behaviour

The term 'antisocial' is also used in relation to a wide spectrum of problem behaviours. In children it may refer to negativity and general behavioural problems such as lying, stealing, or cheating on school tests, or to clinical diagnoses of Conduct Disorder in those with severe difficulties. In adults it may refer to criminal behaviour (determined by arrest records or by self report), or to clinically defined Antisocial Personality Disorder. Wakschlag and colleagues⁷ provide a review of the literature on associations between prenatal smoking and antisocial outcomes of these kinds.

Evidence for an association between maternal prenatal smoking and disruptive and negative behaviour in childhood has been demonstrated in children as young as age two,⁸ even after controlling for confounding risks. Furthermore, this association is also found later in childhood, in adolescence, and in adulthood. For example, rates of Conduct Disorder were twice as high in the children of mothers who smoked at least 20 cigarettes per day during pregnancy as in those who did not.⁹ Another study demonstrated that boys aged 7-12 years old had over a four-fold increase in risk for Conduct Disorder if their mothers smoked more than 10 cigarettes per day.¹⁰ Similarly, males whose mothers smoked more than 20 cigarettes per day during the third trimester of pregnancy were 1.6 times more likely to be arrested for a non-violent crime, 1.8 times more likely to be 'life-course persistent' offenders, and twice as likely to be arrested for a violent crime in adulthood than males whose mothers did not smoke during the third trimester.¹¹ A meta-analysis of studies of maternal prenatal smoking as a risk for criminal behaviour and conduct disordered outcomes in offspring demonstrated an effect size of approximately 0.1¹², and 3% of the variance of adolescent conduct problems appears to be due to maternal prenatal smoking.¹³

Some studies of maternal smoking in pregnancy suggest that the stage of pregnancy at which the mother smoked is particularly salient to antisocial outcomes; as yet, however, findings in this area are inconclusive. In part, this reflects methodological difficulties: many studies only have data on smoking in pregnancy as a whole, or at a single time-point, and sub-groups that could provide key tests of timing effects (such as women who smoke only in one trimester) are inevitably rare. A small number of studies do, however, contain information on smoking in each trimester, and have tested the significance of smoking in specific trimesters while controlling for effects of smoking at other time points. One study¹⁴ demonstrated a dose-response relationship between smoking during early pregnancy and offspring externalizing behaviour, even after controlling for smoking at other times throughout pregnancy, whereas smoking in later pregnancy did not confer a significant risk.¹⁴ This appears to be in contrast with another study¹¹ that showed a dose-response relationship between smoking during the third trimester and criminal behaviour.¹¹ However, this latter study¹¹ did not have information

on earlier pregnancy smoking; assuming that the two are likely to be highly correlated, direct controls for prior smoking might have reduced the observed association to non-significance.

B. Substance misuse

There is a smaller body of evidence describing associations between maternal prenatal smoking and substance misuse and associated problems, although results largely mirror those described for hyperactivity and antisocial behaviour. One study demonstrated that adolescents whose parents smoked during late pregnancy were approximately twice as likely to smoke themselves by age 14 as the offspring of non-smokers.¹⁵ Furthermore, a dose-response effect was observed. Associations have also been reported in relation to other substances. For example, one study of hospitalization for substance abuse in late adolescence (including either alcohol or illicit substances) demonstrated a significant association with prenatal smoking, which remained after controlling for a number of confounding risk factors.⁹ A study by another group confirmed those findings in adults, showing that the risk of hospitalization for nicotine, alcohol and illicit substance abuse in the adult male offspring of mothers who smoked more than 10 cigarettes per day during the third trimester of pregnancy was 2.2 times greater than in the adult male offspring of non-smokers. The risk was also 2.7 times greater in the adult female offspring of smokers compared to non-smokers.¹⁶

A. Possible Mechanisms

B. Direct cause and effect relationship

A variety of mechanisms might underlie these associations. The first key possibility is of a direct cause and effect association, i.e. that some component of the cigarettes smoked by the mother (possibly the nicotine, or the carbon monoxide), may directly affect the developing foetus. In the absence of experimental evidence, a variety of criteria can be applied to evidence from observational (non-experimental) human studies to assess the likelihood that reported associations reflect causal mechanisms. These are: strength and consistency of the reported association, temporal ordering, a dose-response relationship, and biological plausibility.

C. Strength and consistency of the association—A strong and consistent association between a risk factor and an outcome is a first requirement in demonstrating the possibility of a causal association. Results of studies such as those described in this review show a moderate association between maternal prenatal smoking and psychological problems in offspring. Prenatal smoking is associated with a 2 – 4-fold increase in risk for all the ‘psychological’ outcomes discussed here. Furthermore, this finding is consistent across studies, outcomes, and age of study sample, and has also been reported in animal studies.¹⁷ Animal studies are especially important in this area as they allow for direct experimental manipulation (not possible in human samples), and can ensure that results are independent of confounders deriving from other maternal characteristics, or from social background variations, that present major challenges in human studies. In addition, animal studies can test effects of specific exposures (e.g. to nicotine), whereas cigarettes contain a large number of chemicals, each of which may impact on fetal development.

C. Temporal ordering—A second requirement for demonstrating the plausibility of a causal association is that the risk exposure should predate the outcome. Prenatal smoking necessarily, of course, precedes the onset of ADHD, antisocial behaviour, or substance use in offspring. At first glance, this might be thought to offer support for the possibility of a causal relationship. In practice, however, we suggest that conclusions derived from temporal ordering should be considered with caution in this context, given the long time lapse between exposure to prenatal smoking and the onset of problem behaviours, and the likelihood of numerous other intervening exposures.

C. Dose-response relationship—If a causal association exists between a risk factor and an outcome, we would expect that the higher the level of exposure, the more pronounced the risk. Almost all of the studies described in this review have demonstrated a dose-response relationship, with a linear relationship between the extent of smoking in pregnancy and severity of problem outcomes in offspring.

C. Biological Plausibility—To identify biological mechanisms by which smoking in pregnancy might cause psychological problems in offspring, we have looked briefly at the limited evidence from human studies, and then at results from animal studies,, which (as noted above) allow for clearer manipulation and control.

A single study of human fetal development demonstrated that the fetuses of mothers who smoked more than 10 cigarettes per day suffered from reduced blood flow to the brain due to increased resistance in uterine, umbilical and fetal middle cerebral arteries than the fetuses of non-smokers.¹⁸ Lack of blood to the brain of the developing fetus may thus provide a mechanism by which smoking during pregnancy may impact upon the psychological development of children.

Studies of the effects of nicotine on the brains of animals are more common, and have pointed to a variety of mechanisms that may account for effects on psychological outcomes. Prenatal exposure to nicotine in rats reduces the neuronal area of various regions of the hippocampus, resulting in alterations to the brain cell structure which persist to young adulthood.¹⁹ Nicotine exposure also results in increased serotonin transporter density in the rat brain,²⁰ which would influence the activity of serotonin, a neurotransmitter that has been strongly linked to behavioural problems in humans. Prenatal nicotine exposure also appears to lead to reduction in both dopamine and serotonin turnover in the brains of rats.²¹

These findings suggest that prenatal nicotine exposure can be responsible for a number of changes to the structure and functioning of the brain of the developing fetus, and ultimately the live progeny. Each of these effects may impact, either additively or even interactively, on the psychological development of exposed offspring, although not all such effects will necessarily contribute to problematic development.

B. Confounding and compounding risk factors

One key difficulty in identifying the aetiology of the association between maternal prenatal smoking and adverse psychological outcomes in human studies is the presence of numerous confounding and compounding risks. Studies have consistently demonstrated that mothers who continue to smoke during pregnancy have different characteristics from those who never smoked, and from those who quit when they learn that they are pregnant. Many of these characteristics are also known to index increased risk for psychological problems in offspring. Research has shown, for example, that mothers whose smoking persists in pregnancy are generally younger, less educated, poorer, and have less prenatal care than those who quit. Each of these factors is known to be associated with variations in the psychological welfare of the offspring, and so might contribute to, or possibly even explain, the association between maternal prenatal smoking and psychological problems. Hill²² has given an overview of the social characteristics associated with maternal prenatal smoking and psychological problems in the offspring.

C. Pre- and post-natal use of other substances—A further mechanism that might account for the observed association between smoking in pregnancy and psychological problems in the offspring is the mothers' use of other substances, either before or after the child's birth. Many women who smoke during pregnancy also use other substances during, as

well as before or after their pregnancy, and it may be these, rather than cigarettes, that adversely affect the development of the foetus.

C. Post natal smoking—Mothers who smoke during pregnancy are also more likely to smoke after their pregnancy. Once again, it may be this, rather than smoking during pregnancy, that influences some aspects of the child's behaviour, especially, perhaps, outcomes reflecting the child's own use of substances. Although it is possible that there are chemical effects of maternal smoking predisposing a child to smoke, learned behaviour modelled on the mother seems more likely. Mechanisms underlying other behavioural outcomes are less certain. Evidence from one study²³, for example, showed that if a mother smoked during pregnancy but gave up shortly after the child's birth, the child's risk of antisocial behaviour was not much higher than that of children whose mothers refrained from smoking during pregnancy.

B. Smoking as marker of maternal behavioural problems

In addition, it has been suggested that smoking during pregnancy is an index of underlying behavioural problems in the mother, and that risk factors that predispose to smoking during pregnancy could be the same as those that predispose to behavioural problems in the mother and subsequently in the child. ADHD, conduct problems and substance use problems, as well as smoking per se, all demonstrate an underlying genetic risk. Therefore, it is possible that a mother who smokes does so in part as a result of an underlying genetic predisposition, and that it is this predisposition that is inherited by the child and manifests as behavioural problems. On this argument, a genetic risk common to both the maternal and offspring phenotypes could account for the association between them.

There is considerable evidence to support this view. First, as described above, smoking, and each of the psychological problems described here, have an underlying genetic predisposition. Second, evidence suggests that women who display behavioural problems in adolescence or adulthood are more likely to smoke,²⁴ particularly during pregnancy.²⁵ Third, women who smoke in pregnancy generally smoke prior to becoming pregnant and often continue smoking after pregnancy, indicating that smoking is an enduring behaviour that may be a marker of a genetically influenced trait. Although not compelling when considered individually, the combination of these arguments provides some support for the view that the association between maternal prenatal smoking and childhood behavioural problems may be the result of genetic transmission of a behavioural problem that manifests itself in the mother, along with other symptoms of antisocial behaviour, as prenatal smoking, and in the child as psychological problems. Unfortunately, because genetically informative samples (i.e. twins) share the same gestational and rearing environments, as well as the same genes, there are difficulties in testing this hypothesis in traditional twin studies. More recently, investigators have used the Children-of-Twins (CoT) design (which avoids these difficulties) to show that the influence of smoking during pregnancy has an environmental influence on birth weight;²⁶ so far, as we are aware, this approach has not been used in relation to other outcomes to date.

B. Genotype-Maternal Prenatal Smoking Interactions

Whether or not smoking directly influences psychological outcomes via *in-utero* influences, or is associated with psychological problems via some other means (e.g. common genetic liability), recent research has demonstrated further complications in elucidating the nature of the association. Studies have demonstrated that smoking during pregnancy influences ADHD, but only in individuals with particular variants of the dopamine transporter (*DAT*). This has been demonstrated for a variety of variants of this gene,²⁷ although not all.²⁸ This shows that individuals with a particular genotype may be more vulnerable to the effects of maternal smoking. Findings of this kind are often referred to as reflecting genotype-environment

interactions; in this instance, however, as it is unclear whether maternal prenatal smoking exerts a solely environmental risk, the effects are more correctly referred to as a genotype-maternal prenatal smoking interaction.

A. Key Guidelines

- Smoking during pregnancy is associated with increased levels of ADHD, CD and substance use problems in offspring
- Animal studies indicate a possible causal relationship
- Correlated risk factors might contribute to the association

A. Research Direction

- Identify the aetiology of the association between maternal prenatal smoking during pregnancy and psychological outcomes in the offspring
- Expand on gene-environment studies to tests for other genetic variants that confer a risk to exposure to maternal prenatal smoking, and if they affect outcomes other than ADHD (e.g. antisocial behaviour)

Acknowledgements

TMMB is supported by the National Institute for Drug Abuse, grant DA011015

BM is supported by the Medical Research Council

Reference List

1. Linnet KM, Dalsgaard S, Obel C, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry* 2003;160:1028–40. [PubMed: 12777257]
2. Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S. Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. *J Am Acad Child Adolesc Psychiatry* 2002;41:378–85. [PubMed: 11931593]
3. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? *Am J Psychiatry* 1996;153:1138–42. [PubMed: 8780415]
4. Milberger S, Biederman J, Faraone SV, Jones J. Further evidence of an association between maternal smoking during pregnancy and attention deficit hyperactivity disorder: findings from a high-risk sample of siblings. *J Clin Child Psychol* 1998;27:352–8. [PubMed: 9789194]
5. Linnet KM, Wisborg K, Obel C, et al. Smoking during pregnancy and the risk for hyperkinetic disorder in offspring. *Pediatrics* 2005;116:462–7. [PubMed: 16061604]
6. Thapar A, Fowler T, Rice F, et al. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *Am J Psychiatry* 2003;160:1985–9. [PubMed: 14594745]
7. Wakschlag LS, Pickett KE, Cook EH 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]
8. Wakschlag LS, Keenan K. Clinical significance and correlates of disruptive behavior in environmentally at-risk preschoolers. *J Clin Child Psychol* 2001;30:262–75. [PubMed: 11393926]
9. 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]
10. Wakschlag LS, Lahey BB, Loeber R, Green SM, Gordon RA, Leventhal BL. Maternal smoking during pregnancy and the risk of conduct disorder in boys. *Arch Gen Psychiatry* 1997;54:670–6. [PubMed: 9236551]

11. Brennan PA, Grekin ER, Mednick SA. Maternal smoking during pregnancy and adult male criminal outcomes. *Arch Gen Psychiatry* 1999;56:215–9. [PubMed: 10078497]
12. Pratt TC, McGloin JM, Fearn NE. Maternal cigarette smoking during pregnancy and criminal/deviant behavior: a meta-analysis. *Int J Offender Ther Comp Criminol* 2006;50:672–90. [PubMed: 17068192]
13. Button TMM, Thapar A, McGuffin P. Relationship between antisocial behaviour, attention-deficit hyperactivity disorder and maternal prenatal smoking. *Br J Psychiatry* 2005;187:155–60. [PubMed: 16055827]
14. Williams GM, O'Callaghan M, Najman JM, et al. Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study. *Pediatrics* 1998;102:e11. [PubMed: 9651463]
15. O'Callaghan FV, O'Callaghan M, Najman JM, Williams GM, Bor W, Alati R. Prediction of adolescent smoking from family and social risk factors at 5 years, and maternal smoking in pregnancy and at 5 and 14 years. *Addiction* 2006;101:282–90. [PubMed: 16445557]
16. Brennan PA, Grekin ER, Mortensen EL, Mednick SA. Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. *Am J Psychiatry* 2002;159:48–54. [PubMed: 11772689]
17. Ajarem JS, Ahmad M. Prenatal nicotine exposure modifies behavior of mice through early development. *Pharmacol Biochem Behav* 1998;59:313–8. [PubMed: 9476975]
18. Albuquerque CA, Smith KR, Johnson C, Chao R, Harding R. Influence of maternal tobacco smoking during pregnancy on uterine, umbilical and fetal cerebral artery blood flows. *Early Hum Dev* 2004;80:31–42. [PubMed: 15363837]
19. Roy TS, Sabherwal U. Effects of gestational nicotine exposure on hippocampal morphology. *Neurotoxicol Teratol* 1998;20:465–73. [PubMed: 9697973]
20. Muneoka K, Ogawa T, Kamei K, Mimura Y, Kato H, Takigawa M. Nicotine exposure during pregnancy is a factor which influences serotonin transporter density in the rat brain. *Eur J Pharmacol* 2001;411:279–82. [PubMed: 11164385]
21. Muneoka K, Ogawa T, Kamei K, et al. 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.
22. Hill J. Biological, psychological and social processes in the conduct disorders. *Journal of Child Psychology and Psychiatry* 2002;43:133–64. [PubMed: 11848334]
23. Maughan B, Taylor C, Taylor A, Butler N, Bynner J. Pregnancy smoking and childhood conduct problems: a causal association? *J Child Psychol Psychiatry* 2001;42:1021–8. [PubMed: 11806683]
24. Bardone AM, Moffitt TE, Caspi A, Dickson N, Stanton WR, Silva PA. Adult physical health outcomes of adolescent girls with conduct disorder, depression, and anxiety. *J Am Acad Child Adolesc Psychiatry* 1998;37:594–601. [PubMed: 9628079]
25. Wakschlag LS, Pickett KE, Middlecamp MK, Walton LL, Tenzer P, Leventhal BL. Pregnant smokers who quit, pregnant smokers who don't: does history of problem behavior make a difference? *Soc Sci Med* 2003;56:2449–60. [PubMed: 12742608]
26. D'Onofrio BM, Turkheimer EN, Eaves LJ, et al. The role of the children of twins design in elucidating causal relations between parent characteristics and child outcomes. *J Child Psychol Psychiatry* 2003;44:1130–44. [PubMed: 14626455]
27. Kahn RS, Khoury J, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *J Pediatr* 2003;143:104–10. [PubMed: 12915833]
28. Brookes KJ, Mill J, Guindalini C, et al. A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Arch Gen Psychiatry* 2006;63:74–81. [PubMed: 16389200]

Figure 1.
Prader staging system - differential virilisation of the external genitalia from normal female (left) to normal male (right).

Figure 2.
pathway for adrenal steroid hormone synthesis

Table 1

revised nomenclature for DSD (1)

Previous	Revised
Intersex	DSD
Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinization of an XY male	46,XY DSD
Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Table 2

Hypoglycaemia screen - intermediary metabolites and hormones to be measured at the point of hypoglycaemia

Blood	Urine
Glucose	Ketones
Lactate/pyruvate	Reducing substances
Ketone bodies	Organic acids
Free fatty acids	
Amino acids	
Ammonia	
Total free carnitine	
Acylcarnitine profile	
Insulin/ C-peptide	
Cortisol/ Growth hormone	