

Maternal Smoking During Pregnancy and Severe Antisocial Behavior in Offspring: A Review

Lauren S. Wakschlag, PhD, Kate E. Pickett, PhD, Edwin Cook Jr, MD, Neal L. Benowitz, MD, and Bennett L. Leventhal, MD

Smoking during pregnancy represents a major public health problem. Nearly half of all women who smoke continue to do so throughout their pregnancies.¹ As a result, in the United States alone, more than half a million infants per year are prenatally exposed to maternal smoking.² It has long been established that maternal smoking during pregnancy has adverse perinatal consequences. Newer evidence suggests that it may have consequences that extend far beyond the perinatal period.^{3,4}

Recently, associations between maternal smoking during pregnancy and subsequent mental health problems in offspring have been reported. Specifically, youths whose mothers smoked during pregnancy are significantly more likely to develop severe antisocial behavior, including conduct disorder and delinquency.^{5–12} The consistency of findings in studies to date is striking, but their interpretation is less clear. Exposure during pregnancy may play a causal role in the onset of severe antisocial behavior via teratological effects on the fetus. Alternatively, these data may represent a spurious association in that women who smoke during pregnancy have other risk factors that could lead to the development of psychiatric morbidity in their children. This issue bears more careful examination, because modifying the prevalence of exposure could present a rare opportunity to prevent serious psychopathology and reduce the social burden of severe antisocial behavior.¹³

Antisocial behavior, defined as chronic violation of social rules and norms, can have both violent and nonviolent manifestations.¹⁴ When it occurs in a pattern that is severe, chronic, and pervasive, antisocial behavior is categorized as a mental disorder. In youths, severe antisocial behavior is diagnosed as conduct disorder; the adult diagnosis is antisocial personality disorder.¹⁵ Delinquency, in contrast, is the legal system's way of conceptualizing antisocial behavior that is subject to

Objectives. Recent research suggests that in utero exposure to maternal smoking is a risk factor for conduct disorder and delinquency. We review evidence of causality, a controversial but important public health question.

Methods. We analyzed studies of maternal prenatal smoking and offspring antisocial behavior within a causal framework.

Results. The association is (1) independent of confounders, (2) present across diverse contexts, and (3) consistent with basic science. Methodological limitations of existing studies preclude causal conclusions.

Conclusions. Existing evidence provides consistent support for, but not proof of, an etiologic role for prenatal smoking in the onset of antisocial behavior. The possibility of identifying a preventable prenatal risk factor for a serious mental disorder makes further research on this topic important for public health. (*Am J Public Health.* 2002;92: 966–974)

adjudication. Delinquency involves commission of an illegal act, at times including criminal conviction. Delinquent behavior and conduct disorder symptoms are viewed as manifestations of the same underlying difficulty in modulating behavior and conforming to social norms.¹⁴ However, as with criteria for any behaviorally defined disorder (and in contrast to disorders for which a biological marker exists), diagnostic criteria and criminal records are imperfect proxies for severe antisocial behavior.

Severe antisocial behavior is a substantial public health problem because of its prevalence, the significant associated economic and social costs, and the increased morbidity and mortality of individuals with an antisocial history.^{13,16,17} Conduct disorder is one of the most severe mental disorders of childhood and the most frequent reason for referral to mental health clinics for mental health assessment and treatment. Prevalence estimates from a review of international studies range from 1% to 16%, and prevalence is higher in boys.¹⁸

The idea that an individual's long-term mental health and social adjustment might be constrained by exposure to maternal smoking prenatally may seem overly deterministic. However, increasing evidence shows that early life events, such as prenatal trauma, ex-

posures, and deprivations, have a long-lasting influence on development and health.^{19–24}

The evidence linking maternal smoking during pregnancy with antisocial behavior in adolescent and adult offspring, which has been reported largely within the psychiatric and teratological literature, has not been critically examined from a public health perspective. Our objective in this article is to analyze existing studies within an epidemiological framework.

METHODS

MEDLINE and PsychINFO were searched to identify all studies published before June 2001 that examined the association between maternal smoking during pregnancy and severe antisocial behavior in offspring. Search terms were *maternal smoking, pregnancy, and prenatal exposure* and either *child behavior disorders, behavior problems, conduct disorder, delinquency, or antisocial personality disorder or behavior*. Relevant articles also were identified via consultation with experts in the field and review of references cited in all published studies. For the causal analysis, *severe antisocial behavior* was defined as either (1) presence of conduct disorder symptoms or receipt of a conduct disorder diagnosis, reflecting a clinically significant pattern of antisocial

TABLE 1—Review of Studies of Maternal Smoking During Pregnancy and Severe Antisocial Behavior in Offspring

Study ^a	Design	Sample	Measurement of Exposure	Exposed, %	Measurement of Outcome	Main Outcomes (Adjusted)
Studies of conduct disorder (CD)						
Wakschlag et al. ⁹	Clinic-based case-control	177 males (7–17 y), Georgia and Pennsylvania	Retrospective, self-report: “How much did you smoke during pregnancy?”	37	CD by diagnostic interview, multiple time points	OR for CD in boys = 3.3 (> ½ pack/day)
Fergusson et al. ⁶	Population-based prospective cohort	1265 males and females (18 y), New Zealand	Self-report at birth: “How much did you smoke during pregnancy (each trimester)?”	32	CD symptoms by diagnostic interview	Linear increase in boys’ mean CD score as exposure increased: 0.48 for nonexposed, 0.76 for < ½ pack/day, 1.04 for ≥ ½ pack/day, 1.32 for ≥ pack/day
Weissman et al. ¹²	Offspring of case-control study of maternal depression	147 males and females (17–36 y), New York	Retrospective, self-report: “Did you ever smoke more than ½ pack/day during pregnancy?”	34	CD by diagnostic interview	RR for male early-onset CD = 4.1 (≥ ½ pack/day)
Wakschlag and Keenan ¹⁰	Clinic-based case-control	129 males and females (2–5 y), Chicago, Ill	Retrospective, self-report: “How much did you smoke during pregnancy?”	23	ODD and CD symptoms by diagnostic interview	Mean ODD and CD score was 1.54 higher for exposed vs nonexposed
Studies of criminal offending						
Brennan et al. ⁵	Population-based prospective cohort	4169 males (34 y), Denmark	Prospective, self-report, while pregnant: “How much have you been smoking daily during the third trimester?”	51	Arrest history from national criminal register	OR for male persistent offending = 1.5, OR for male violent offending = 1.7 (> ½ pack/day) ^b
Rasanen et al. ⁸ (see also Rantakallio et al. ¹⁰⁴)	Population-based prospective cohort	3883 males (16 y), Finland	Prospective, self-report, while pregnant: “Have you been smoking daily during pregnancy?”	16	Criminal offense from national criminal register	OR for male recidivism = 2.4, OR for male violent offending = 2.1 (any exposure)
Gibson et al. ³³ (see also Gibson and Tibbetts ^{7,100})	Population-based prospective cohort	200 males and females (17 y), Philadelphia, Pa	Prospective, self-report: “How much have you been smoking daily during pregnancy?”	50	Age at first police contact from city police records	OR for early-onset offending = 2.6 for boys and 3.5 for girls (> ½ pack/day) ^b

Note. OR = odds ratio; RR = relative risk; ODD = oppositional defiant disorder.

^aRelated findings from the same cohort that have been reported in multiple articles are represented only once in this review.

^bCalculated from data presented by the authors.

behavior based on diagnostic measures, or (2) a history of delinquency or antisocial behavior as measured via records of criminal offending. Table 1 summarizes studies that met inclusion criteria. The findings of studies that used nonspecific checklist ratings of child behavior problems rather than measures of more severe antisocial behavior are generally consistent with those presented here and are reviewed elsewhere.^{3,25}

RESULTS OF CRITICAL ANALYSIS OF STUDIES

Temporality

Because fetuses do not develop conduct disorder in utero, intrauterine cigarette smoke exposure clearly precedes the disorder. Although this sequence is a necessary condition for causality, recognizing it adds little to our understanding of possible causal pathways,

because the exposure precedes the outcome by a period of many years and may involve the interaction of exposure-related vulnerabilities with multiple other perinatal and postnatal risk factors.

Strength of Association

The association between maternal smoking during pregnancy and severe antisocial behavior is moderate. The odds of developing

severe antisocial behavior are approximately 1.5 to 4 times greater for exposed than for nonexposed youths (Table 1).

Accurate estimation of the strength of this association is significantly constrained, however, by limitations of exposure measurement in research to date. Virtually no studies have used repeated, prospective measures of exposure. Many women stop smoking spontaneously when they learn that they are pregnant, but others quit, reduce, and relapse multiple times during pregnancy.²⁶ Thus, relying on measurement of exposure at a single time point often will not accurately characterize history of exposure. Furthermore, as can be seen in Table 1, characterization of exposure has varied widely in existing studies (e.g., “ever smoked” vs “smoked ½ pack/day or more”). Existing studies also have relied exclusively on self-reported smoking. In the absence of biological measurement of exposure, error is likely because of nondisclosure and underreporting. Self-reported cigarettes per day is also a relatively crude measure of exposure, because variations in smoking topography and metabolism result in differential exposure for the same “amount smoked.”^{27–29} Cotinine (a biomarker of tobacco exposure detectable in plasma, urine, and saliva) is a more precise measure of fetal exposure than maternal report.^{30–32}

For these reasons, substantial misclassification of exposure in existing studies is likely, although the effects of such misclassification are unclear. The reported association may be underestimated because social sanctions against smoking during pregnancy increase the likelihood that smokers will not report truthfully. Such nondisclosure would tend to attenuate the effect, because it would lead to misclassification of exposed youth as nonexposed. Conversely, pregnant smokers with an antisocial history may be more likely to report smoking, because they presumably are less concerned about social norms than are pregnant smokers without an antisocial history. In this case, lack of inhibition might lead to artificial inflation of the association, because youths classified as exposed would be more likely to have other risk factors (e.g., hereditary factors) for conduct disorder.

Consistency

Studies of male offspring of mothers who smoked during pregnancy are notable for the consistency of their findings despite differing designs and populations. These studies have included clinic and community populations as well as populations at high risk for psychiatric disorders.^{6,9,12,33} Because conduct disorder and criminal offending are overlapping constructs, we would expect—and, indeed, we observe—a similar pattern of effects for both types of outcomes. This consistency is in contrast to the absence of a systematic pattern of behavioral effects of exposure to illicit drugs, particularly cocaine.^{34,35}

The apparent consistency may be due to the presence of similar methodological flaws in all of the existing studies. For example, although some of the studies controlled for maternal antisocial behavior, the extent to which maternal antisocial behavior overlaps with smoking status was not reported. If all of the mothers with an antisocial history were smokers, statistical control alone would be inadequate to separate these effects.

Studies are inconsistent in regard to possible behavioral effects in female offspring. Prenatal exposure to maternal smoking is not associated with increased relative risk (RR) of conduct disorder in girls.^{6,11,12} However, several limitations of outcome measurement in studies to date make these negative findings difficult to interpret. First, conduct disorder is less prevalent in girls, and as a result, existing studies may have inadequate power to detect effects. In addition, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, diagnoses of conduct disorder and antisocial personality disorder capture only the extreme end of the spectrum of antisocial behavior, especially in girls.³⁶ Because rates of offending are much lower in females than in males, sample size issues also have led to the exclusion of females in all but 1 existing study of offending.³³ In this study, the odds of early-onset offending were actually comparable in boys and girls.³³ A second limitation of outcome measurement in existing studies is that whereas behavioral effects may manifest differently in boys and girls, sex differences in the pattern of effects have not been systematically examined. For example, conduct problems may take different forms for males and

females (e.g., rape vs early unprotected sex), but *DSM-IV* criteria for conduct disorder are based primarily on male manifestations.^{37,38}

Possible support for differential manifestations by sex may be found in the inconsistent findings to date on the relation of prenatal nicotine exposure to subsequent development of attention deficit–hyperactivity disorder.^{9,39,40} Some of the studies in which exposure was found to be associated with attention deficit–hyperactivity disorder included girls^{12,40} (e.g., RR of attention deficit–hyperactivity disorder in girls = 2.16 vs RR = 0.44 in boys),¹² whereas several of the studies in which attention deficit–hyperactivity disorder was not found to be associated with exposure consisted of boys only.^{9,41}

Exposure may have a *lesser or minimal effect* on girls. Some evidence from animal studies indicates that males are more vulnerable to negative effects of prenatal exposure to nicotine.⁴² Also, there may be no sex differences in the *original* behavioral vulnerabilities associated with exposure, but the *long-term* effect of these vulnerabilities may differ for girls and boys.¹¹ Clearly, more systematic examination of sex differences is needed, including use of large, population-based samples and measurement of a wide range of outcomes.

Specificity

In boys, the association of prenatal exposure to maternal smoking with psychiatric morbidity appears to be specific to antisocial behavior. Such exposure is unrelated to other disturbances of mental health and adjustment, such as mood or anxiety disorders.^{6,9,12} In both clinic and community samples, studies that have examined the association between maternal smoking during pregnancy and conduct disorder relative to other psychiatric disorders in offspring found that exposure was specifically associated with conduct disorder.^{6,9,12}

A major shortcoming of existing studies is that measurement of outcomes has been cross-sectional. As a result, we do not know anything about the developmental progression of conduct symptoms in youths with prenatal exposure. Existing diagnostic studies of exposed youths either have been clinic-based or have used samples of older children, who are already in the risk period for the development

of conduct disorder. Most children who develop early-onset conduct disorder have a long history of behavior problems (e.g., temperamental difficulties as infants, oppositional defiant disorder as younger children) before manifesting a full-blown disorder or committing a delinquent act.^{43,44} Thus, a specific causal pathway might include early symptoms of oppositional defiant disorder followed by the development of conduct disorder in adolescence. Recently, maternal smoking during pregnancy has been linked with oppositional defiant disorder symptoms in young children.^{10,41,45} Also, preliminary evidence from studies of older youths shows that exposure is associated with early- rather than adolescent-onset conduct problems.^{12,33} However, longitudinal research is needed to establish whether there is a specific and coherent pathway of exposure-related behavioral effects over time. Longitudinal data are also critical for testing whether there are specific behavioral effects of exposure or whether these are secondary to other perinatal and neurodevelopmental effects of maternal smoking.^{46,47}

Dose–Response Relationship

There is preliminary evidence of a dose–response relationship from studies that have shown a linear relationship between number of cigarettes smoked and percentage of offspring with severe antisocial behavior.⁵ There is also evidence of dose–response effects from animal studies.⁴⁸ To adequately confirm evidence of a dose–response relationship, precision in measurement of exposure is critical. The possibility that the shape of the dose–response curve is nonlinear has not been examined. No existing studies of the association between smoking during pregnancy and severe antisocial behavior in offspring have used measures of exposure sufficient to establish the existence—much less the shape—of a dose–response curve. Current evidence is insufficient to allow us to establish a threshold above which adverse behavioral effects might become clinically relevant.

Cessation of Exposure (Experimental Evidence)

Although exposure cannot be experimentally manipulated in humans, proving that cessation or reduction of exposure decreases

risk to offspring would add substantial weight to a causal argument. One approach would be to compare outcomes of children whose mothers have a smoking history but did not smoke during pregnancy (“spontaneous quitters”) with those of children whose mothers are persistent smokers.⁴⁹ One limitation of this approach is that women who are able to quit are likely to differ from women who are not, along precisely those psychological and psychiatric dimensions that may underlie the apparent exposure effect. For example, persistent smokers are more likely to have a history of conduct symptoms, less likely to have stable home environments, and more likely to have problematic relationships.⁵⁰

Although women cannot be randomized to smoking and nonsmoking conditions, another strategy would be to follow the offspring of participants randomized to receive prenatal smoking cessation interventions.⁵¹ However, current smoking cessation interventions are successful in only a minority of women.⁵² The types of factors that reduce the likelihood that a woman will benefit from the intervention are the same factors that increase the risk of offspring conduct problems.⁵³ As a result, such studies cannot fully separate cessation effects from maternal characteristics that influence smoking behavior and, therefore, may provide biased estimates.

Biological Plausibility

Because true experimental evidence in humans cannot be obtained, findings from basic science are critically important for establishing causality.^{25,54} Substantial evidence indicates that nicotine crosses the placental barrier and that smoking during pregnancy is associated with fetal neurotoxicity.⁵⁵ Neurotoxic effects are hypothesized to occur via (1) hypoxic effects on the fetal–placental unit (e.g., reduction of fetal blood flow) and (2) teratological effects on the developing fetal nervous system.⁴² Animal research has established that in utero exposure to nicotine has enduring effects on neural function.⁵⁴ Although intrauterine exposure to maternal smoking involves exposure to many toxins, most evidence points to carbon monoxide and nicotine as the key neurobehavioral teratogens.^{56–59}

Nicotine acts primarily through its action on nicotinic acetylcholine receptors.²⁵ Nico-

tinic receptors are present early in gestation, which suggests that nicotinic signaling plays a key role in neural development.²⁵ The fetal brain is protected against many neurotoxins, but it is exquisitely vulnerable to exogenous nicotine because it contains specific nicotine-sensitive receptors.⁵⁴ Continuous patterns of maternal smoking behavior (i.e., the tendency to smoke in a manner that maintains plasma nicotine levels at a steady state) also are likely to heighten the adverse effects of exogenous nicotine on the fetal brain, in contrast to the more episodic pattern of illicit drug use, which allows for central nervous system recovery.⁵⁴ This exogenous stimulation of nicotinic acetylcholine receptors in the immature nervous system interacts with the genes that direct differentiation of cells, thereby causing permanent alterations in cell functioning.^{25,54} Exposure also has been shown to disrupt developmental actions of hormones and to interfere with processes related to sexual dimorphism of the brain, which may explain apparent sex differences in effects.^{12,42}

In animals, demonstrated effects of prenatal exposure to nicotine and carbon monoxide include structural (e.g., abnormalities of cell differentiation), neuroregulatory (e.g., disruptions in neurotransmitter activity), and neurobehavioral (e.g., hyperactivity, deficits in arousal modulation) deficits.^{48,54,60–62} In human infants, prenatal exposure to cigarette smoke also has been associated with early neurotoxic effects.⁶³

The evidence that cigarette smoke constituents are behavioral teratogens fulfills the criterion of biological plausibility but is not sufficient proof that exposure to cigarette smoke in humans *causes* a disorder as complex and multifaceted as conduct disorder.

Consideration of Alternative Explanations

The greatest challenge in establishing whether prenatal exposure actually has a teratological effect is ruling out the possibility that the apparent effects are caused by confounding. Many obvious potential confounders have been statistically controlled in published studies (Table 2). Statistical control for a wide range of empirically and theoretically derived confounders has not appreciably al-

TABLE 2—Testing of Primary Alternative Explanations in Existing Studies

Study	Sociodemographic Factors	Parental Psychiatric Factors ^a	Parenting and Quality of Home Environment Factors ^b	Perinatal and Child Factors
Wakschlag et al. ⁹	Maternal age SES Marital status Ethnicity	Antisocial personality Substance abuse	Discipline, communication, supervision	Exposure to illicit drugs or alcohol Pregnancy or birth complications Low birthweight
Fergusson et al. ⁶	Maternal age SES Maternal education	Offending Substance abuse	Responsiveness (age 3) Parental conflict Youth report of: Parental physical discipline History of child abuse	Exposure to illicit drugs or alcohol Unplanned pregnancy
Weissman et al. ¹²	Maternal age SES Marital status Ethnicity No. of children	Antisocial personality Substance abuse Depression Anxiety	Parental conflict Marital adjustment Youth report of: Family cohesion	Exposure to alcohol or caffeine Pregnancy or birth complications Low birthweight Environmental tobacco smoke
Wakschlag and Keenan ¹⁰	Maternal age Public aid recipient Marital status Ethnicity	Maternal antisocial personality Offending Maternal depression	Observed responsiveness Harsh discipline Parenting stress and support	Low birthweight IQ
Brennan et al. ⁵	Maternal age SES	Paternal offending Psychiatric hospitalization	Rejection (age 1)	Exposure to prescription drugs Pregnancy or birth complications
Rasanen et al. ⁸	Maternal age SES Marital status	Maternal depression	...	Exposure to illicit drugs or alcohol Pregnancy or birth complications Unplanned pregnancy Infant developmental status
Gibson et al. ³³	Maternal age SES	...	Unstable home environment	Pregnancy or birth complications Low birthweight IQ

Note. SES = socioeconomic status.

^aMeasured for both parents, unless noted.

^bMeasured concurrently with outcome and by maternal report, unless noted.

tered associations between smoking during pregnancy and offspring antisocial behavior. However, in addition to the potential for as-yet-unmeasured confounders,^{64–66} statistical control alone does not rule out the possibility of residual confounding.⁶⁷

Three primary alternative explanations have been proposed:

1. *Confounding by social class.* Women who smoke are more likely than nonsmokers to be of low socioeconomic status,⁶⁸ which is associated with increased risk of antisocial behavior.⁶⁹ Although virtually all existing studies have controlled for some socioeconomic factors, socioeconomic status is likely to be

both a strong confounder and poorly measured. The potential for residual confounding is therefore great. The association of maternal smoking during pregnancy and offspring behavior problems has been reported in Yugoslavia, a country where smoking and social class are positively associated, the reverse of the situation in the United States.⁷⁰ The association also has been replicated in samples with more uniform socioeconomic status distributions.^{10,11,33}

2. *Confounding by parental psychiatric history.* Women with mental health problems are more likely to smoke than are healthy women, and their children are at increased risk for antisocial behavior.⁷¹ This increased

risk is the result of both genetic and environmental factors. In terms of possible genetic confounding, parental antisocial history has been controlled in all clinical studies but in only 1 of the existing studies of offending. Even in those studies that controlled for antisocial history, there may be substantial error in these measures because of (1) heavy reliance on maternal report of *paternal* antisocial behavior, (2) underestimation of parental antisocial behavior when measures of parental offending are used, and (3) limitations of diagnostic measures for capturing manifestations of conduct problems in women.³⁷

Broadening assessment of familial risk to a wider range of traits might address some of

these methodological issues.⁷² However, even robust and varied measures of antisocial behavior may contain substantial error, because there are still no pathognomonic markers by which conduct disorder and antisocial personality disorder can be diagnosed with certainty.^{73,74} For this reason, statistical control alone is insufficient to rule out the hypothesis of genetic confounding. Family studies that more directly assess contributions of heritability and environment (e.g., comparisons of siblings discordant for in utero exposure or twin-study designs in which some twin pairs have been exposed and some have not) would more clearly disaggregate contributions of exposure and of genetic factors in the development of offspring antisocial behavior.^{64,74,75}

However, examining the question of genetic and teratological contributions to the development of antisocial behavior in offspring as an “either/or” issue is probably too simplistic. One possibility is that the “true” effect is neither wholly teratological nor solely genetic, but rather an interaction of these 2 processes. Current evidence on the genesis of psychiatric disorders supports a model in which susceptibility genes increase vulnerability but lead to disorder only in interaction with other environmental and biological factors (e.g., prenatal toxins).^{74,76}

Parental psychiatric history also may be an environmental confounding factor because of the deleterious effects of parental psychopathology on the family environment.^{77,78} For example, smoking and depression are associated, and depression is a barrier to quitting, particularly for women.^{79,80} Women who are depressed are more likely to provide problematic parenting and to have marital discord, both of which are associated with increased risk of offspring behavior problems.⁷⁸ Several studies of maternal smoking and offspring conduct problems (including 1 study in which clinically depressed women were oversampled) have controlled for maternal depression.^{9,12}

3. Confounding by quality of family environment. Women who smoke are more likely to provide inconsistent, harsh discipline and unresponsive parenting.^{49,81,82} These same factors have been associated with the development of antisocial behavior in youth.^{77,83} Virtually all of the existing studies have con-

trolled for the quality of parenting and the home environment in some way. This control has not appreciably altered the association. However, a major limitation is that parenting generally has been measured via self-report, often concurrently with conduct problems. Proxy measures of poor-quality care, which are likely to contain substantial error, also have been used.⁵ Observational measures of parenting provide a more objective assessment of the caregiving environment, and we have recently shown that exposure effects are independent of the observed quality of parenting.^{10,11} Paternal behavior has not been directly assessed. Future studies should consider a wider range of family environmental factors (e.g., parenting stress, exposure to family violence).

One other important issue that has been examined only cursorily in these studies is that of separating the effects of prenatal smoking from the effects of postnatal exposure to environmental tobacco smoke. This is difficult to do, because prenatal smoking and environmental tobacco smoke are highly collinear. Environmental tobacco smoke exposure has been associated with neurodevelopmental and milder behavior problems (for a review, see Eskenazi and Castorina⁸⁴) but not with severe antisocial behavior.

Consistency With Other Knowledge (Coherence)

The possibility that maternal smoking may play a causal role in the development of antisocial behavior in offspring is consistent with existing knowledge that prenatal insults and exposures have long-term adverse effects on health.^{20,24,85} For example, exposure to wartime famine during pregnancy has been associated with increased risk of antisocial personality disorder,⁸⁶ and long-term behavioral effects have been found in the case of prenatal alcohol and lead exposure.⁸⁷ On the other hand, as discussed earlier, long-term behavioral effects of fetal exposure to cocaine have not been seen.

DISCUSSION

The body of existing evidence is consistently supportive, but certainly not definitive proof, of an etiologic role for prenatal expo-

sure to nicotine in the onset of severe antisocial behavior in offspring. Published studies yield no evidence that is incompatible with a causal explanation for this association. These studies must be viewed as preliminary (because of the methodological limitations detailed above), but the cumulative evidence is provocative and sufficiently compelling to make further research in this area a matter of public health interest. Estimates of smoking-attributable risk for conduct problems suggest that if a causal relationship were established, the public health burden would be substantial.^{4,88} Even if a modest effect were to be established, this would be significant because of the high prevalence of conduct disorder and delinquency.

Cigarette smoke is a powerful toxin for a broad spectrum of the population. There is little doubt that it is a risk factor for cancer and cardiovascular disease.⁸⁹ Similarly, it is widely accepted that intrauterine exposure to the constituents of cigarette smoke adversely affects fetal development, including birthweight and respiratory function.⁸⁹ This knowledge leads to the obvious question: Why is it important to invest further effort in establishing yet another problematic outcome of maternal smoking? We would answer this question by noting that once antisocial behavior has developed, it is highly persistent and difficult to treat.⁹⁰ Identified risk factors (e.g., low socioeconomic status, unstable family structure, and parental psychopathology) are often chronic and difficult to modify.

Future research must move beyond replication of these findings in different samples⁹¹ toward more explicit attempts at refutation in studies specifically designed to test causality. Most critical for answering the question posed at the outset of this article—*Does maternal smoking during pregnancy cause severe antisocial behavior in offspring?*—is a program of research that (1) measures exposure with precision; (2) uses study designs that can separate risk factors associated with being a maternal smoker from exposure per se; (3) follows up exposed youths from infancy through adolescence to identify early exposure-related behavioral vulnerabilities and factors that determine whether these result in adverse behavioral outcomes over time; and (4) combines both observational and basic science

approaches. Fundamental to this endeavor is the modeling and testing of specific causal pathways. A teratological effect may be direct or indirect. For example, a direct effect might occur via alterations in neurotransmitter systems that interfere with modulation of arousal (e.g., dopaminergic systems).²⁵ In contrast, the increased risk of antisocial behavior in exposed youths may be secondary to other exposure-related problems. For example, the increased risk of conduct problems in exposed youths might occur indirectly via effects of maternal smoking on birthweight and perinatal problems⁴⁶ and neuropsychological difficulties,⁴⁷ all of which increase the risk for later antisocial behavior.^{92,93}

This article highlights the challenges and complexities of establishing a causal path from a perinatal event to a disorder that emerges sometimes decades later.²⁰ These challenges are not specific to prenatal exposure to maternal smoking and offspring antisocial behavior. Rather, they reflect the more general challenges of establishing causal pathways from risk factors operative during the first few years of life to pathological processes manifesting decades later.⁹⁴

Most psychiatric syndromes are the result of complex causal chains involving genetic and other biological factors, proximal environmental factors, and distal social risk factors.⁹⁵ The lengthy time from perinatal exposure to the development of disorder makes it particularly difficult to establish causal pathways, especially because the ways in which risk factors work together are very complex, and the many intervening factors make it difficult to isolate effects of a single, specific factor. In addition, children are born with behavioral susceptibilities to a psychiatric disorder rather than the disorder itself.^{74,96} Thus, establishing coherent temporal pathways is fundamental to establishing for whom and how these susceptibilities actually lead to disorder. This objective requires articulating developmental models that identify age-specific manifestations of vulnerabilities and dysfunction,⁹⁷ an area of science that is just emerging.^{98,99}

Accurate identification of "caseness" is fundamental to establishing etiologic pathways, yet existing methods of classification do not fully capture the wide variation in phenotypic expression of psychiatric disorder.⁷⁴ In addition,

potential effect modifiers must be identified and tested,^{5,11,100} a daunting task because of the vast array of relevant risk factors and the fact that salient risks may be different in different developmental periods.¹⁰¹

The importance of this area of research extends far beyond the specific question at hand, which in turn provides a unique opportunity to develop and test etiologic pathways that can serve as a paradigm for broader research, because (1) there are well-quantified methods for measuring prenatal exposure to maternal smoking,¹⁰² (2) a consistent association to a specific psychiatric disorder has been established, and (3) early manifestations of conduct problems emerge in the first few years of life.¹⁰³ For these reasons, the study of the long-term effects of maternal smoking holds much promise for informing our understanding of how insults to the developing brain affect early behavior and how the effects of such insults interact with contextual factors over time in the etiology of psychiatric disorders. ■

About the Authors

Lauren S. Wakschlag, Edwin Cook, and Bennett L. Leventhal are with the Department of Psychiatry, University of Chicago, Chicago, Ill. Kate E. Pickett is with the Departments of Health Studies and Obstetrics and Gynecology, University of Chicago, Chicago, Ill. Neal L. Benowitz is with the Division of Clinical Pharmacology and Experimental Therapeutics, Department of Medicine and Biopharmaceutical Sciences, University of California, San Francisco.

Requests for reprints should be sent to Lauren S. Wakschlag, PhD, University of Chicago, Department of Psychiatry, MC3077, 5841 S Maryland, Chicago, IL 60637 (e-mail: laurie@yoda.bsd.uchicago.edu).

This article was accepted December 14, 2001.

Contributors

L.S. Wakschlag and K.E. Pickett conducted the review of studies and placed them within the causal framework. All authors contributed to the conceptualization and writing of the article.

Acknowledgments

The writing of this article was supported in part by grants from the National Institute on Drug Abuse (K08 DA00330 to L.S. Wakschlag; DA02277 and DA01696 to N.L. Benowitz), the National Institute of Mental Health (K02 MH01389 to E. Cook), and the Walden and Jean Young Shaw Foundation and the Irving B. Harris Center for Developmental Studies to the Department of Psychiatry, University of Chicago.

References

1. Ebrahim S, Floyd L, Merritt R, Decoufle P, Holtzman D. Trends in pregnancy-related smoking rates in

the United States, 1987–1996. *JAMA*. 2000;283:361–366.

2. Smith B, Martin J, Ventura S. *Births and Deaths: Preliminary Data for July 1997–June, 1998*. Hyattsville, Md: National Center for Health Statistics; 1999. Report 25.
3. Olds D. Tobacco exposure and impaired development: a review of the evidence. *Ment Retard Dev Disabil Res Rev*. 1997;3:257–269.
4. Wakschlag L, Leventhal B, Cook E Jr, Pickett K. Intergenerational health consequences of maternal smoking. *Econ Neurosci*. 2000;2:47–54.
5. Brennan P, Grekin E, Mednick S. Maternal smoking during pregnancy and adult male criminal outcomes. *Arch Gen Psychiatry*. 1999;56:215–219.
6. Fergusson D, Woodward L, Horwood L. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry*. 1998;55:721–727.
7. Gibson C, Tibbetts S. Interaction between maternal cigarette smoking and Apgar scores in predicting offending behavior. *Psychol Rep*. 1998;83:579–586.
8. Rasanen P, Hakko H, Isohanni M, Hodgins S, Jarvelin MR, Tiihonen J. Maternal smoking during pregnancy and risk of criminal behavior among adult male offspring in the Northern Finland 1966 Birth Cohort. *Am J Psychiatry*. 1999;156:857–862.
9. Wakschlag L, Lahey B, Loeber R, Green S, Gordon R, Leventhal B. Maternal smoking during pregnancy and the risk of conduct disorder in boys. *Arch Gen Psychiatry*. 1997;54:670–676.
10. Wakschlag L, Keenan K. Clinical significance and correlates of disruptive behavior symptoms in environmentally at-risk preschoolers. *J Clin Child Psychol*. 2001;30:262–275.
11. Wakschlag L, Hans S. Maternal smoking during pregnancy and conduct problems in high-risk youth: a developmental framework. *Dev Psychopathol*. 2002;14:351–369.
12. Weissman M, Warner V, Wickramaratne P, Kandel D. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *J Am Acad Child Adolesc Psychiatry*. 1999;38:892–899.
13. Potter L, Mercy J. Public health perspectives on interpersonal violence among youth in the United States. In: Stoff D, Breiling R, Maser J, eds. *Handbook of Antisocial Behavior*. New York, NY: John Wiley & Sons; 1997:3–11.
14. Hinshaw S, Zupan B. Assessment of antisocial behavior in children and adolescents. In: Stoff D, Breiling J, Maser J, eds. *Handbook of Antisocial Behavior*. New York, NY: John Wiley & Sons; 1997:36–50.
15. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
16. Bardone A, Moffitt T, Caspi A, Dickson N, Silva P. Adult mental health and social outcomes of adolescent girls with depression and conduct disorder. *Dev Psychopathol*. 1996;8:811–830.
17. Pajer K. What happens to "bad" girls? A review of the adult outcomes of antisocial adolescent girls. *Am J Psychiatry*. 1998;155:862–870.
18. Lahey B, Miller T, Gordon R, Riley A. Developmental epidemiology of the disruptive behavior disorders. In: Quay H, Hogan A, eds. *Handbook of Disruptive*

- Behavior Disorders*. New York, NY: Plenum Press; 1999:23–48.
19. Anand K, Scalzo F. Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol Neonate*. 2000;77:69–82.
 20. Gillman MW, Rich-Edwards JW. The fetal origin of adult disease: from sceptic to convert. *Paediatr Perinat Epidemiol*. 2000;14:192–193.
 21. Glaser D. Child abuse and neglect and the brain—a review. *J Child Psychol Psychiatry*. 2000;41:97–116.
 22. Graham Y, Heim C, Goddman S, Miller A, Nemeroff C. The effects of neonatal stress on brain development: implications for psychopathology. *Dev Psychopathol*. 1999;11:545–567.
 23. Osmond C, Barker D. Fetal, infant and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ Health Perspect*. 2000;108(suppl 3):545–553.
 24. Waton J, Mednick S, Huttunen M, Wang X. Prenatal teratogens and the development of adult mental illness. *Dev Psychopathol*. 1999;11:457–466.
 25. Ernst M, Moolchan E, Robinson M. Behavioral and neural consequences of prenatal exposure to nicotine. *J Am Acad Child Adolesc Psychiatry*. 2001;40:630–642.
 26. Pickett K, Wakschlag L, Leventhal B. Maternal smoking during pregnancy: not a stable phenomenon. *Paediatr Perinat Epidemiol*. 2001;15:A27.
 27. Dempsey D, Jacob III P, Benowitz NL. Accelerated metabolism of nicotine and cotinine in pregnant smokers. *J Pharmacol Exp Ther*. In press.
 28. Haddow H, Knight G, Palomaki G. Measuring serum cotinine to aid in smoking cessation during pregnancy and to enhance assessment of smoking-related fetal morbidity. In: Poswillo D, Alberman E, eds. *Effects of Smoking on the Fetus, Neonate and Child*. Oxford, England: Oxford University Press; 1992:207–222.
 29. Zacny JP, Stitzer ML. Cigarette brand-switching: effects on smoke exposure and smoking behavior. *J Pharmacol Exp Ther*. 1988;246:619–627.
 30. Benowitz N. Biomarkers of environmental tobacco smoke exposure. *Environ Health Perspect*. 1999;107(suppl):349–355.
 31. Dempsey D, Hanjnal B, Partridge J, et al. Tone abnormalities are associated with maternal smoking during pregnancy in in utero cocaine-exposed infants. *Pediatrics*. 2000;106:79–85.
 32. Wang X, Tager I, Van Vunakis H, Sperizer F, Hanrahan J. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. *Int J Epidemiol*. 1997;26:978–987.
 33. Gibson C, Piquero A, Tibbets S. Assessing the relationship between maternal cigarette smoking during pregnancy and age at first police contact. *Justice Q*. 2000;17:519–542.
 34. Frank D, Augustyn M, Grant K, Pell T, Zuckerman B. Growth, development and behavior in early childhood following prenatal cocaine exposure: a systematic review. *JAMA*. 2001;285:1613–1625.
 35. Hans S. Prenatal drug exposure: behavioral functioning in late childhood and adolescence. In: Wetherington C, Smeriglio V, Finnegan L, eds. *Behavioral Studies of Drug-Exposed Offspring: Methodological Issues in Human and Animal Research*. Rockville, Md: US Dept of Health and Human Services; 1996;164:261–276. Research Monograph 114, National Institute on Drug Abuse Monograph Series.
 36. Zoccolillo M, Tremblay R, Vitaro F. DSM-III-R and DSM-III criteria for conduct disorder in preadolescent girls: specific but insensitive. *J Am Acad Child Adolesc Psychiatry*. 1996;35:461–470.
 37. Wakschlag L, Gordon R, Lahey B, Loeber R, Green S, Leventhal B. Maternal age at first birth and boys' risk of conduct disorder. *J Res Adolescence*. 2000;10:417–441.
 38. Zoccolillo M. Gender and the development of conduct disorder. *Dev Psychopathol*. 1993;1–2:65–78.
 39. 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;153:1138–1142.
 40. Milberger S, Biederman J, Faraone S, 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;27:352–358.
 41. Pickett K, Wakschlag L, Loeber R, Stouhamer-Loeber L, Lahey B, Leventhal B. Multigenerational effects of maternal smoking during pregnancy. Paper presented at: Annual Meeting of the American Public Health Association; November 2000; Boston, Mass.
 42. Lichtensteiger W, Schlumpf M. Prenatal nicotine exposure: biochemical and neuroendocrine bases of behavioral dysfunction. *Dev Brain Dysfunct*. 1993;6:279–304.
 43. Lahey B, Waldman I, McBurnett K. The development of antisocial behavior: an integrative causal model. *J Child Psychol Psychiatry*. 1999;40:669–682.
 44. Loeber R, Farrington D. Young children who commit crime: epidemiology, developmental origins, risk factors, early interventions and policy implications. *Dev Psychopathol*. 2000;12:737–763.
 45. Day NL, Richardson GA, Goldschmidt L, Cornelius MD. Effects of prenatal tobacco exposure on preschoolers' behavior. *J Dev Behav Pediatr*. 2000;21:180–188.
 46. Walsh R. Effects of maternal smoking on adverse pregnancy outcomes: examination of the criteria of causation. *Hum Biol*. 1994;66:1059–1092.
 47. Fried P, Watkinson B, Gray R. Differential effects on cognitive functioning in 9 to 12 year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol*. 1997;20:293–306.
 48. Ankarberg E, Fredriksson A, Eriksson P. Neurobehavioral defects in adult mice neonatally exposed to nicotine: changes in nicotine-induced behavior and maze learning performance. *Behav Brain Res*. 2001;123:185–192.
 49. Brook J, Brook D, Whiteman M. The influence of maternal smoking during pregnancy on the toddler's negativity. *Arch Pediatr Adolesc Med*. 2000;154:381–385.
 50. Wakschlag L, Pickett K, Leventhal B. Smoking during pregnancy: problem behavior or behavior problem? 2001 Congress of Epidemiology; a joint meeting of the American College of Epidemiology, American Public Health Association (Epidemiology Section), Canadian Society for Epidemiology and Biostatistics, and Society for Epidemiologic Research. Toronto, Canada, June 13–16, 2001. Abstracts. *Am J Epidemiol*. 2001;153(suppl 11):S1–274. *Am J Epidemiol*. 2001;153:S244.
 51. Quing Li C, Windsor R, Perkins L, Goldenberg R, Lowe J. The impact on infant birth weight and gestational age of cotinine-validated smoking reduction during pregnancy. *JAMA*. 1993;269:1519–1524.
 52. Orleans CT, Barker DC, Kaufman NJ, Marx JF. Helping pregnant smokers quit: meeting the challenge in the next decade. *Tob Control*. 2000;9(suppl 3):III6–III11.
 53. Pritchard C. Depression and smoking in pregnancy in Scotland. *J Epidemiol Community Health*. 1994;48:377–382.
 54. Slotkin T. Fetal nicotine or cocaine exposure: which one is worse? *J Pharmacol Exp Ther*. 1998;285:931–945.
 55. Benowitz N, ed. *Nicotine Safety and Toxicity*. New York, NY: Oxford University Press; 1998.
 56. Navarro HA, Seidler FJ, Schwartz RD, Baker FE, Dobbins SS, Slotkin TA. Prenatal exposure to nicotine impairs nervous system development at a dose which does not affect viability or growth. *Brain Res Bull*. 1989;23:187–192.
 57. Richardson S, Tizabi Y. Hyperactivity in the offspring of nicotine-treated rats: role of the mesolimbic and nigrostriatal dopaminergic pathways. *Pharmacol Biochem Behav*. 1994;47:331–337.
 58. Singh J. Early behavioral alterations in mice following prenatal carbon monoxide exposure. *Neurotoxicology*. 1986;7:475–481.
 59. Storm JE, Valdes JJ, Fechter LD. Postnatal alterations in cerebellar GABA content, GABA uptake and morphology following exposure to carbon monoxide early in development. *Dev Neurosci*. 1986;8:251–261.
 60. Ajarem J, Ahmad M. Prenatal nicotine exposure modifies behavior of mice through early development. *Pharmacol Biochem Behav*. 1998;59:313–318.
 61. Thomas J, Garrison M, Slawicki C, Ehlers C, Riley E. Nicotine exposure during the neonatal brain growth spurt produces hyperactivity in preweanling rats. *Neurotoxicol Teratol*. 2000;22:695–701.
 62. Tizabi Y, Popke EJ, Rahman M, Nespor S, Grunberg N. Hyperactivity induced by prenatal nicotine exposure is associated with an increase in cortical nicotine receptors. *Pharmacol Biochem Behav*. 1997;58:141–146.
 63. Lackmann G, Angerer J, Tollner U. Parental smoking and neonatal serum levels of polychlorinated biphenyls and hexachlorobenzene. *Pediatr Res*. 2000;47:598–601.
 64. Fergusson D. Prenatal smoking and antisocial behavior. *Arch Gen Psychiatry*. 1999;56:223–224.
 65. Koren G. The association between maternal cigarette smoking and psychiatric diseases or criminal outcome in offspring: a precautionary note about the assumption of causation. *Reprod Toxicol*. 1999;13:345–346.
 66. Wakschlag L, Pickett K, Leventhal B. Re: The association between maternal cigarette smoking and psychiatric diseases or criminal outcomes in the offspring [letter]. *Reprod Toxicol*. 2000;14:579–580.
 67. Marshall J, Hastrup J, Ross J. Mismeasurement and the resonance of strong confounders: correlated errors. *Am J Epidemiol*. 1999;150:88–96.

68. Ventura S, Mathews J, Curtin S, Mathews T, Park M. *Births: Final Data for 1998*. Hyattsville, Md: National Center for Health Statistics; 2000. Report 48.
69. Loeber R, Stouthamer-Loeber M. Family factors as correlates and predictors of juvenile conduct problems and delinquency. In: Tonry M, Morris N, eds. *Crime and Justice: An Annual Review of Research*. Chicago, Ill: University of Chicago Press; 1986:29–149.
70. Wasserman G, Liu X, Pine D, Graziano J. Contribution of maternal smoking during pregnancy and lead exposure to early behavior problems. *Neurotoxicol Teratol*. 2001;23:13–21.
71. Fergusson D, Woodward L. Educational, psychosocial and early sexual outcomes of girls with conduct problems in early adolescence. *J Child Psychol Psychiatry*. 2000;41:779–792.
72. Goldman D. The search for genetic alleles contributing to self-destructive and aggressive behaviors. In: Stoff D, Cairns R, eds. *Aggression and Violence: Genetic, Neurobiological and Biosocial Perspectives*. Mahwah, NJ: Lawrence Erlbaum; 1996:23–41.
73. Carey G, Goldman D. The genetics of antisocial behavior. In: Stoff D, Breiling R, Maser J, eds. *Handbook of Antisocial Behavior*. New York, NY: John Wiley & Sons; 1997:243–254.
74. Merikangas K. Familial and genetic factors and psychopathology. In: Nelson C, ed. *The Effects of Early Adversity on Neurobehavioral Development*. Mahwah, NJ: Lawrence Erlbaum; 2000:281–316.
75. Cleveland HH, Wiebe RP, van den Oord EJ, Rowe DC. Behavior problems among children from different family structures: the influence of genetic self-selection. *Child Dev*. 2000;71:733–751.
76. Hyman S, Nestler E. *The Molecular Foundations of Psychiatry*. Washington, DC: American Psychiatric Press; 1993.
77. Capaldi D, Clark S. Prospective family predictors of aggression towards female partners for at-risk young men. *Dev Psychol*. 1998;34:1175–1188.
78. Fendrich M, Warner V, Weissman M. Family risk factors, parental depression and psychopathology in offspring. *Dev Psychol*. 1990;26:40–50.
79. Borrelli B, Bock B, King T. The impact of depression on smoking cessation in women. *Am J Prev Med*. 1996;12:378–387.
80. Breslau N, Kilbey M, Andreski P. Nicotine dependence and major depression: new evidence from a prospective investigation. *Arch Gen Psychiatry*. 1993;50:31–35.
81. Chassin L, Presson C, Todd M, Rose J, Sherman D. Maternal socialization of adolescent smoking: the intergenerational transmission of parenting and smoking. *Dev Psychol*. 1998;34:1189–1202.
82. Kandel D, Wu P. The contributions of mothers and fathers to the intergenerational transmission of cigarette smoking in adolescence. *J Res Adolescence*. 1995;5:225–252.
83. Wakschlag L, Hans S. Relation of maternal responsiveness during infancy to the development of behavior problems in high risk youths. *Dev Psychol*. 1999;37:569–579.
84. Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. *Environ Health Perspect*. 1999;107:991–1000.
85. Olson J. Prenatal exposures and long-term health effects. *Epidemiol Rev*. 2000;22:76–81.
86. Neugebauer R, Hoek H, Susser E. Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. *JAMA*. 1999;282:455–462.
87. Streissguth A. *Fetal Alcohol Syndrome: A Guide for Families and Communities*. Baltimore, Md: Paul H Brookes; 1997.
88. Williams GM, O'Callaghan M, Najman JM, et al. Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study. *Pediatrics*. 1998;102:e11.
89. *The Health Benefits of Smoking Cessation*. Rockville, Md: Office on Smoking and Health; 1990.
90. Kazdin AE. Psychosocial treatments for conduct disorder in children. *J Child Psychol Psychiatry*. 1997;38:161–178.
91. Buck C. Popper's philosophy for epidemiologists. *Int J Epidemiol*. 1975;4:159–168.
92. Moffitt T. The neuropsychology of conduct disorder. *Dev Psychopathol*. 1993;5:135–152.
93. Raine A, Brennan P, Mednick S. Birth complications combined with early maternal rejection at age one predispose to violent crime at age 18 years. *Arch Gen Psychiatry*. 1994;51:984–988.
94. Cicchetti D, Cannon T. Neurodevelopmental processes in the ontogenesis and epigenesis of psychopathology. *Dev Psychopathol*. 1999;11:375–394.
95. Kraemer H, Stice E, Kazdin A, Offord D, Kupfer D. How do risk factors work together? Mediators, moderators and independent, overlapping and proxy risk factors. *Am J Psychiatry*. 2001;158:848–856.
96. Rutter M. Nature-nurture integration: the example of antisocial behavior. *Am Psychol*. 1997;52:390–398.
97. Cannon T, Rosso I, Bearden C, Sanchez L, Hadley T. A prospective cohort study of neurodevelopmental processes in the genesis and epigenesis of schizophrenia. *Dev Psychopathol*. 1999;11:467–486.
98. Cole P, Michel M, Teti L. The development of emotion regulation and dysregulation: a clinical perspective. In: Fox N, ed. *The Development of Emotion Regulation: Biological and Behavioral Considerations*. Chicago, Ill: University of Chicago Press; 1994:73–102.
99. Keenan K. Emotion dysregulation as a risk factor for psychopathology. *Clin Psychol Sci Pract*. 2000;7:418–434.
100. Gibson CL, Tibbetts SG. A biosocial interaction in predicting early onset of offending. *Psychol Rep*. 2000;86:509–518.
101. Shaw D, Winslow E. Precursors and correlates of antisocial behavior from infancy to preschool. In: Stoff D, Breiling R, Maser J, eds. *Handbook of Antisocial Behavior*. New York, NY: John Wiley & Sons; 1997:148–158.
102. Benowitz N, SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. *Nicotine Tob Res*. In press.
103. Keenan K, Wakschlag L. More than the terrible twos: the nature and severity of behavior problems in clinic-referred preschool children. *J Abnorm Child Psychol*. 2000;28:33–46.
104. Rantakallio P, Laara E, Isohanni M, Moilanen I. Maternal smoking during pregnancy and delinquency of the offspring: an association without causation? *Int J Epidemiol*. 1992;21:1106–1113.



Topics in Maternal and Infant Health:

Selections from the American Journal of Public Health

This volume demonstrates the great diversity in the types of problems being faced around the world and the kinds of solutions being evaluated in the area of maternal and infant health. An excellent resource for classroom use!

ISBN 0-87553-026-5
2002 ■ 288 pages ■ softcover
\$19.95 APHA Members
\$26.95 Nonmembers
Plus shipping and handling

American Public Health Association



Publication Sales
Web: www.apha.org
E-mail: APHA@TASCO1.com
Tel: (301) 893-1894
FAX: (301) 843-0159

MCH05J6