Maternal Lifestyle Factors in Pregnancy Risk of Attention Deficit Hyperactivity Disorder and Associated Behaviors: Review of the Current Evidence

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Objective: The purpose of this review was to examine the literature assessing the relationship between prenatal exposure to nicotine, alcohol, caffeine, and psychosocial stress during pregnancy to the risk of developing behavioral problems related to attention deficit hyperactivity disorder (ADHD) in childhood.

Method: PubMed, MEDLINE, EMBASE, and PsycINFO were searched systematically. Studies using DSM diagnostic criteria and other validated diagnostic or screening instruments for ADHD and those examining ADHD symptoms were included. A narrative approach was used because the studies differed too much in methods and data sources to permit a quantitative meta-analysis.

Results: Twenty-four studies on nicotine (tobacco smoking), nine on alcohol, one on caffeine, and five on psychosocial stress were identified. All were published between 1973 and 2002. In spite of inconsistencies, the studies on nicotine indicated a greater risk of ADHD-related disorders among children whose mothers smoked during pregnancy. Contradictory findings were reported in the alcohol studies, and no conclusion could be reached on the basis of the caffeine study. Results from studies on psychological stress during pregnancy were inconsistent but indicated a possible modest contribution to ADHD symptoms in the offspring. Many studies suffered from methodological shortcomings, such as recall bias, crude or inaccurate exposure assessments, low statistical power, and lack of or insufficient control of confounders. A general lack of information on familial psychopathology also limited the interpretations.

Conclusions: Exposure to tobacco smoke in utero is suspected to be associated with ADHD and ADHD symptoms in children. Other maternal lifestyle factors during pregnancy may also be associated with these disorders. Further studies are needed to reach conclusions.

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Attention deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in child and adolescent psychiatry. Prevalence varies between 3% and 5% (1), and up to 10% has been reported in recent studies (2). Children with ADHD are characterized by early onset of symptoms of hyperactivity, impulsivity, and poor sustained attention. They show considerable variation in severity of their symptoms, degree of impairment, and presence of comorbid disorders (3). Moreover, the clinical presentation of ADHD varies by gender; boys tend to show more disruptive behavior and a higher frequency of comorbid disorders than girls, which may be one reason boys are overrepresented in clinical settings (4).

Brain imaging suggests that children with ADHD have a dopaminergic midbrain dysfunction at the level of the dopaminergic nuclei (5), decreased regional cerebral blood flow in parts of the prefrontal cortex (6), and alterations in prefrontal cortical asymmetry, right frontal-striatal circuitry, and the cerebellum (7). The mechanisms behind observed differences in the brain and the etiology of ADHD remain unknown (1); however, both genetic and environmental factors have been associated with the severity and maintenance of ADHD (8). Adoption, segregation, and genetic studies suggest an interaction between genetic and environmental factors, such as toxins in utero and pregnancy and delivery complications (1, 9).

According to Barkley (10), as early as 1902 Still proposed that the predisposition to behavioral problems was inherited for some children and a result of prenatal and postnatal injury for others. Pasamanick and co-workers (11) hypothesized that pre- and perinatal injury to the brain could be sufficient to cause childhood behavior disorders. More recently, the programming hypothesis suggests that fetal adaptation to an unfavorable intrauterine environment permanently increases susceptibility to chronic diseases or disorders later in life (12). Apart from the effect of high levels of exposure to alcohol during pregnancy (13), the effects of other agents on brain function remain unknown.

Neurobehavioral changes similar to ADHD symptoms in human children have been found in animals exposed in

utero to nicotine, caffeine, ethanol, and stress (14–17). Nicotine, caffeine, and ethanol and its metabolites, as well as stress hormones, cross the placental barrier and reach the human fetal brain. From a public health perspective, it is important to learn to what extent and which of these common lifestyle factors contribute to the development of ADHD and ADHD-related disorders. Preventive actions may limit the poor psychiatric and criminality outcome of ADHD children in adulthood (18, 19).

The purpose of this review is to examine the state of the evidence linking common lifestyle factors during pregnancy such as smoking tobacco, alcohol and caffeine use, and maternal psychological stress to the development of ADHD and ADHD-like symptoms in children.

Method

Literature Search

We identified studies for review from the U.S. National Library of Medicine (PubMed) from 1966 until April 2002, EMBASE from 1990 until January 2002, and PsycINFO from 1966 to February 2002. The following keywords were used to search these databases: pregnancy, prenatal, intrauterine, ADHD, attention, hyperactivity, impulsivity, externalizing behavior, smoking, cigarettes, nicotine, alcohol, caffeine, coffee, stress, psychosocial stress, and psychological distress. The bibliographies of articles were examined to identify further citations.

All human studies concerning prenatal exposure to nicotine, alcohol, caffeine, or psychological stress and an outcome measure that fulfilled one of the following three criteria were included in the review: 1) diagnosis of ADHD in accordance with DSM diagnostic criteria made with either a structured diagnostic interview or a clinical interview, 2) symptoms of inattention, hyperactivity, or impulsivity measured with a validated screening instrument, or 3) neuropsychological tests reflecting inattention, impulsivity, or externalizing behavior. The last two criteria designate subgroups of ADHD. Children's age at the time of the diagnosis was limited to 4 years and older because diagnosis of ADHD is difficult to determine for younger children (20). Case series were excluded.

Diagnostic Criteria and Assessments

The diagnostic criteria for ADHD have changed and been further developed since the late 1960s. In 1968, DSM-II defined three areas of core symptoms: inattention, hyperactivity, and impulsivity. These were later expanded into an operational list of 16 specific symptoms in 1980 with DSM-III, revised in 1987 (DSM-III-R), and, finally, divided into three subtypes in DSM-IV in 1994. These subtypes are predominantly inattentive, predominantly hyperactive and impulsive, and combined type. These criteria are used today in clinical and research settings.

This review includes studies using a validated diagnostic instrument or a clinical interview assessing DSM-III or DSM-III-R criteria. None of the available studies used DSM-IV criteria. The Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (21) is a commonly used validated semi-structured diagnostic interview for clinicians and is currently considered one of the best diagnostic assessments. Alternatively, specific rating scales can assess DSM criteria for ADHD; Conners' Parent Rating Scale (22) is one of the best validated.

Several validated questionnaires—the Child Behavior Checklist (23), the Strengths and Difficulties Questionnaire (24), and Rutter's questionnaires for parents and teachers (25)—are included in this review, as well as their subscales or modified versions for inattention, hyperactivity, and impulsivity. The responses can be calculated into a total problem score or into factor-analytically derived subscales such as externalizing behavior (aggressive, oppositional, and hyperactive symptoms) and inattentive and hyperactive symptoms. Although scores based on inattentive and hyperactive subscales focus mostly on ADHD-like symptoms, these psychometric instruments are designed as screening tools for general psychopathology rather than as diagnostic instruments.

The Child Behavior Checklist (23) is a questionnaire designed to measure multidimensional child behavior rather than ADHD per se. Subscales of hyperactivity and inattention of the Child Behavior Checklist are rather crude measures that have a relatively low correlation with a diagnostic interview like K-SADS. A higher correlation is achieved with the Strengths and Difficulties Questionnaire (26).

Neuropsychological tests are used to provide a cognitive profile and to evaluate executive functions. The Continuous Performance Test (27) is used to test the core symptoms of ADHD (i.e., impulsivity and inattention). The Continuous Performance Test has high sensitivity (83%–90%), but specificity is poorer (59%–61%) when measured against clinical diagnosis (27). As with other rating scales, the test provides one source of information that needs to be integrated with other sources in reaching a final diagnostic decision (27).

The available studies differed vastly in methods, measure of exposure, and outcomes, as well as in the subjects studied, which ranged from unselected samples to highly selected hospital samples. The use of different comparison groups also caused lack of comparability among studies. A variety of diagnostic instruments were used, including DSM-III; DSM-III-R; clinical interviews like K-SADS; questionnaires with different calculations of scores on inattentive, hyperactive, and externalizing behavior symptoms; vigilance scores on the Continuous Performance Test; and nonvalidated outcome measures reflecting child behavior. Assigning a weight to each study, therefore, has no scientific value. Because the requirement for a meta-analysis leading to a pooled risk estimate (i.e., that studies have comparable methods and similar measurements of exposures and endpoints) was not met, we conducted an annotated review.

Results

Evidence of Maternal Smoking During Pregnancy and ADHD

Results from animal studies indicate that hyperactivity in the offspring may result from prenatal nicotine exposure (14) and that the effects are long-lasting (28). Possible mechanisms may be modulation of the dopaminergic system and a greater number of nicotine receptors (29, 30). Human data (31–33) show an association between maternal smoking during pregnancy and low birth weight, preterm delivery, and stillbirth. However, one review (34) reported inconsistent associations between prenatal smoking and long-term intellectual and developmental abilities.

We identified 24 studies that evaluated the association between smoking during pregnancy and ADHD or ADHD symptoms. Eight studies (35–42) used the diagnostic criteria of ADHD as the outcome, and 16 (43–58) studied ADHD subgroups. Deficit in attention, motor control, and perception (47) and minimal brain dysfunction (57) were examined in two of the studies and were included in the review because these diagnoses encompass the core symptoms of

TABLE 1. Case-Control Studies[a] of Prenatal Exposure to Tobacco Smoke

Study	Year	Country	Number of Cases	Number of Control Subjects	Assessment	Children's Age (years)	Children's Sex	Outcome
Mick et al. (35)	2002	United States	280	242	>20 cigarettes/day during 3 months of pregnancy	6–17	Boys and girls	ADHD[c]
Milberger et al. (36)	1998	United States	132	139	>20 cigarettes/day during 3 months of pregnancy	6–17	Boys	ADHD[c]
Milberger et al. (37)	1996	United States	140	120	Same as Milberger et al. (36)	6–17	Boys	ADHD[c]
McIntosh et al. (38)	1995	United States	130	135	Did or did not smoke during pregnancy	6–13	Boys and girls	ADHD; undifferentiated attention deficit disorder
Landgren et al. (47)	1998	Sweden	62	51	More than occasional cigarette during pregnancy	6	Boys and girls	Deficit in attention, motor control, and perception
Denson et al. (58)[e]	1975	Canada	20	40	No smoking, average smoker, maximum smoker; smoking at follow-up	5–15	Boys and girls	Hyperactivity improved by methylphenidate

[a] Information on exposure collected retrospectively in all studies.
[b] K-SADS-E=Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version.
[c] Diagnosis based on a structured diagnostic interview.
[d] Birth weight, gestational age, or pregnancy or delivery complications, for example.
[e] There were two control groups: 20 normal subjects and 20 subjects with dyslexia.

ADHD. Table 1 lists the main characteristics of the case-control studies, and Table 2 lists the main characteristics of the cohort studies.

The case-control studies presented in Table 1 provide support for the hypothesis that prenatal exposure to nicotine may result in ADHD symptoms. Milberger et al. (36) attempted to differentiate between genetic vulnerability and prenatal smoking by controlling for parental ADHD and by including siblings of children with ADHD in the model. The results showed that prenatal maternal smoking was associated with a fourfold higher risk of ADHD in the offspring independently of maternal disorder, similar to the risk accounted for by maternal ADHD. Results of the study of Mick et al. (35), based on the 1996 data of Milberger and co-workers (36, 37) and supplemented with data for girls, showed a lower odds ratio of 2.1.

Table 2 presents 18 follow-up studies of maternal smoking during pregnancy (39–46, 48–57). Four of these studies (39–42) classified ADHD according to DSM criteria and collected information on maternal smoking habits during pregnancy retrospectively. Two of the studies (40, 42) assessed smoking as a dichotomized measure. The children were selected from families with alcoholism (39), major depression (40), and other clinical referral symptoms (41). In contrast, McGee and Stanton (42) examined a sample of 765 children whose mothers were randomly selected and recruited at the time of the child's birth. No association between prenatal smoking and ADHD was found in any of these four studies (39–42).

Eleven of the follow-up studies assessing only prenatal maternal smoking or both prenatal and postnatal smoking indicated an association between smoking and ADHD or ADHD-related symptoms.

Six cohort studies (40, 44, 46, 50–52) and one case-control study (58) aimed at differentiating the effect of in utero and postnatal exposure to smoke in relation to ADHD (40) and ADHD subgroups (44, 46, 50–52, 58). Several studies measured prenatal maternal smoking on an ordinal scale, but one dichotomized groups into no smoking and smoking 10 or more cigarettes per day or less frequently during pregnancy (40). Only one study used maternal serum cotinine to verify smoking status (50).

The results from the studies examining differences between prenatal and postnatal smoking varied. In a study by Weissman et al. (40), postpartum smoking was not associated with ADHD in the offspring. Information on exposure for this study was collected retrospectively (three times over a 10-year period) for a small group ranging widely in age from 6 to 23 years. Similarly, prenatal and postnatal maternal smoking were not found to have any impact on attention deficits or impulsivity in a larger sample of 10-year-olds (44).

Two other studies on relatively large samples of about 2,000 children (50, 52) revealed statistically significant associations between postnatal but not prenatal smoking and hyperactivity (52) and activity level (50). There was a very low frequency of exclusively prenatal or postnatal smokers in the study by Weitzman and co-workers (52), which makes it difficult to disentangle the independent contribution made by each variable. Eskenazi and Trupin (50) primarily designed their study to test cognitive deficits and included only three items on activity level (the child has more energy than most, hates to sit still, and likes to play quietly) rated by the mother. It is unlikely that the selected items were sensitive enough to capture the full concept of hyperactivity.

Statistically significant associations between prenatal smoking and the outcome were reported in two studies concerning externalizing behavior (46) and inattentive symptoms (51). The studies collected data prospectively,

Method of Case Definition[b]	Confounder Control	Results
DSM-III-R; K-SADS-E	Maternal use of alcohol, illicit drugs; socioeconomic status; parental ADHD; parental IQ; birth weight	Odds ratio=2.1, 95% CI=1.1–4.1
DSM-III-R; K-SADS-E	Maternal use of alcohol, illicit drugs; socioeconomic status; parental ADHD; parental IQ; birth weight	Odds ratio=4.4, 95% CI=1.2–15.5
DSM-III-R; K-SADS-E	Same as Milberger et al. (36)	Odds ratio=2.7, 95% CI=1.1–7.0
DSM-III-R	None	p<0.03
Parent preschool questionnaire; motor examination	Socioeconomic status; perinatal data[d]	Risk ratio=2.5, 95% CI=0.8–7.3
Teacher report of hyperactivity; child interview	Socioeconomic status	p<0.05 for mean value of smoking during pregnancy; p<0.15 for maximum smoker; p<0.001 at follow-up

had large samples, and controlled for maternal postpartum smoking and socioeconomic status (46, 51). The study by Fergusson and co-workers (51) used teachers as informants in addition to maternal reports.

Eight of the follow-up investigations are particularly important because of large samples, prospective exposure assessments (43, 46, 48, 49, 55–57), and appropriate designs with respect to control for potential confounders such as alcohol (43, 48, 53, 56) and socioeconomic status (43, 46, 48, 49, 53, 55–57). Moreover, a variety of techniques were employed in these studies to assess symptoms, including observational measures of child behavior. These studies reported small but independent effects of smoking on a variety of symptoms related to ADHD in younger children (4–7-year-olds). Four (46, 48, 55, 57) of the eight studies found a dose-response-like association.

Alcohol Consumption During Pregnancy and ADHD in Childhood

Disturbed attention and neuromotor development has been found in monkeys prenatally exposed to moderate levels of ethanol (15). Ethanol enhances migration of nerve cells, which is hypothesized to be involved in behavioral difficulties in childhood. It also interferes with the production of neuroendocrine hormones, which may perturb brain growth (59).

In humans, high levels of alcohol consumption during pregnancy are associated with a greater risk of congenital malformations (60) and possibly stillbirth (61). Alcohol is widely recognized as a teratogenic agent causing CNS dysfunction and impaired mental functioning, including fetal alcohol effect (62) and fetal alcohol syndrome, which incorporates the core symptoms of ADHD (63).

Table 3 presents nine studies investigating the association between prenatal alcohol exposure and ADHD (35, 39) or ADHD subgroups (43, 45, 53, 64–67). Alcohol consumption was significantly associated with ADHD (35) and subgroups of ADHD (64–66) in four of these nine studies, two of which involved high levels of alcohol exposure during pregnancy (35, 65).

A recent case-control study of prenatal exposure to alcohol by Mick and co-workers (35), which also studied smoking, found that twice as many children with ADHD had mothers who either drank alcohol daily or binged heavily during pregnancy (N=10) than children without ADHD (N=5). However, these results were not supported by Hill and colleagues (39), who used dichotomized exposure data collected retrospectively. In this cohort study, the univariate association between prenatal alcohol exposure and ADHD disappeared after the authors adjusted for familial risk of alcoholism, intrauterine exposure to smoking, maternal current alcohol intake, or information on alcohol and parental psychopathology. Studies using the Continuous Performance Test (45, 53, 67) and Conners' Parent Rating Scale (53) reported no effect of prenatal exposure to alcohol on inattention or impulsivity.

The Pregnancy and Health Study of Streissguth et al. (13) is a birth cohort of 582 children exposed to alcohol in utero. Mothers were categorized as abstainers (light/infrequent drinkers or abstainers) or heavy drinkers (one drink or more per day) during pregnancy. The 4–7-year-old children of heavy drinkers were more likely to exhibit attention deficits and impulsivity on the Continuous Performance Test than were children of abstainers. The association remained statistically significant after adjustment for prenatal maternal smoking, prenatal caffeine intake, and socioeconomic status. In the study by Brown et al. (66), prenatal alcohol exposure was found to be related to externalizing behavior problems, and in the study of Delaney-Black et al. (64) it was related to atten-

TABLE 2. Cohort Studies of Prenatal Exposure to Tobacco Smoke

Study	Year	Country	N	Assessment	Children's Age (years)	Children's Sex	Outcome
Hill et al. (39)	2000	United States	109	Retrospective report of smoking in each trimester: no smoking or smoking	8–18	Boys and girls	ADHD[b]
Weissman et al. (40)	1999	United States	147	Retrospective report of smoking during pregnancy and postpartum: no smoking or smoking ≥10 cigarettes/day	6–23; 8–25; 17–36	Boys and girls	ADHD[b]
Wakschlag et al. (41)	1997	United States	177	Retrospective report of smoking during pregnancy: no smoking or smoking ≤10 or >10 cigarettes/day	7–12	Boys	ADHD; conduct disorder
McGee and Stanton (42)	1994	New Zealand	765	Retrospective report: no smoking or smoking <10, 10–20, or >20 cigarettes/day	9	Boys and girls	ADHD
O'Connor et al. (43)	2002	England	7,447	16–18 gestational weeks: no smoking or smoking	4	Boys and girls	Behavioral and emotional problems
Cornelius et al. (44)	2001	United States	593	Each trimester follow-up: no smoking or smoking 1–20 or >20 cigarettes/day	10	Boys and girls	Inattention; impulsivity
Leech et al. (45)	1999	United States	608	Each trimester: no smoking or smoking 1–9, 10–19, or ≥20 cigarettes/day	6	Boys and girls	Inattention; impulsivity
Williams et al. (46)	1998	Australia	4,879	Early/late pregnancy, 6 months, 5 years postpartum: no smoking or smoking 1–9, 10–19, or ≥20 cigarettes/day	5	Boys and girls	Externalizing behavior; internalizing behavior; Social, Attentional, and Thought Problem Scale
O'Callaghan et al. (48)	1997	Australia	5,005	18 gestational weeks: no smoking or smoking 1–9, 10–19, 20–29, or ≥30 cigarettes/day	5	Boys and girls	Externalizing behavior; internalizing behavior; Social, Attentional, and Thought Problem Scale
Bor et al. (49)	1997	Australia	5,296	18 gestational weeks: no smoking or some or moderate-to-heavy smoking	5	Boys and girls	Externalizing behavior; internalizing behavior; Social, Attentional, and Thought Problem Scale
Eskenazi and Trupin (50)	1995	United States	2,124	Serum cotinine at 22 gestational weeks and follow-up: no smoking or smoking 1–9, 10–19, or ≥20 cigarettes/day	5	Boys and girls	Activity level
Fergusson et al. (51)	1993	New Zealand	1,020	Each trimester; annually for 5 years: no smoking or smoking 1–9, 10–19, or ≥20 cigarettes/day	8, 10, 12	Boys and girls	Inattention; conduct disorder
Weitzman et al. (52)	1992	United States	2,095	Prenatal and postnatal: no smoking, smoking 1–20 or >20 cigarettes/day	4–11	Boys and girls	Hyperactivity
Fried et al. (53)	1992	United States	126	Each trimester: no smoking or smoking <20 or ≥20 cigarettes/day	6	Boys and girls	Inattention; impulsivity
Kristjansson et al. (54)	1989	Canada	79	No nicotine or >1 mg nicotine/day (mean= 16 mg/day, about one pack of cigarettes)	4–7	Boys and girls	Vigilance performance
Naeye and Peters (55)	1984	United States	9,024	No smoking or 1–10, 11–20, ≥20 cigarettes/day	7	Boys and girls	Inattention; hyperactivity
Streissguth et al. (56)	1984	United States	452	5 months of pregnancy: no nicotine or 1–15 mg/day (about 10 cigarettes/day) or ≥16 mg/day	4	Boys and girls	Inattention; orientation
Nichols and Chen (57)	1981	United States	38,624	During pregnancy: smoking mean of 9–15 cigarettes/day or >40 cigarettes/day	7	Boys and girls	Hyperactivity; impulsivity

[a] K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children; SADS-LA=Schedule for Affective Disorders and Schizophrenia—Lifetime Version Modified for the Study of Anxiety Disorders.
[b] ADHD diagnosis based on a structured diagnostic interview.

tion deficits. The largest cohort study, that of O'Connor et al. (43), which involved nearly 7,500 children, did not find an association between alcohol exposure and general behavioral problems.

Caffeine Intake and Psychological Distress

Caffeine may cause a persistent effect on the neurochemical system (16). In some epidemiological studies, fetal exposure to caffeine has been associated with first-trimester spontaneous abortions (68) and low birth weight (69).

We identified no study investigating the association between maternal caffeine exposure during pregnancy and ADHD in childhood. A follow-up study by Barr and Streissguth (70) evaluated the effect of caffeine on Continuous Performance Test performance in 7-year-old children. In-

Method of Case Definition[a]	Confounder Control	Results
K-SADS; DSM-III	Maternal alcohol use; maternal delinquency; parental psychiatric disorders	Odds ratio=1.38, 95% CI=0.47–4.09: no association
DSM-III-R; SADS-LA	Maternal substance abuse; socioeconomic status; parental psychopathology; perinatal data[c]; postpartum smoking; smoking in offspring	Risk ratio=0.44, 95% CI=0.09–2.09, for boys <13 years old; risk ratio=2.26, 95% CI=0.13–34.71, for girls <13 years old: no association
DSM-III-R	Maternal alcohol use; socioeconomic status; maternal characteristics[d]; parental antisocial personality; perinatal data[c]	p=0.76 for ADHD: no association
DSM-III; teacher and parent report	Socioeconomic status; maternal characteristics[d]; maternal neuroticism; perinatal data	No association
Strengths and Difficulties Questionnaire	Maternal alcohol use; socioeconomic status; postpartum anxiety or depression	Odds ratio=1.42, 95% CI=1.03–2.01, for boys
Continuous Performance Test; neuropsychological tests	Maternal alcohol, marijuana use; socioeconomic status; maternal characteristics[d]; postnatal life events; maternal depression	No association
Continuous Performance Test; IQ; Home Screening Questionnaire	Substance abuse; maternal characteristics[d]	p<0.05 for inattention
Modified Child Behavior Checklist: extreme 10%	Socioeconomic status; anxiety or depression; perinatal data[c]; postpartum smoking	Risk ratio=1.52 for externalizing behavior and smoking 1–9 cigarettes/day; risk ratio=2.03[e] for externalizing behavior and smoking 10–19 cigarettes day; risk ratio=2.16[e] for externalizing behavior and smoking ≥20 cigarettes/day; dose-response effect
Modified Child Behavior Checklist: extreme 10%	Maternal alcohol use; socioeconomic status; maternal characteristics[d]; perinatal data[c]	Odds ratio=1.3, 95% CI=1.2–1.5, for externalizing behavior; dose-response effect
Child Behavior Checklist	Socioeconomic status; depression	No association
Neurobehavioral assessment; activity level by maternal report (three items)	Maternal alcohol use; socioeconomic status; maternal characteristics[d]; perinatal data[c]	p=0.04 for follow-up
Conners' Parent Rating Scale—mother and teacher	Socioeconomic status; maternal characteristics[d]; parental offending behavior; postpartum smoking	p<0.05 for inattention; p<0.02 for conduct disorder
Parent report of Child Behavior Problem Index (based on Child Behavior Checklist)	Maternal alcohol use; socioeconomic status; maternal characteristics[d]; perinatal data[c]	p≤0.05 for postnatal; p≤0.01 for prenatal and postnatal
Continuous Performance Test; Conners' Parent Rating Scale—mother and teacher	Maternal alcohol, marijuana, caffeine use; maternal nutrition; socioeconomic status; perinatal data[c]	p<0.05 for impulsivity
Continuous Performance Test	Maternal alcohol use; caffeine; nutrition; socioeconomic status; maternal characteristics[d]; postnatal smoking	p>0.05 for increased activity level: no association
Behavior scale score; achievement test	Socioeconomic status; perinatal data	p<0.001 for inattention and p<0.001 for hyperactivity and ≥20 cigarettes/day; dose-response effect
Neurodevelopment scale; Continuous Performance Test; IQ	Maternal alcohol use; caffeine; nutrition; socioeconomic status; maternal characteristics[d]	p=0.01 for inattention; p=0.001 for poorer orientation
Minimal brain dysfunction	Socioeconomic status; maternal characteristics[d]; education; mental health; perinatal data[c]	Risk ratio=1.28, p<0.001, for total group; risk ratio=1.54, p<0.01, for >40 cigarettes/day (N=447); dose-response effect

[c]Birth weight, gestational age, or pregnancy or delivery complications, for example.
[d]Age or parity, for example.
[e]95% CI excludes unity.

gestion of caffeine (coffee, tea, chocolate) was assessed in early pregnancy and during the fifth month of gestation. Caffeine intake was categorized into three levels equivalent to 0–3, 4–5, and 6 or more cups of coffee per day. Few women were unexposed (0.5%). After adjustment for a large number of potential confounders, including maternal smoking, alcohol intake, and other maternal characteristics, no association was found between exposure to caffeine in utero and the children's performance on the Continuous Performance Test.

Prenatal stress has been linked to the serotonergic system in late gestation by means of interference with neuron development (71). Cortisol has been linked to interference with neuron development in the serotonergic system during late gestation, and it may also influence the fetal hypothalamic-pituitary-adrenal axis (71).

TABLE 3. Case-Control Study and Cohort Studies of Prenatal Exposure to Alcohol

Study	Year	Country	N	Assessment	Children's Age (years)	Children's Sex	Outcome
Case-control study Mick et al. (35)	2002	United States	280 cases; 242 control subjects	Retrospective report of drinking during pregnancy: no drinking, daily drinking, or binge drinking[c]	6–17	Boys and girls	ADHD[b]
Cohort studies							
Hill et al. (39)	2000	United States	150	Retrospective report of alcohol intake during pregnancy: no drinking or drinking; postnatal alcohol intake	8–18	Boys and girls	ADHD[b]
O'Connor et al. (43)	2002	England	7,447	Drinking during first trimester: no drinking or drinking ≥1 units of alcohol/day	4	Boys and girls	Behavior and emotional problems
Leech et al. (45)	1999	United States	608	Drinking during first trimester: ≥1 drinks/week	6	Boys and girls	Inattention; impulsivity
Fried et al. (53)	1992	United States	126	Each trimester: no drinking or light or moderate/heavy drinking	6	Boys and girls	Inattention; impulsivity
Delaney-Black et al. (64)	2000	United States	556	Drinking during pregnancy: ounces of alcohol intake/day	6	Boys and girls	Inattention; externalizing behavior; internalizing behavior
Streissguth et al. (13, 65)	1989, 1994	United States	582	5 months: mostly abstaining or drinking	4–7, 14	Boys and girls	Inattention; impulsivity
Brown et al. (66)	1991	United States	68	Second trimester and follow-up postpartum drinking: never drank, stopped drinking, or continued drinking	5, 10	Boys and girls	Inattention; externalizing behavior; internalizing behavior
Boyd et al. (67)	1991	United States	245	15–17 gestational weeks: average consumption/day during pregnancy	5	Boys and girls	Inattention

[a] K-SADS-E=Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version; K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children.
[b] ADHD diagnosis based on a structured diagnostic interview.
[c] Age or parity, for example.
[d] Birth weight, gestational age, or pregnancy or delivery complications, for example.

The maternal psychological state may influence the intrauterine environment by altering the uterine blood flow (72), thereby possibly impeding nutrient supply to the fetus. Maternal stress during pregnancy has been associated with greater prevalence of some congenital malformations (73) and with changes in fetal levels of cortisol, the main hormone associated with stress (74), infant attention regulation (75), schizophrenia (76), social behavior (77), and depression (78).

We identified one study on maternal stress during pregnancy and ADHD (38) and four on ADHD subgroups (43, 79–81), as shown in Table 4. Results from the case-control study (38) showed that mothers of children with ADHD and undifferentiated attention deficit disorder reported psychological stress more frequently during pregnancy. No adjustment for confounding was performed. Thirty years ago, a host of possibly stressful circumstances during pregnancy (measured 1 month postpartum) were found to predict behavioral disturbances in childhood (81). A more recent study (79) used the attention scale on the Child Behavior Checklist and found that children of mothers exposed to stressful family circumstances during pregnancy had a higher likelihood of attention problems. The definition of stressful family circumstances was a combination of genetic and psychosocial factors. Meijer (80) conducted a natural experiment by comparing children of mothers exposed to wartime stress with children born 2 years later. The mothers' and teachers' ratings of child behavior problems were higher in the group exposed to war during the early postpartum months rather than during pregnancy. None of these studies assessed the amount of stress experienced during pregnancy with a validated instrument, nor did they control for confounding.

Recently, a large community-based study assessing psychosocial stress during pregnancy was conducted in England (43). After controlling for maternal smoking, alcohol intake (dichotomized variables), and postpartum depression, the authors found that maternal anxiety at week 32, but not at week 18, was associated with hyperactivity and inattention in boys. The results were statistically significant, not only when the upper extreme of the behavioral problem distribution was examined but also when behavioral problems were examined as a continuous variable. Women with high scores on anxiety at gestational week 18 were more likely to drop out of the study. There was no control for parental psychopathology. Furthermore, a high correlation between anxiety scores measured during and after pregnancy makes it difficult to exclude the possibility that the association was due to genetics rather than anxiety in the mother.

Method of Case Definition[a]	Confounder Control	Results
DSM-III-R; K-SADS-E	Maternal smoking, use of illicit drugs; socioeconomic status; parental ADHD; parental IQ; birth weight	Odds ratio=2.5, 95% CI=1.1–5.5
K-SADS; DSM-III	Maternal smoking; socioeconomic status; parental psychiatric disorders; comorbidity; current maternal alcohol intake	No association: crude odds ratio=4.00, 95% CI=1.08–19.90
Strengths and Difficulties Questionnaire	Maternal smoking; socioeconomic status; postpartum anxiety or depression	Odds ratio=0.79, 95% CI=0.28–2.28, for boys; odds ratio=1.19, 95% CI=0.46–3.12, for girls: no association
Continuous Performance Test; IQ	Prenatal substance exposure; maternal characteristics[c]	No association
Continuous Performance Test; Conners' Parent Rating Scale	Maternal smoking, marijuana use, caffeine use, nutrition, education; socioeconomic status; perinatal data[d]	No association
Achenbach Teacher's Report Form; parent report of psychopathology; observation	Maternal substance abuse	p=0.003 for inattention
Neurodevelopment scale; Continuous Performance Test; IQ	Maternal smoking, caffeine use; maternal characteristics[c]; socioeconomic status	p=0.01 for inattention and p=0.02 for impulsivity at age 4; p=0.03 for inattention and p<0.01 for impulsivity at age 7
Child Behavior Checklist; Achenbach Teacher's Report Form; Continuous Performance Test	Maternal smoking, marijuana use; maternal characteristics[c]; socioeconomic status; current maternal alcohol intake	p=0.001 for continued to drink and externalizing behavior
Continuous Performance Test	Maternal smoking; maternal characteristics[c]; perinatal data[d]	No association

Discussion

The reviewed studies indicate that maternal lifestyle during pregnancy may contribute to behavior problems in the offspring. However, because of methodological limitations, these studies are only suggestive; no causal conclusions can be drawn. The majority of studies indicated an association between exposure to tobacco smoke in utero and inattention and hyperactivity, but not all studies found a statistically significant association.

The results for alcohol exposure were inconsistent. Only half of the papers included in the review showed a statistically significant association with inattention and impulsivity. Results from four studies (35, 64–66) support the hypothesis that alcohol contributes to CNS impairment that need not be as severe as fetal alcohol syndrome/fetal alcohol effect. Two of these studies were based on exposure in utero to very high levels of alcohol (35, 65). Studies on high levels of maternal alcohol intake, however, are vulnerable to confounding by social, dietary, and genetic factors. None of the studies adjusted for a family risk of behavioral problems.

Only one study explored the possibility that caffeine exposure in utero could affect child behavior, and the small number of unexposed children hampers the interpretation of the results.

Studies regarding stress showed a small but statistically significant association with disturbances in attention and activity. The study on stress done by O'Connor et. al. (43) in ADHD subgroups is the best of these because of its large sample size of children of the same age, prospective exposure assessment twice during pregnancy, use of a validated scale for psychological stress, and adjustment for potential confounders. The other studies (38, 79–81) did not adjust for potential confounders such as maternal smoking. Smoking may be a potential alternative explanation for the results in these studies in view of the fact that smoking is more common among stressed pregnant women (82).

Methodological Issues

There are several methodological issues common to studies on the lifestyle factors reviewed here. These issues are discussed below with illustrations from the studies under review.

Study design and assessment of exposure. Prospective collection of data minimizes the risk of recall bias and differential misclassification; in contrast, these problems are maximized in studies with retrospectively collected data. Nonetheless, all studies concerning smoking and ADHD (35–42) or alcohol (35, 39) collected exposure information retrospectively.

Selective attrition is another methodological problem that limits the interpretation of results. For example, only

TABLE 4. Case-Control Study and Cohort Studies of Prenatal Exposures to Psychological Stress

Study	Year	Country	N	Assessment	Children's Age (Years)	Children's Sex
Case-control study: McIntosh et al. (38)	1995	United States	130 cases; 135 control subjects	Retrospective report of stress during pregnancy	6–13	Boys and girls
Cohort studies						
O'Connor et al (43)	2002	England	7,447	Self-report of anxiety at 18 and 32 gestational weeks: score in the top 15% of Crown Crisp Index	4	Boys and girls
Laucht et al. (79)	2000	Germany	348	Psychosocial family/biological risk: none, moderate, or high	8	Boys and girls
Meijer (80)	1985	Israel	57	Exposure to Six-Day War	First grade, elementary school	Boys and girls
Stott (81)	1973	Canada	153	Self-reported psychological state <1 month postpartum: presence or absence of situational stresses and personal tension	4	Boys and girls

44% of the eligible families participated in one study (39), and women experiencing greater amounts of psychological stress were more likely to drop out in another study (41).

Results must always be judged on the accuracy with which the exposure variables are measured. Dichotomizing smoking as either smoking more than 20 cigarettes or 20 cigarettes or fewer per day, as in some studies (35–37), or dichotomization of alcohol consumption into abstainers versus any alcohol intake during pregnancy (65) may be too crude. Dichotomization (39, 43) may hide a true association, as well as hinder the detection of a possible dose-response effect or a threshold value.

Statistical Issues

The statistical power was limited in many of the studies, particularly the studies on smoking. To detect a 50% increase in ADHD with 80% power, a sample size of 6,000 with 3,000 exposed and 3,000 unexposed children is needed. None of the published studies had that size. Three studies on ADHD subgroups with large sample sizes found a dose-response-like relation with smoking (46, 48, 55). A large cohort sample, as in some studies (43, 55, 57), is especially needed when outcome is rare or the effect is small (83), as we would expect for the reviewed lifestyle factors.

The maternal lifestyle variables studied in this review have all previously been shown to be correlated with each other (84). When studying high-risk populations, multicollinearity may render invalid results (85).

Control of Confounders

Some studies carried out little control (45, 47, 49, 55, 58, 64, 79) or no control (38, 80, 81) for confounding variables. Apart from parental socioeconomic status, the main potential confounders considered in the studies of the single lifestyle factors are maternal alcohol intake and smoking habits. Stratification, rarely used or reported in the reviewed papers, is a useful and simple tool to assess the effect of interactions on outcome. This procedure requires understanding of the possible mechanisms behind and the quality of underlying variables. Highly selected at-risk populations in some studies (36, 37, 39–41, 65) may complicate the issue of confounding further.

Family studies show that 70%–90% of the variance in the ADHD phenotype may be attributed to hereditary factors (9, 86), which, therefore, may be strong independent risk factors for ADHD in offspring. However, few studies (35–37, 39, 41, 43, 45, 46, 49, 51) were able to take familial psychopathology into consideration. Furthermore, little is known about the etiology of ADHD, making it difficult to fully adjust for confounding.

Long-term follow-up studies of children with ADHD have shown a greater risk of adulthood antisocial personality and anxiety disorders, which may be important to assess in addition to ADHD (86). Thus, maternal depression and paternal antisocial behavior (86) could be evaluated in future studies, depending on design issues and sampling.

Smoking is prominent among ADHD patients (87). Cigarette smoke, alcohol, and caffeine are known stimulants of the CNS, and the use of these stimulants reflects certain personality traits (88). Nicotine is a psychomotor stimulant, which reduces the core symptoms of ADHD as well as anxiety and tension (89). Cigarette smoking and drinking alcohol or large amounts of coffee could be pharmacological ways of coping with the psychopathology linked to ADHD. It is possible that maternal smoking during pregnancy may be a proxy variable for the genetic risk of the child to develop ADHD. Adjustment for maternal or parental psychopathology may not solve the problem, but exploring the interaction between ADHD and maternal or parental psychopathology may better enlighten the possible causal paths.

The age of the children at the time of assessment may be important because symptoms become less conspicuous over time and only 30%–40% of children with ADHD retain their diagnosis in adulthood (90). Studies have shown that children with ADHD have a tendency to remit from hyperactive symptoms but to have persistent inattention (91, 92). Therefore, Barkley and Biederman (93) suggested that the age criterion of 7 years for the diagnosis of ADHD be broadened or abandoned. They recommended that the

Outcome	Method of Case Definition	Confounder Control	Results
ADHD/undifferentiated attention deficit disorder	DSM-III-R	None	p<0.001
Hyperactivity; inattention; conduct disorder; emotional	Maternal report; Strengths and Difficulties Questionnaire	Maternal smoking; maternal alcohol use; socioeconomic status; postpartum depression	Odds ratio=1.9, 95% CI=1.3–2.8, for boys, and odds ratio=1.43, 95% CI=0.96–2.11, for girls for anxiety at 32 gestational weeks and hyperactivity and inattention
Externalizing behavior; internalizing behavior	Child Behavior Checklist	Gender	p<0.001 for attention in the biological risk group
Hyperactivity; perseverance; distractive; concentrated	Maternal/teachers rating; mother child questionnaire; Child Behavior Inventory	None	p<0.03 for hyperactivity
Behavior disturbances	Child morbidity score	None	Personal tension related to behavioral disturbances

appearance of ADHD symptoms anytime during childhood is a more appropriate criterion for ADHD. In the evaluation of adults with ADHD, the official DSM-IV items are still recommended (91). However, in research, advantages of the age criterion of symptoms ensure a relatively homogeneous sample, reliability of selection criteria across studies, and a high probability of subjects having a valid disorder (93).

Many studies did not distinguish between prenatal and postnatal exposure to tobacco smoke. We believe this to be a minor problem because environmental exposure to tobacco smoke is of much lower magnitude and hardly capable of influencing brain development (94). Prenatal and postnatal smoking are highly correlated and difficult to separate. Because postnatal smoking is most likely on the causal pathway (95), adjustment for postnatal exposure may lead to overadjustment and obscure a potential true association with prenatal exposure. We believe that intrauterine exposure of the child to cigarette smoke may be of importance in ADHD and ADHD-related disorders. This is supported by a recent experimental report (96), which found that exposure to nicotine during pregnancy was associated with behavioral problems in the offspring.

Maternal smoking during pregnancy has been associated with adult criminal outcome, conduct disorders, and substance abuse (40, 97, 98) and with problems in cognitive development (99). Offspring exposed to alcohol in utero exhibit symptoms characterized by deficiencies in regulation of behavior, cognitive flexibility, response inhibition, and planning, as well as lower IQ (100)—symptoms that encompass many different clinical diagnoses. ADHD includes a number of these behavioral aspects, which may be present together because of common etiology or because ADHD is a specific pathogenetic entity. In any case, we would expect that ADHD would be associated with some of the prenatal lifestyle factors because of the familial predisposition of the disorder.

Exposure to several other factors during pregnancy may have effects on long-term development of the child; these include pre-, peri-, and postnatal complications, diseases, trauma, medication, and neurologically compromising events that may occur during development of the nervous system before and after birth (8).

The use of recreational drugs during pregnancy may have serious long-term consequences (101), but the effect of this exposure is difficult to interpret because it is often associated with other putative risk factors like smoking and alcohol abuse (102). Six (35–37, 44, 45, 53) of the 24 studies on smoking and five (35, 45, 53, 64, 66) of the nine studies on alcohol adjusted for illicit drug use during pregnancy but with no effect on the results. A recent review of cocaine abuse during pregnancy concluded that negative effects may be secondary to the effect of smoking or alcohol intake (103).

Conclusions

Studies on maternal lifestyle factors and ADHD or ADHD-like symptoms in the offspring are few and of poor quality. The research is characterized by retrospective assessment of prenatal exposure and lack of diagnostic assessment of ADHD. Few studies adjusted for familial psychopathology. Because of these limitations, no sound conclusion can be drawn regarding the association between maternal lifestyle factors and ADHD and ADHD symptoms in the offspring. However, there may be an association with exposure to tobacco smoke in utero.

This review illustrates the need for more rigorous studies. New studies should avoid recall bias and selection bias, and their designs should result in sufficient statistical power. Follow-up studies based on large community-based samples with prospectively collected exposure measures during pregnancy are preferable. The optimal measures of exposure should include a quantitative measure during each trimester, preferably a biochemical measure (if needed or available in each trimester), to improve the validity of the self-reported measures. Since we do not know if ADHD represents an etiologic entity, studies should focus either on specific behavioral aspects or

on a well-defined ADHD phenotype for a broader age category of children.

Information on parental psychopathology is essential to fully exploring the association between ADHD and exposure to maternal lifestyle factors.

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