Maternal Smoking and Attention-Deficit/Hyperactivity Disorder in Offspring: A Meta-analysis

Lan Huang, PhD,[a,b] Yan Wang, MD,[a,b] Li Zhang, MD,[a,b] Zhen Zheng, PhD,[a,b] Tingting Zhu, MD,[a,b] Yi Qu, PhD,[a,b] Dezhi Mu, MD, PhD[a,b]

abstract

CONTEXT: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood. Exploring the risk factors for ADHD is helpful in preventing ADHD.

OBJECTIVE: To explore the association between maternal smoking during pregnancy and the occurrence of ADHD in offspring.

DATA SOURCES: PubMed, Embase, and Cochrane Library were searched from inception to May 2017 for studies.

STUDY SELECTION: Cohort or case-control studies in which the association between maternal smoking and ADHD in offspring were investigated were eligible if they included odds ratios (ORs), hazard ratios, or risk ratios and 95% confidence intervals (CIs).

DATA EXTRACTION: Two investigators independently extracted data on definition of exposure and outcome, number of cases and total sample population, and potential confounders adjusted. Any dose-relationship data for smoking and ADHD risk were also extracted.

RESULTS: Fifteen cohort studies and 5 case-control studies with 50 044 cases and 2 998 059 participants were included. Smoking during pregnancy increased the risk of offspring ADHD (OR: 1.60; 95% CI: 1.45–1.76). The risk of ADHD was greater for children whose mothers were heavy smokers (OR: 1.75; 95% CI: 1.51–2.02) than for those mothers were light smokers (OR: 1.54; 95% CI: 1.40–1.70).

LIMITATIONS: The limitations of our study included different assessment tools of ADHD and a lack of objective biological measures for maternal smoking.

CONCLUSIONS: With our meta-analysis, we provide evidence for an association between maternal smoking and offspring ADHD but do not solve the causality issues concerning potential confounding by other risk factors. More high-quality studies are needed to establish whether the association with smoking is causal.

[a]*Department of Pediatrics, West China Second University Hospital and* [b]*Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects, Ministry of Education, Sichuan University, Chengdu, China*

Drs Mu and Huang conceptualized the study, designed the study, and reviewed and revised the manuscript; Drs Wang and Zhang collected data, drafted the initial manuscript, and conducted the initial analyses; Drs Zheng, Qu, and Zhu designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2017-2465

Accepted for publication Oct 3, 2017

To cite: Huang L, Wang Y, Zhang L, et al. Maternal Smoking and Attention-Deficit/Hyperactivity Disorder in Offspring: A Meta-analysis. *Pediatrics.* 2018;141(1):e20172465

Attention-deficit/hyperactivity disorder (ADHD), a common neurodevelopmental disorder, is characterized by inattention, impulsivity, and/or hyperactive or impulsive behaviors and often persists into adulthood, with worldwide prevalence estimates ranging from 3% to 10% of school-aged children.[1–3] ADHD is associated with co-occurring psychiatric disorders in both boys and girls, including comorbid mood disorders (depression, anxiety), other disruptive behaviors (oppositional defiant disorder and conduct disorder), antisocial activities, poor verbal working memory, and substance abuse and dependency.[4,5] In the United States, overall annual incremental costs of ADHD have been calculated at $143 billion to $266 billion, including productivity and income losses for adults and health care and education losses for ADHD children.[6] The high prevalence, chronic nature, and heavy economic burden associated with ADHD make it a concern in public health.

Although the etiology of ADHD is poorly understood, a line of evidence suggests that this is a genetically- as well as environmentally-determined disorder. The authors of familial, twin, and adoption studies have indicated that there is a genetic component, with a heritability estimate of 70% to 80%.[7] Environmental factors, including lead exposure, alcohol exposure, and cigarette smoking, and nutritional factors in pregnancy may also be related to the occurrence and severity of ADHD. The effect of cigarette smoking during pregnancy on the outcomes of offspring attracts extensive attention. It is reported that 4.9% of pregnant women still smoke during pregnancy[8] in Japan. In the United States, the prevalence of maternal smoking during the third trimester of pregnancy was ~10% in 2010.[9]

The adverse effects of maternal smoking on pregnancy outcomes in the offspring include preterm delivery, low birth weight, placenta abruption, reduced fetal lung development, increased infection in infancy, sudden infant death syndrome, the development of obesity or overweight, and an increased probability of smoking.[10,11] Evidence regarding the association between maternal smoking during pregnancy and the development of ADHD is inconsistent. Several studies have found that maternal smoking during pregnancy was a risk factor for the development of ADHD in offspring.[12,13] Animal experiments have also revealed that the offspring of rats with prenatal nicotine exposure are hyperactive.[14] However, the authors of other studies have failed to find an increased risk of ADHD in children whose mothers smoked during pregnancy, compared with those whose mothers did not smoke.[15–17] Therefore, we performed the current study to systematically evaluate the association between maternal smoking during pregnancy and ADHD risk in offspring. Given the high prevalence of maternal smoking and ADHD, establishing whether maternal smoking during pregnancy and ADHD in offspring is associated is meaningful from a clinical and public health perspective. Additionally, the finding of a significant association would prompt efforts to advocate smoking cessation during pregnancy for the prevention of ADHD.

METHODS

Retrieval of Studies

A systematic search of PubMed, Embase, and Cochrane Library was conducted to locate related studies. The following keywords, including medical subject heading terms and free-text terms, were used in the search strategy: "attention-deficit/hyperactivity disorder" or "ADHD" or "attention deficit disorders with hyperactivity" or "hyperkinetic disorder" or "hyperkinetic syndrome and pregnancy" or ''pregnancies" or "perinatal" or "gestation" or "prenatal" or "antenatal" or "maternal and smoke" or "smoking" or "tobacco" or "nicotine." We limited all results to studies in humans that were published in English. No restrictions were placed on location of the study or age of the participants. The single study with the largest sample size was included if participants overlapped between studies. Clearly irrelevant studies were excluded by scanning the titles and abstracts. We also reviewed searches of references of key retrieved articles manually. Next, 2 investigators independently read the full text of the remaining articles to assess their eligibility according to our inclusion criteria. Disagreements on the inclusion eligibility were resolved by a third author when required.

Eligibility Criteria

Inclusion criteria for our study were as follows: (1) those with a cohort or case-control design, (2) those in which the association between maternal smoking during pregnancy and ADHD risk in offspring was reported, and (3) those in which the authors reported the total number of participants, number of cases, odds ratios (ORs), hazard ratios, or risk ratios and 95% confidence intervals (CIs). Exclusion criteria for the study were as follows: (1) case reports, conference abstracts, reviews, and animal studies; (2) studies with overlapping data; (3) studies on passive smoking; and (4) studies without raw data.

Data Extraction

Two reviewers independently extracted data on the first author, publication year, country, study design, age, definition of exposure and outcome, number of cases and total sample population, and potential confounders adjusted. Any

dose-relationship data for smoking and ADHD risk were also extracted.

Quality Assessment

The methodological quality of studies was examined by using the Newcastle-Ottawa Scale, which was recommended for quality assessment of cohort and case-control studies with a maximum score of 9. The quality of the study was divided into 3 categories: high quality (scored 7–9), moderate quality (scored 4–6), and low quality (scored 0–3).[18]

Statistical Analysis

The ORs were used as a measure of the association between maternal smoking and the risk of offspring ADHD among studies. The hazard and risk ratios were directly considered as ORs in the pooled analysis. We used a random effects model to calculate the pooled ORs. The I^2 statistic[19] (significance level, >50%) and Q statistic (significance level at $P < .10$) were used to assess heterogeneity among studies. Subgroup analyses were stratified by study design, study location, study quality, and the degree of smoking exposure. Additionally, we conducted the sensitivity analysis by excluding 1 study in each turn. The possibility of publication bias was visually assessed by using the Begg's test (significance level, $P < .05$). We also performed the "trim-and-fill" procedure to further assess the possible effect of publication bias in our meta-analysis. Stata version 12.0 (StataCorp, College Station, TX) was used for all analyses.

RESULTS

Literature Search and Selection

A total of 650 articles were identified, with 300 from PubMed, 345 from Embase, and 5 from the Cochrane Database. Of these, 160 duplicates, 128 reviews, 11 animal experiments, and 273 irrelevant studies were excluded, resulting in 78 studies for full-text review. After careful screening, 20 studies[12,13,15,20–36] were selected for final inclusion in this study (Fig 1).

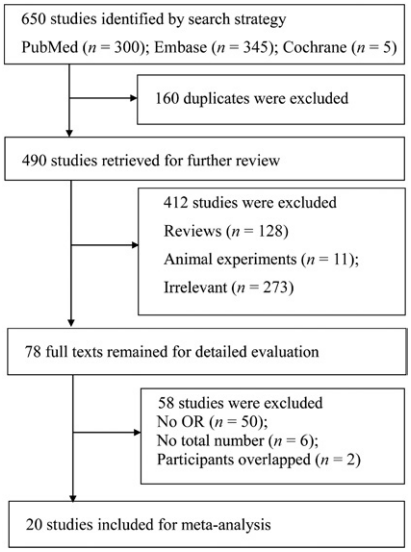

FIGURE 1
Flow diagram of the study selection process.

Study Characteristics

Characteristics of the 20 selected studies are shown in Table 1. The selected studies were published between 1998 and 2017. Of the 20 studies, there were 5 case-control studies and 15 cohort studies, with a total of 50 044 cases and 2 998 059 participants. In 5 of the selected studies,[12,13,20,22,27] authors reported the ORs separately for boys and girls, including 634 229 boys and 576 170 girls. In the 3 cohort studies,[20,27,36] the authors used sibling analysis to control for shared genetic and social confounding. The sample size of the studies ranged from 260 to 982 856. Seven studies were performed in the United States,[15,23,30,31,33–35] 9 were performed in Europe,[12,13,20,21,24,25,27,28] 1 was performed in Brazil,[32] 1 was performed in Japan,[29] and 2 were performed in Australia.[22,26] For the diagnosis of ADHD, the authors of most of the studies reported the criteria for the diagnosis of ADHD; only 1 study did not include this information.[28] In 12 of the selected studies, researchers adopted the diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM-III-R*)[30,31,34,35] or the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*),[15,23–25,29,32,33] whereas the *International Classification of Diseases, 10th Revision* (*ICD-10*) was used as the diagnostic method for ADHD in only 3 studies.[20,27,36] In 2 studies, the authors chose measures to assess ADHD, such as the Strengths and Difficulties Questionnaire (SDQ)[13,21] and Child Behavior Questionnaire (Rutter B2).[12] The information about smoking was generally collected by interviews or according to related registers. According to the Newcastle-Ottawa Scale, the overall methodological quality was good, with 15 studies that were high quality and 5 studies that were moderate quality (Supplemental Table 3).

Maternal Smoking During Pregnancy and the Risk of ADHD in Offspring

Smoking during pregnancy increased the risk of ADHD in offspring with a pooled adjusted OR of 1.60 (95% CI: 1.45–1.76), indicating the positive association between maternal smoking during gestation and ADHD in offspring (Fig 2).Statistically significant heterogeneity was found across studies ($I^2 = 79.2\%$; $P < .001$).

Subgroup and Sensibility Analyses

To explore heterogeneity, we performed subgroup analyses stratified by adjustment for confounders, study design, study location, study quality, diagnosis of ADHD, and the degree of smoking exposure (Table 2). A lower pooled OR was observed in studies conducted in the United States (OR: 1.25, 95% CI: 1.07–1.47) or Europe (OR: 1.67, 95% CI: 1.50–1.86) than in studies conducted in other places (OR: 1.86, 95% CI: 1.57–2.21), including Japan, Australia, and Brazil. Notably, there seems to be a

TABLE 1 Characteristics of Included Studies of Maternal Smoking During Pregnancy and ADHD

Study	Location	Design	ADHD Cases/Total Participants	Age (y)	Ascertainment of Smoking	Ascertainment of ADHD	Diagnosis of ADHD	Confounding Factors
Milberger et al[35]	United States	ML	140/260	6–17	Diagnostic interview for children and adolescents–parent version	Children were interviewed by a specialist in child and adolescent psychiatry	*DSM-III-R*	Socioeconomic status, maternal IQ, maternal ADHD, paternal IQ, and paternal ADHD
Mick et al[34]	United States	ML	280/522	6–17	Collected by structured diagnostic interview and self-reported regarding her own psychiatric history	Interviews with each parent and medical record	*DSM-III-R*	Maternal age at child's birth, indicators of social adversity, parental history of ADHD, parental history of CD and/or ASPD, and comorbid CD
Kotimaa et al[12]	Northern Finland	C	808/8478	8	Recorded at recruitment	Parents and teachers completed questionnaires on the child's development or behavior	Child Behavior Questionnaire (Rutter B2)	Sex, family structure, socioeconomic status, maternal age, and alcohol use during pregnancy
Knopik et al[33]	United States	C	255/3872	14.4	Extracted from maternal interview data	Interview with mother	*DSM-IV*	Birth wt, parental alcohol history, and maternal alcohol use during pregnancy
Schmitz et al[32]	Brazil	ML	100/200	6–18	Collected by direct interview with the biological mother	Screened by SNAP-IV and diagnosed by child and adolescent psychiatrist	*DSM-IV*	Alcohol use during pregnancy, birth wt, maternal ADHD, and oppositional defiant disorder
Wakschlag et al[31]	United States	C	78/448	7	Extract from maternal report on background interview	Interview with parents and children	*DSM-III-R*	Drug use
Nigg and Breslau[30]	United States	ML	94/713	6 and 11	Collected by direct interview with the biological mother	Interview with mothers	*DSM-III-R*	Maternal substance use disorders, birth wt, education level, and location
Yoshimasu et al[29]	Japan	ML	90/360	6–15	Investigated by a questionnaire	Diagnosed by experienced psychiatrists or pediatricians	*DSM-IV*	Children's sex, family income, maternal drinking during pregnancy, pregnancy-induced hypertension, birth wt, children's iron intake, maternal tendency of ADHD, parental history of mental disorders, and maternal mental stress during pregnancy
Ball et al[15]	United States	C	219/2024	7	Collected beginning with the initial prenatal assessment and prospectively up to the day of birth by interview	Diagnosed by psychologists	*DSM-IV*	Ascertainment source, family psychopathology, maternal education, and sex of offspring

TABLE 1 Continued

Study	Location	Design	ADHD Cases/Total Participants	Age (y)	Ascertainment of Smoking	Ascertainment of ADHD	Diagnosis of ADHD	Confounding Factors
Lindblad and Hjern[28]	Sweden	C	6496/982 856	6–19	Collected by the midwife at the first visit to the maternity health clinic, 8–12 wk after conception	Swedish Prescribed Drug Register	Not mentioned	Age, year of birth, sex, county of residence, maternal age, birth order, maternal education, single parent, social assistance, maternal and/or paternal psychiatric and/or addictive disorders, small for gestational age, and low Apgar score
Hutchinson et al[13]	United Kingdom	C	1199/13 654	3	Collected by interview	Interview with mothers	SDQs	Mother's age (y) at index, child's birth; No. children in the household, mother's ethnicity, and psychosocial and parenting domains
Obel et al[27]	Finland	C, sibling analysis	7023/868 449	NA	Finnish Medical Birth Register	Finnish Hospital Discharge Register	*ICD-10*	Sex, year of birth, maternal age, gestational age at birth, and parity
Sciberras et al[26]	Australia	C	64/3474	6–7	Investigated by a questionnaire	Interview with the primary caregiver	*DSM-IV*	Maternal alcohol use during pregnancy, maternal postnatal depression, intensive care at birth, child's birth wt, sociodemographic factors, maternal age at child birth, No. people in the household, primary caregiver education, and marital status
Langley et al[25]	United Kingdom	C	121/5637	7.6	Collected at 18 and 32 weeks' gestation by interview	Interview with parents	*DSM-IV*	Child's sex, ethnicity, multiple births (twins), maternal alcohol use during pregnancy, and social class
Sagiv et al[23]	United States	C	75/601	8	Extract from a questionnaire administered 2 wk after birth	Pediatric medical records	*DSM-IV*	Maternal age at child's birth, maternal education, paternal education, maternal marital status and annual household income at child's school age, maternal alcohol consumption during pregnancy, maternal illicit drug use in year before birth, maternal IQ, maternal depression symptoms, HOME score, children's gestational age, sex, race, breastfeeding, type of school, No. siblings living in house
Jaspers et al[24]	Netherlands	C	419/1816	1.5–4	Preventive Child Healthcare files	Interview with parents	*DSM-IV*	Alcohol use during pregnancy, low birth wt, and birth defects
Silva et al[22]	Australia	ML	12 991/43 062	<25	Records of midwives notification system	Monitoring of Drugs of Dependence system	*DSM-IV* or *ICD-10*	Maternal age, marital status, first pregnancy, threatened abortion, threatened preterm labor, maternal UTI, preeclampsia, onset of labor induced, augmentation of labor, complications of labor, type of delivery, weeks' gestation, and birth wt

TABLE 1 Continued

Study	Location	Design	ADHD Cases/Total Participants	Age (y)	Ascertainment of Smoking	Ascertainment of ADHD	Diagnosis of ADHD	Confounding Factors
Melchior et al[21]	France	C	176/1113	5	Investigated by a questionnaire	Interview with mothers	SDQ	Children's sex, premature birth, birth wt, duration of breastfeeding, maternal age at birth, maternal psychological difficulties in pregnancy, maternal depression postpregnancy, maternal alcohol use in pregnancy, maternal smoking postpregnancy, paternal tobacco smoking during and postpregnancy, study center, parents' educational attainment, family income, parental separation, No. siblings, and negative life events
Obel et al[20]	Denmark	C, sibling analysis	17 381/968 665	NA	Medical Birth Register	Medical Birth Register or medication record	*ICD-10*	Sex, birth year, parity, and mother's age
Gustavson et al[36]	Norway	C, sibling analysis	2035/104 846	5–15	Mother self-report	Norwegian Patient registry	*ICD-10*	Maternal and paternal age, maternal and paternal education, maternal and paternal ADHD symptoms, maternal (prepregnancy) and paternal BMI, maternal alcohol consumption during pregnancy, parity, child's birth year, and geographical region

ASPD, antisocial personality disorder; C, cohort; CD, conduct disorder; HOME, home observation for measurement of the environment; ML, case control; NA, not applicable; SNAP-IV, Swanson, Nolan, and Pelham Teacher and Parent Rating Scale, UTI, urinary tract infection.

dose-response relationship between maternal smoking and ADHD in children. The sibling analysis failed to reveal the relationship between maternal smoking and AHDH in offspring with a pooled OR of 1.04 (95% CI: 0.95–1.15). The child whose mother is a heavy smoker (10 or more cigarettes per day) seems to have a greater risk for the development of ADHD (OR: 1.75, 95% CI: 1.51–2.02) compared with those whose mother is a light smoker (10 or fewer cigarettes per day; OR: 1.54, 95% CI: 1.40–1.70). The risk of developing ADHD is comparable for boys (OR: 1.51, 95% CI: 1.30–1.76) and girls (OR: 1.43, 95% CI: 1.15–1.78) whose mothers smoked during pregnancy. A stronger association was found in studies unadjusted for maternal alcohol (OR: 1.74, 95% CI: 1.57–1.92) than in studies that adjusted for this confounder (OR: 1.43, 95% CI: 1.31–1.57). The pooled OR of studies adjusted for parental ADHD (OR: 1.59, 95% CI: 1.44–1.75) was comparable to that of studies not adjusted for parental ADHD (OR: 1.58, 95% CI: 1.41–1.76). The overall pooled result did not vary substantially (Supplemental Table 4) after excluding 1 study in each turn.

Publication Bias

Visual inspection of the funnel plot revealed a potential publication bias (Supplemental Fig 3), although the Begg's test was not statistically significant (z score = 1.2; P = .23). We further undertook a sensitivity analysis by using the trim-and-fill method[37] to estimate the number of missing studies that may have caused funnel plot asymmetry, and we imputed the hypothetical studies to produce a symmetrical funnel plot. No theoretical missing trials were incorporated, which reveals a remarkable association between maternal smoking during pregnancy and ADHD in offspring.

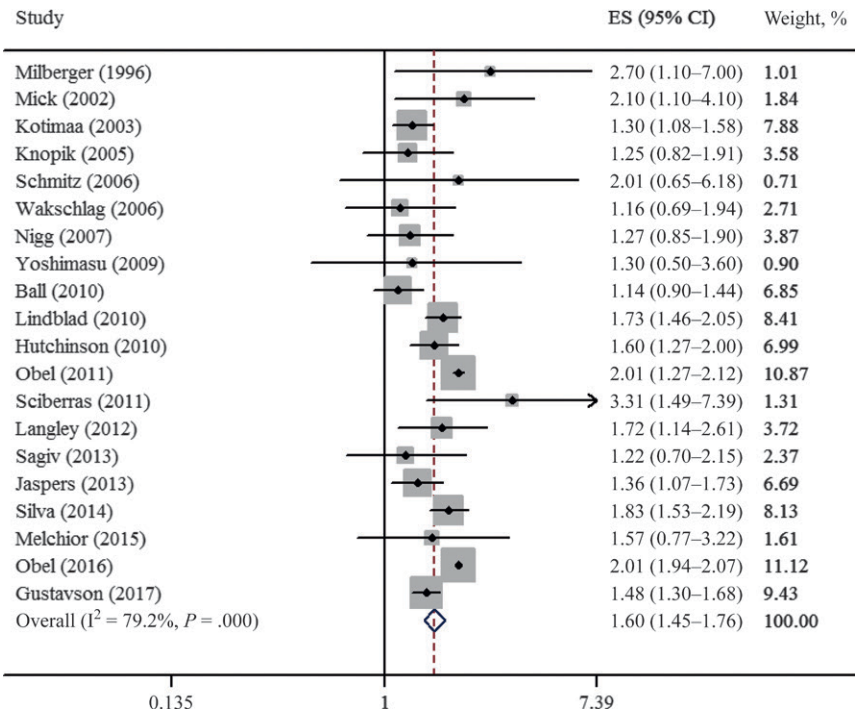

FIGURE 2
Adjusted ORs expressing the association between maternal smoking and offspring ADHD. Weights are from random effects analysis. ES, effect size.

TABLE 2 Pooled ORs and Heterogeneity in Subgroups Analyses

Variables	No. Studies	OR (95% CI)	I^2%	*P* for Heterogeneity
Study design				
Cohort	15	1.35 (1.20–1.52)	59.5	.002
Case control	5	1.85 (1.57–2.19)	0	.859
Location				
United States	7	1.25 (1.07–1.47)	0	.452
Europe	9	1.67 (1.50–1.86)	85.2	<.001
Others	4	1.86 (1.57–2.21)	0	.466
Study quality				
M	5	1.55 (1.25–1.91)	50.5	.088
H	15	1.62 (1.46–1.80)	79.6	<.001
Sibling design				
Yes	3	1.04 (0.95–1.15)	44.7	.164
No	17	1.50 (1.35–1.67)	37.7	.059
Smoking categories of mother				
Light	6	1.54 (1.40–1.70)	58.9	.03
Severe	6	1.75 (1.51–2.02)	77	.001
Sex				
Male	5	1.43 (1.15–1.78)	74.1	.004
Female	5	1.51 (1.30–1.76)	0	.465
Adjusted factors				
Maternal alcohol				
Yes	10	1.43 (1.31–1.57)	0	.582
No	10	1.74 (1.57–1.92)	76.7	<.001
Parental ADHD				
Yes	6	1.59 (1.44–1.75)	0	.486
No	14	1.58 (1.41–1.76)	81.9	<.001

Others include Japan, Australia, and Brazil. Light referred to 1–9 cigarettes/d or 1–10 cigarettes/d; Severe referred to ≥10 cigarettes/d. H, high; M, moderate.

DISCUSSION

The results of our meta-analysis based on 20 observational studies with a total a total of 50 044 cases and 2 998 059 participants reveal that maternal smoking during pregnancy is associated with a 60% increased odds of ADHD in offspring in the pooled estimate, after adjusting for the potential confounders.

Our study also reveals that there may be a dose-response relationship between smoking during pregnancy and the risk of ADHD in offspring. The dose-related concentration of cotinine in cord serum and urine of newborns was observed, and the neonates with fetal exposure of consistently high daily nicotine had the most elevated cotinine level.[38]

However, high heterogeneity was detected in this meta-analysis; therefore, further analysis was required. To explore the heterogeneity of the studies, we conducted subgroup analysis stratified by several key study characteristics, such as study design, location, and study quality. In the subgroup analysis, we found that the heterogeneity decreased significantly when studies were categorized by sibling design, revealing that different study analyses may contribute to the heterogeneity. The participants of sibling-analysis were limited to matched siblings, which were different from traditional case-control study or cohort study.

We found that lower pooled OR was observed in studies conducted in the United States or Europe. Smoking cessation rates during pregnancy that were relatively higher in the United States and Europe than in other regions may have led to the difference. The cessation rates during pregnancy were reported as 35% to 42.5% in the United States,[39] 27% to 47% in Europe,[40] 18% to 21% in Brazil,[41] and 4% to 34.1% in Australia.[40]

A key issue when investigating the role of a certain environmental factors in the development of ADHD is the possibility of confounding by genetics and other environmental factors. It was reported that the prevalence of parental ADHD was higher in children with ADHD,[34] and children born to parents with ADHD had an increased risk of ADHD.[42] We also noted that the authors of studies with a sibling design did not show the relationship between maternal smoking and ADHD,[20,27,36] suggesting a key role for genetics in the development of ADHD. In those sibling-design studies, the authors suggested that the family context and genetic factors are similar in siblings. However, Frisell et al[43] pointed out that in studies of pairs of siblings, more bias exists when there are nonshared factors. Although mothers shared some characteristics with siblings, differing characteristics such as maternal age, paternal age, parity, and gravidity still existed. All of these differences may result in biased conclusions regarding the relationship between maternal smoking and ADHD in sibling studies. Meanwhile, Mick et al[34] found that the relationship between ADHD and maternal smoking was significant after adjustment for parental ADHD. Our subgroup analysis also found that there was no difference in the increased risk of offspring ADHD, regardless of whether parental ADHD was adjusted. Therefore, maternal smoking might be a risk factor for ADHD.

Smoking and alcohol consumption often coexist. Maternal alcohol consumption, an important perinatal factor, was reported to increase the risk of ADHD in several studies.[12,16,44] However, the authors of other studies provided contradictory evidence.[12,21] We searched the databases to locate studies on the association between alcohol consumption during pregnancy and ADHD. The pooled OR from the 10 included studies was 1.40 (95% CI: 1.22–1.61)* (Supplemental Fig 4). These findings revealed that alcohol consumption during pregnancy may be associated with offspring ADHD.

All of the included studies except the one conducted by Melchior et al[21] were not adjusted for paternal smoking. Therefore, we could not complete a subgroup analysis for paternal smoking. Keyes et al[45] found that there was no association between paternal smoking and offspring ADHD after adjustment for several covariates. In contrast, Gustavson et al[36] reported that paternal smoking increased the risk of ADHD by 1.23 times. We searched the databases, and 7 related studies were included for further analysis.[21,25,36,45–48] The pooled OR was 1.20 (95% CI: 1.08–1.32) (Supplemental Fig 5), revealing a potential association between paternal smoking and offspring ADHD. However, Zhu et al[47] found that children born to smoking mothers and nonsmoking fathers had a higher risk of ADHD than those who born to nonsmoking mothers and smoking fathers, which suggested that maternal smoking was more important than paternal smoking in the development of ADHD.

The possible mechanism by which maternal smoking results in the onset of ADHD in offspring includes the direct adverse effects of tobacco smoke on the structure and function of the developing brain, as well as the relative gene alteration. Tobacco smoke contains more than 4000 different ingredients, and many of these compounds may have a potential adverse effect on neurodevelopment. As the major psychoactive chemical in tobacco, nicotine is the chemical that most probably adversely effects neurodevelopment.[49] De Zeeuw et al[50] compared brain volumes derived from anatomic magnetic resonance imaging scans and found that ADHD patients with a prenatal cigarette exposure history had a smaller cerebellum volume. Roy et al[51] reported that a substantial decrease in cell size in the hippocampus and a reduction in the proportion of medium-sized pyramidal neurons in the somatosensory cortex were found in rats exposed to nicotine prenatally. Animal models also revealed that prenatal nicotine exposure disrupted the proliferation and differentiation of neuronal progenitors.

Our study has several merits. Because of the large sample size of our study, the possibility of reaching reasonable conclusions about the association between maternal smoking and ADHD was much greater. The positive association between maternal smoking during pregnancy and ADHD in offspring remained across a number of stratified analyses, which revealed the high reliability of our findings. By using the 2-level categorical smoking variable, we also found a positive dose-response relationship between maternal smoking and ADHD in children.

Limitations of our analysis also must be considered. First, the different assessments of ADHD used among studies may have led to misclassification bias. Diagnostic criteria have been identified as a factor associated with variability in the prevalence of ADHD. The *ICD-10* and *DSM-IV* criteria include similar lists of symptoms, but the recommended methods for establishing a diagnosis were different. Polanczyk et al[52] reported that the prevalence rates based on the *DSM-III-R*, *ICD-10*, and *DSM-IV* varied, with the highest estimated prevalence calculated by using the *DSM-IV*. The authors of further

*Refs 12,16,21,26,30,32–34,55,56.

studies should attempt to adopt similar diagnostic criteria for the selection of the cases. Second, the important confounding factors were not fully adjusted in the included studies, which may have resulted in confusion in relation to the conclusion. Third, tobacco use during pregnancy was generally ascertained by self-report without objective biological measures, so there was a possibility that participants tended to narrow their smoking status, which may have led to the misclassification of maternal smoking. To avoid the misclassification bias, combining self-report with biological assessment may be the optimal method to ascertain the prevalence and degree of maternal smoking during pregnancy in future studies. Fourth, Gard et al[53] reported that girls prenatally exposed to nicotine had greater hyperactivity and/or impulsivity symptoms. Joo et al[54] also found that prenatal secondhand smoke exposure increased the risk of ADHD, especially in terms of hyperactivity and/or impulsivity. It seems that prenatal smoking and/or nicotine exposure may be more relevant to the hyperactivity components of ADHD. Knowing the specific symptom domain of ADHD associated with prenatal smoking and/or nicotine exposure may be helpful in understanding the toxicological mechanism. However, the authors of the included studies did not distinguish among the components of ADHD in reporting the effect of maternal smoking on offspring. More studies are needed to explore the relationship between prenatal nicotine exposures and the specific symptoms of ADHD.

CONCLUSIONS

On the basis of our analyses, we suggest that there is a link between maternal smoking during pregnancy and ADHD in offspring. However, the association between maternal smoking during pregnancy and ADHD in offspring should be interpreted cautiously, because it may be confounded by familial and genetic factors. There is a need for more high-quality studies in which potential confounding factors are adjusted for fully and in which standardized diagnostic approaches are adopted to establish whether the association with smoking is causal. The authors of future studies should also focus on the explicit mechanism of maternal smoking during pregnancy that increases the risk of ADHD in offspring.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
CI: confidence interval
DSM-III-R: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*
DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
ICD-10: *International Classification of Diseases, 10th Revision*
OR: odds ratio
SDQ: Strengths and Difficulties Questionnaire

Address correspondence to Dezhi Mu, MD, PhD, Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China. E-mail: mudz@scu.edu.cn

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the National Science Foundation of China (81330016 and 81630038); the National Key Research and Development Program (2017YFA0104200), the Major State Basic Research Development Program (2013CB967404, 2012BAI04B00), a grant from the Ministry of Education of China (IRT0935), grants from Science and Technology Bureau of Sichuan province (2014SZ0149, 2016TD0002), and a clinical discipline program (neonatology) grant from the Ministry of Health of China (1311200003303).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Faraone SV, Doyle AE. The nature and heritability of attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am*. 2001;10(2):299–316, viii–ix
2. Rommelse NN, Geurts HM, Franke B, Buitelaar JK, Hartman CA. A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. *Neurosci Biobehav Rev*. 2011;35(6):1363–1396
3. Linnet KM, Dalsgaard S, Obel C, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry*. 2003;160(6):1028–1040
4. Biederman J, Petty CR, Monuteaux MC, et al. Adult psychiatric outcomes of girls with attention deficit hyperactivity disorder: 11-year follow-up in a longitudinal case-control study. *Am J Psychiatry*. 2010;167(4):409–417
5. McGough JJ, Smalley SL, McCracken JT, et al. Psychiatric comorbidity in adult attention deficit hyperactivity disorder:

findings from multiplex families. *Am J Psychiatry*. 2005;162(9):1621–1627

6. Doshi JA, Hodgkins P, Kahle J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry*. 2012;51(10):990–1002.e2
7. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2005;57(11):1313–1323
8. Mine T, Tanaka T, Nakasone T, Itokazu T, Yamagata Z, Nishiwaki Y. Maternal smoking during pregnancy and rapid weight gain from birth to early infancy. *J Epidemiol*. 2017;27(3):112–116
9. Tong VT, Dietz PM, Morrow B, et al; Centers for Disease Control and Prevention (CDC). Trends in smoking before, during, and after pregnancy–pregnancy risk assessment monitoring system, United States, 40 sites, 2000-2010. *MMWR Surveill Summ*. 2013;62(6):1–19
10. Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. *Am J Epidemiol*. 2014;179(7):807–823
11. Herrmann M, King K, Weitzman M. Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. *Curr Opin Pediatr*. 2008;20(2):184–190
12. Kotimaa AJ, Moilanen I, Taanila A, et al. Maternal smoking and hyperactivity in 8-year-old children. *J Am Acad Child Adolesc Psychiatry*. 2003;42(7):826–833
13. Hutchinson J, Pickett KE, Green J, Wakschlag LS. Smoking in pregnancy and disruptive behaviour in 3-year-old boys and girls: an analysis of the UK Millennium Cohort Study. *J Epidemiol Community Health*. 2010;64(1):82–88
14. Zhu J, Zhang X, Xu Y, Spencer TJ, Biederman J, Bhide PG. Prenatal nicotine exposure mouse model showing hyperactivity, reduced cingulate cortex volume, reduced dopamine turnover, and responsiveness to oral methylphenidate treatment. *J Neurosci*. 2012;32(27):9410–9418
15. Ball SW, Gilman SE, Mick E, et al. Revisiting the association between maternal smoking during pregnancy and ADHD. *J Psychiatr Res*. 2010;44(15):1058–1062
16. Hill SY, Lowers L, Locke-Wellman J, Shen SA. Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. *J Stud Alcohol*. 2000;61(5):661–668
17. Thapar A, Rice F, Hay D, et al. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. *Biol Psychiatry*. 2009;66(8):722–727
18. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603–605
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560
20. Obel C, Zhu JL, Olsen J, et al. The risk of attention deficit hyperactivity disorder in children exposed to maternal smoking during pregnancy - a re-examination using a sibling design. *J Child Psychol Psychiatry*. 2016;57(4):532–537
21. Melchior M, Hersi R, van der Waerden J, et al; EDEN Mother-Child Cohort Study Group. Maternal tobacco smoking in pregnancy and children's socio-emotional development at age 5: the EDEN mother-child birth cohort study. *Eur Psychiatry*. 2015;30(5):562–568
22. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. *Pediatrics*. 2014;133(1). Available at: www.pediatrics.org/cgi/content/full/133/1/e14
23. Sagiv SK, Epstein JN, Bellinger DC, Korrick SA. Pre- and postnatal risk factors for ADHD in a nonclinical pediatric population. *J Atten Disord*. 2013;17(1):47–57
24. Jaspers M, de Winter AF, Buitelaar JK, Verhulst FC, Reijneveld SA, Hartman CA. Early childhood assessments of community pediatric professionals predict autism spectrum and attention deficit hyperactivity problems. *J Abnorm Child Psychol*. 2013;41(1):71–80
25. Langley K, Heron J, Smith GD, Thapar A. Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. *Am J Epidemiol*. 2012;176(3):261–268
26. Sciberras E, Ukoumunne OC, Efron D. Predictors of parent-reported attention-deficit/hyperactivity disorder in children aged 6-7 years: a national longitudinal study. *J Abnorm Child Psychol*. 2011;39(7):1025–1034
27. Obel C, Olsen J, Henriksen TB, et al. Is maternal smoking during pregnancy a risk factor for hyperkinetic disorder?–Findings from a sibling design. *Int J Epidemiol*. 2011;40(2):338–345
28. Lindblad F, Hjern A. ADHD after fetal exposure to maternal smoking. *Nicotine Tob Res*. 2010;12(4):408–415
29. Yoshimasu K, Kiyohara C, Minami T, et al; Wakayama ADHD Study Group. Maternal smoking during pregnancy and offspring attention-deficit/hyperactivity disorder: a case-control study in Japan. *Atten Defic Hyperact Disord*. 2009;1(2):223–231
30. Nigg JT, Breslau N. Prenatal smoking exposure, low birth weight, and disruptive behavior disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46(3):362–369
31. Wakschlag LS, Pickett KE, Kasza KE, Loeber R. Is prenatal smoking associated with a developmental pattern of conduct problems in young boys? *J Am Acad Child Adolesc Psychiatry*. 2006;45(4):461–467
32. Schmitz M, Denardin D, Laufer Silva T, et al. Smoking during pregnancy and attention-deficit/hyperactivity disorder, predominantly inattentive type: a case-control study. *J Am Acad Child Adolesc Psychiatry*. 2006;45(11):1338–1345
33. Knopik VS, Sparrow EP, Madden PA, et al. Contributions of parental alcoholism, prenatal substance exposure, and genetic transmission to child ADHD risk: a female twin study. *Psychol Med*. 2005;35(5):625–635
34. Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S. Case-control study of attention-deficit hyperactivity disorder

and maternal smoking, alcohol use, and drug use during pregnancy. *J Am Acad Child Adolesc Psychiatry*. 2002;41(4):378–385

35. Milberger S, Biederman J, Faraone SV, Jones J. Further evidence of an association between maternal smoking during pregnancy and attention deficit hyperactivity disorder: findings from a high-risk sample of siblings. *J Clin Child Psychol*. 1998;27(3):352–358
36. Gustavson K, Ystrom E, Stoltenberg C, et al. Smoking in pregnancy and child ADHD. *Pediatrics*. 2017;139(2):e20162509
37. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455–463
38. Pichini S, Basagaña XB, Pacifici R, et al. Cord serum cotinine as a biomarker of fetal exposure to cigarette smoke at the end of pregnancy. *Environ Health Perspect*. 2000;108(11):1079–1083
39. Tong VT, Dietz PM, Farr SL, D'Angelo DV, England LJ. Estimates of smoking before and during pregnancy, and smoking cessation during pregnancy: comparing two population-based data sources. *Public Health Rep*. 2013;128(3):179–188
40. Schneider S, Huy C, Schütz J, Diehl K. Smoking cessation during pregnancy: a systematic literature review. *Drug Alcohol Rev*. 2010;29(1):81–90
41. Dias-Damé JL, Cesar JA. Disparities in prevalence of smoking and smoking cessation during pregnancy: a population-based study. *Biomed Res Int*. 2015;2015:345430
42. Joelsson P, Chudal R, Uotila J, et al. Parental psychopathology and offspring attention-deficit/hyperactivity disorder in a nationwide sample. *J Psychiatr Res*. 2017;94:124–130
43. Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology*. 2012;23(5):713–720
44. Bhatara V, Loudenberg R, Ellis R. Association of attention deficit hyperactivity disorder and gestational alcohol exposure: an exploratory study. *J Atten Disord*. 2006;9(3):515–522
45. Keyes KM, Davey Smith G, Susser E. Associations of prenatal maternal smoking with offspring hyperactivity: causal or confounded? *Psychol Med*. 2014;44(4):857–867
46. Nomura Y, Marks DJ, Halperin JM. Prenatal exposure to maternal and paternal smoking on attention deficit hyperactivity disorders symptoms and diagnosis in offspring. *J Nerv Ment Dis*. 2010;198(9):672–678
47. Zhu JL, Olsen J, Liew Z, Li J, Niclasen J, Obel C. Parental smoking during pregnancy and ADHD in children: the Danish national birth cohort. *Pediatrics*. 2014;134(2). Available at: www.pediatrics.org/cgi/content/full/134/2/e382
48. Kovess V, Keyes KM, Hamilton A, et al. Maternal smoking and offspring inattention and hyperactivity: results from a cross-national European survey. *Eur Child Adolesc Psychiatry*. 2015;24(8):919–929
49. Smith AM, Dwoskin LP, Pauly JR. Early exposure to nicotine during critical periods of brain development: mechanisms and consequences. *J Pediatr Biochem*. 2010;1(2):125–141
50. De Zeeuw P, Zwart F, Schrama R, Van Engeland H, Durston S. Prenatal exposure to cigarettes or alcohol affects the volume of cerebellum in attention-deficit/hyperactivity disorder. *Neuropsychopharmacology*. 2011;36:S150–S151
51. Roy TS, Seidler FJ, Slotkin TA. Prenatal nicotine exposure evokes alterations of cell structure in hippocampus and somatosensory cortex. *J Pharmacol Exp Ther*. 2002;300(1):124–133
52. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol*. 2014;43(2):434–442
53. Gard AM, Owens EB, Hinshaw SP. Prenatal smoke exposure predicts hyperactive/impulsive but not inattentive ADHD symptoms in adolescent and young adult girls. *Infant Child Dev*. 2016;25(4):339–351
54. Joo H, Lim MH, Ha M, et al. Secondhand smoke exposure and low blood lead levels in association with attention-deficit hyperactivity disorder and its symptom domain in children: a community-based case–control study. *Nicotine Tob Res*. 2017;19(1):94–101
55. Knopik VS, Heath AC, Jacob T, et al. Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. *Psychol Med*. 2006;36(10):1461–1471
56. Han JY, Kwon HJ, Ha M, et al. The effects of prenatal exposure to alcohol and environmental tobacco smoke on risk for ADHD: a large population-based study. *Psychiatry Res*. 2015;225(1–2):164–168

Maternal Smoking and Attention-Deficit/Hyperactivity Disorder in Offspring: A Meta-analysis

Lan Huang, Yan Wang, Li Zhang, Zhen Zheng, Tingting Zhu, Yi Qu and Dezhi Mu

Pediatrics 2018;141;
DOI: 10.1542/peds.2017-2465 originally published online December 29, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Maternal Smoking and Attention-Deficit/Hyperactivity Disorder in Offspring: A Meta-analysis

Lan Huang, Yan Wang, Li Zhang, Zhen Zheng, Tingting Zhu, Yi Qu and Dezhi Mu

Pediatrics 2018;141;
DOI: 10.1542/peds.2017-2465 originally published online December 29, 2017;