Smoking in Pregnancy and Child ADHD

Kristin Gustavson, PhD,[a,b] Eivind Ystrom, PhD,[a,b] Camilla Stoltenberg, MD, PhD,[a,c] Ezra Susser, MD, DrPH,[d,e] Pål Surén, MD, PhD,[a] Per Magnus, MD, PhD,[a] Gun Peggy Knudsen, PhD,[a] George Davey Smith, MD, DSc,[f] Kate Langley, PhD,[g,h] Michael Rutter, MD,[i] Heidi Aase, PhD,[a] Ted Reichborn-Kjennerud, MD, PhD[a,j]

abstract

BACKGROUND AND OBJECTIVE: There is a well-documented association between maternal smoking during pregnancy and offspring attention-deficit/hyperactivity disorder (ADHD). The degree to which this reflects causal intrauterine effects or is due to unmeasured confounding is not clear. We sought to compare the association between maternal smoking during pregnancy and offspring ADHD with the associations with paternal smoking, grandmother's smoking when pregnant with mother, and maternal smoking in previous pregnancies. Each of these exposures is expected to be influenced by much of the same confounding factors as maternal smoking during pregnancy, but cannot have direct intrauterine effects. A sibling control design was also used.

METHODS: The current study used data from the Norwegian Mother and Child Cohort Study (n > 100 000 children). Mothers and fathers reported on smoking during pregnancy, and mothers reported on smoking in previous pregnancies and their mother's smoking when pregnant with them. Mothers reported on child ADHD symptoms at 5 years of age. Information about child ADHD diagnosis was obtained from the Norwegian Patient Registry.

RESULTS: Maternal smoking during pregnancy was not more strongly associated with offspring ADHD diagnosis than was paternal smoking, grandmother's smoking when pregnant with mother, or maternal smoking in previous pregnancies. Sibling control analyses showed no association between maternal smoking in pregnancy and child ADHD symptoms among siblings discordant for maternal smoking.

CONCLUSIONS: These results suggest that the association between maternal smoking during pregnancy and offspring ADHD is not due to causal intrauterine effects, but reflects unmeasured confounding.

[a]*Norwegian Institute of Public Health, Oslo, Norway;* [b]*Department of Psychology, and* [j]*Institute of Clinical Medicine, University of Oslo, Oslo, Norway;* [c]*Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway;* [d]*Mailman School of Public Health, Columbia University, New York, New York;* [e]*New York State Psychiatric Institute, New York, New York;* [f]*The MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom;* [g]*School of Psychology, and* [h]*MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom; and* [i]*Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, United Kingdom*

Dr Gustavson conceptualized and designed the study, preformed the analyses, interpreted results, and drafted the initial manuscript; Drs Reichborn-Kjennerud, Ystrom, Stoltenberg, Susser, Surén, Magnus, Knudsen, Aase, Davey Smith, Langley, and Rutter conceptualized/designed the study, interpreted the results, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-2509

Accepted for publication Nov 15, 2016

Address correspondence to Kristin Gustavson, PhD, Norwegian Institute of Public Health, Department of Mental Diseases, PO Box 4404 Nydalen, 0403 Oslo, Norway. E-mail: kristinbrun.gustavson@fhi.no

WHAT'S KNOWN ON THIS SUBJECT: There is a well-documented association between maternal smoking in pregnancy and offspring attention-deficit/hyperactivity disorder. Whether this reflects a causal relationship or is due to unmeasured confounding is not clear.

WHAT THIS STUDY ADDS: Three different negative controls, as well as a sibling control, all suggest that the association is due to unmeasured genetic or environmental confounding.

To cite: Gustavson K, Ystrom E, Stoltenberg C, et al. Smoking in Pregnancy and Child ADHD. *Pediatrics.* 2017; 139(2):e20162509

There is a well-documented association between maternal smoking during pregnancy and offspring attention-deficit/hyperactivity disorder (ADHD).[1–3] However, there is debate regarding the degree to which this reflects a causal intrauterine effect of maternal smoking on the fetus or is due to unmeasured confounding.[4–6]

Several approaches can be used to control for unmeasured confounding, and convergence of findings from different methods and cohorts provides the strongest support for causal claims.[7,8] In sibling control designs, siblings discordant for maternal smoking during pregnancy are compared with respect to ADHD. Some studies using this approach have suggested that the association between maternal smoking during pregnancy and offspring ADHD is due to unmeasured confounding,[9–12] whereas a recent study suggested that the association may be causal.[5] The negative control approach compares the association of interest with another association that is affected by many of the same confounding factors, but that is not suspected to be causal.[13,14] For example, if there is a causal intrauterine effect of maternal smoking on offspring ADHD, this association should be stronger than the association with paternal smoking during pregnancy. Findings from studies using paternal smoking as a negative control have been mixed. One study[15] suggested that the association between maternal smoking during pregnancy and offspring ADHD is due to unmeasured confounding, whereas another found results consistent with direct causality.[16] The current study adds to existing knowledge by applying several methods within the same sample. We apply a sibling control design as well as 3 different negative control approaches: (1) paternal smoking during pregnancy, (2) grandmother's smoking when she was pregnant with mother, and (3) maternal smoking in previous pregnancies. If there is a causal intrauterine effect of maternal smoking on offspring ADHD, we expect the association with maternal smoking to be stronger than the association with all the other conditions.

METHODS

Study Population

The current study used data from the Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health.[17] Pregnant women from all over Norway were recruited between 1999 and 2008 when attending the 17-week routine ultrasound examination, and 40.6% of the invited women consented to participate. The current study is based on version 9 of the quality-assured data files released for research in November 2015.

The cohort includes >110 000 children, 95 000 mothers, and 75 000 fathers. In line with previous similar studies, children with congenital malformations (n = 5739) and children from multiple births (n = 3662) were excluded from analyses.[9,16]

MoBa has obtained a license from the Norwegian Data Inspectorate. The current study was approved by The Regional Committee for Medical Research Ethics.

Outcome

Information about children's ADHD diagnosis was obtained from the Norwegian Patient Registry (NPR) (https://helsedirektoratet.no/English). From 2008, all government-financed hospitals and outpatient clinics report individual-level diagnoses according to the 10th revision of the *International Classification of Diseases*[18] to NPR, based on civil registration number. Children diagnosed with an *International Classification of Diseases, 10th Revision* diagnosis of hyperkinetic disorder (F90) between 2008 and 2014 were defined as having ADHD. First time diagnoses as well as later contacts are registered.

This categorical ADHD variable did not give us sufficient statistical power to perform sibling comparisons. A dimensional measure of ADHD symptoms was therefore used. Mothers responded to 6 questions about offspring ADHD in the 5-year questionnaire. These were taken from the Child Behavior Checklist[19] and have been rated by experts as very consistent with *Diagnostic and Statistical Manual for Mental Disorders* criteria for ADHD.[20] The items were "Can't concentrate, can't pay attention for long," "Can't sit still, restless or overactive," "Can't stand waiting, wants everything now," "Demands must be met immediately," "Gets into everything," and "Quickly shifts from one activity to another." Items were rated from 1 (not true) to 3 (very true or often true). Mean scores of the 6 items were used in analyses. Cronbach α was 0.73, mean score 1.42, and SD 0.36.

Exposures

Mothers reported on smoking during the current and previous pregnancies. Both mothers and fathers reported on father's smoking. Mothers also reported on whether her mother smoked during the pregnancy with her.

MoBa contains more detailed smoking information for mothers and fathers (eg, number of cigarettes). This information is not available regarding grandmother's smoking, smoking in previous pregnancies, or mother-reported paternal smoking (used when fathers had not answered). Because the main aim of the current study was to compare maternal smoking with the other 3 smoking variables, only dichotomous smoking variables were used.

Information on maternal smoking was available for 93 285 pregnancies (89.0% of the sample). Data were available for 94 988 pregnancies (90.6%) regarding father's smoking and for 83 658 pregnancies (79.8% of the sample) regarding grandmother's smoking. Information on maternal smoking during previous pregnancies was available for 61 560 mothers (58.7% of the sample, applicable only to those who had been pregnant before).

Detailed information about covariates is given in the Methods section of the Supplemental Material.

Statistical Analyses

Analyses were performed by using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Chicago, IL) and Stata version 14 (Stata Corp, College Station, TX). Multiple imputation (20 repetitions) was performed in SPSS on self-reported covariates and the dimensional ADHD measure at 5 years.

Associations between smoking and offspring ADHD diagnoses were examined in Cox proportional hazard models. The proportional hazard assumption was met for all 4 smoking variables.

Based on previous literature, analyses were controlled for the following covariates: maternal and paternal age, education, and ADHD symptoms; maternal (prepregnancy) and paternal BMI; maternal alcohol consumption during pregnancy; maternal parity; year of child's birth; and geographical residential region. Birth weight appears later in time than smoking during pregnancy and is a more likely mediator than confounder. As expected, there was no association between child sex and maternal smoking (tetrachoric $\rho = 0.00$), and sex was not included as a covariate. Initial analyses showed that the association between maternal smoking and offspring ADHD was similar for boys and girls. Hence, analyses were not stratified on sex.

Sibling control analyses were performed by estimating within- and between-effects, as recommended by Begg and Parides.[21] Within-effects are associations between maternal smoking and offspring ADHD among siblings of mothers who showed discordant smoking habits across pregnancies. Hence, these effects show associations between smoking and child ADHD controlled for time-invariant confounders associated with the mother. Between-effects are effects of having the same mother. These analyses were performed twice: with and without imputations on the 5-year ADHD measure, and were controlled for maternal parity and age, as well as child's birth year.

There were 14 554 mothers who had participated in MoBa more than once: 13 671 twice, 860 three times, and 23 four times. A total of 38 427 respondents from the original sample also responded to the 5-year questionnaire. The number of discordant sibling pairs available for analyses was 530 when using imputed data on ADHD symptoms at 5 years, and 72 when not using imputed ADHD data.

To test our design, we compared the association between maternal smoking and offspring birth weight with the association with the 3 negative controls. This has been done in similar studies before, as smoking during pregnancy has well-documented causal effects on birth weight.[16] We also analyzed the association between maternal smoking and offspring birth weight in a sibling control model.

RESULTS

The total sample included 104 846 children, of which 2035 (2.0%) were registered with an ADHD diagnosis. The prevalence was <1% among those who were 7 years and younger and 4.3% among those who were 14 years old in 2014. Hence, the relatively low proportion of ADHD in the current sample is likely due to the children being young. The sample consisted of 51% boys, and 43.7% of the women were expecting their first child.

The smoking prevalences were 8.5% for mothers, 24.6% for fathers, 27.5% for grandmothers when pregnant with mother, and 15.6% for mothers in previous pregnancies. Descriptive statistics for covariates by smoking status and child diagnosis are presented in Table 1. Overlap between maternal smoking during pregnancy and the other smoking variables is shown in Supplemental Table 5.

Table 2 shows that all smoking variables (maternal and paternal smoking during pregnancy, grandmother's smoking when pregnant with mother, and maternal smoking in previous pregnancies) were associated with offspring ADHD, and that they were similar in magnitude both before and after adjustment for covariates.

Table 3 shows results from χ^2 tests of the null hypotheses that maternal smoking during pregnancy was equally strongly associated with offspring ADHD as were the other smoking variables, when they were entered in the same analysis. The *P* values for these tests were all $\geq .09$.

Results from sibling analyses are presented in Table 4. Maternal smoking during pregnancy was associated with mother-reported ADHD symptoms when the child was 5 years old in the total sample. There was, however, no such association when siblings discordant for maternal smoking were compared. The SE of the sibling control results was less than half of the association in the total sample. Hence, there was sufficient statistical power to detect an association in the sibling comparison that was the same as

TABLE 1 Characteristics of Family Members by Maternal Smoking Status and Child ADHD Diagnosis

	Total Sample, *n* = 104 846	Mother Did Not Smoke, *n* = 85 355	Mother Smoked, *n* = 7930	Not ADHD, *n* = 102 262	ADHD, *n* = 2035
Maternal age, y, *n* (%)					
≤24	12 402 (11.8)	8533 (10.0)	1862 (23.5)	11 847 (11.6)	495 (24.3)
25–34	74 271 (70.8)	61 902 (72.5)	4786 (60.4)	72 602 (71.0)	1276 (62.7)
≥35	18 173 (17.3)	14 920 (17.5)	1282 (16.2)	17 813 (17.4)	264 (13.0)
Paternal age, y, *n* (%)					
≤24	5495 (5.3)	3603 (4.2)	923 (11.7)	5250 (5.1)	223 (11.0)
25–34	63 823 (61.1)	52 648 (61.8)	4468 (56.8)	62 237 (61.0)	1262 (62.5)
≥35	35 184 (33.7)	28 885 (33.9)	2479 (31.5)	34 469 (33.8)	534 (26.4)
Maternal education, *n* (%)					
University/college	57 688 (64.1)	54 743 (67.6)	2029 (27.0)	56 749 (64.5)	647 (38.7)
High school	25 135 (27.9)	21 166 (26.1)	3462 (46.0)	24 310 (27.7)	700 (41.9)
Less than high school	7235 (8.0)	5065 (6.3)	2032 (27.0)	6861 (7.8)	324 (19.4)
Paternal education, *n* (%)					
University/college	43 667 (50.6)	41 635 (53.5)	1336 (19.0)	43 010 (51.0)	425 (27.0)
High school	33 088 (38.3)	28 733 (36.9)	3734 (53.0)	32 152 (38.1)	780 (49.5)
Less than high school	9560 (11.1)	7407 (9.5)	1980 (28.1)	9129 (10.8)	370 (23.5)
Maternal BMI[a] mean (SD)	24.0 (4.3)	24.0 (4.2)	24.5 (4.9)	24.0 (4.3)	25.3 (5.6)
Paternal BMI, mean (SD)	25.8 (3.4)	25.8 (3.3)	26.0 (3.7)	25.8 (3.3)	26.3 (3.9)
Maternal ADHD symptoms, scale 0–4, mean (SD)	1.10 (0.58)	1.08 (0.57)	1.25 (0.64)	1.09 (0.57)	1.30 (0.71)
Paternal ADHD symptoms, scale 0–4, mean (SD)	1.37 (0.53)	1.36 (0.53)	1.50 (0.59)	1.37 (0.53)	1.55 (0.62)
Alcohol consumption during pregnancy, *n* (%)					
None	69 579 (87.0)	63 978 (87.5)	5420 (81.9)	67 964 (87.1)	1283 (86.4)
< once per month	8044 (10.1)	7159 (9.8)	859 (13.0)	7826 (10.0)	155 (10.4)
≥ once per month	2350 (2.9)	2003 (2.7)	336 (5.1)	2281 (2.9)	47 (3.2)
Parity = 0, *n* (%)	45 783 (43.7)	38 184 (44.7)	3432 (43.3)	44 592 (43.6)	943 (46.3)
Child's sex = boy, *n* (%)	53 483 (51.0)	43 559 (51.1)	4031 (50.9)	51 708 (50.6)	1480 (72.7)
Child registered with ADHD diagnosis, *n* (%)	2035 (2.0)	1389 (1.6)	364 (4.6)		
Child's age, y, in 2014, mean (SD), range 5–15	8.9 (2.2)	8.8 (2.1)	9.7 (2.2)	8.9 (2.2)	10.3 (1.9)
Birth weight, g, mean (SD)	3600 (563)	3612 (558)	3475 (577)	3603 (554)	3569 (640)

[a] Maternal BMI when she became pregnant.

TABLE 2 Associations Between Smoking During Pregnancy and Offspring ADHD Diagnoses Examined With 4 Separate Cox Proportional Hazard Analyses

					Crude				Adjusted[a]				
		No. of Person-Months at Observed Risk[b]	No. of Cases	Incidence Rate[c]	Hazard Ratio	SE	95% CI	*P*	Hazard Ratio	SE	95% CI	*P*	*n*
1. Maternal smoking	No	6 956 115	1387	19.9	Ref				Ref				
	Yes	642 996	363	56.5	2.30	0.14	2.05–2.59	<.001	1.48	0.10	1.30–1.68	<.001	92 499
2. Paternal smoking	No	5 835 047	1085	18.6	Ref				Ref				
	Yes	1 903 566	689	36.2	1.76	0.09	1.60–1.93	<.001	1.28	0.07	1.16–1.42	<.001	94 256
3. Grandmother smoked when pregnant with mother	No	4 940 118	938	19.0	Ref				Ref				
	Yes	1 874 925	603	32.2	1.64	0.09	1.48–1.82	<.001	1.28	0.07	1.15–1.42	<.001	82 944
4. Mother smoked in previous pregnancies[d]	No	4 239 521	781	18.4	Ref				Ref				
	Yes	778 489	363	46.6	2.21	0.14	1.95–2.51	<.001	1.53	0.11	1.33–1.75	<.001	61 069

Separate analyses were performed for each of the 4 smoking variables so that the associations between each of them and offspring ADHD are not controlled for each other. CI, confidence interval; Ref, reference group to which smokers are compared.

[a] Adjusted for the following covariates: 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.

[b] Observation period between January 2008 and December 2014 for participants born in or before January 2008.

[c] Per 100 000 person-months under observed risk.

[d] Only applicable to women who had been pregnant before.

TABLE 3 The Association Between Maternal Smoking and Offspring ADHD Diagnoses Compared With the Associations With Three Negative Controls, Mutually Adjusted for Each Other

	Crude[a]					Adjusted[b]				
	Hazard Ratio	*P*	95% CI	χ^2 Value	*P* Value χ^2 Test	Hazard Ratio	*P*	95% CI	χ^2 Value	*P* Value χ^2 Test
Maternal smoking	1.93	<.001	1.70–2.19	7.47	.006	1.39	<.001	1.22–1.59	2.64	.10
Paternal smoking	1.48	<.001	1.34–1.64			1.19	.001	1.07–1.33		
Maternal smoking	2.16	<.001	1.90–2.45	17.47	<.001	1.44	<.001	1.25–1.65	2.89	.09
Grandmother's smoking	1.45	<.001	1.30–1.62			1.22	<.001	1.09–1.36		
Maternal smoking	1.65	<.001	1.37–2.00	0.03	.87	1.29	.008	1.07–1.56	0.06	.81
Maternal smoking in previous pregnancies	1.70	<.001	1.43–2.02			1.34	.001	1.14–1.59		

CI, confidence interval.

[a] Maternal smoking and the negative controls mutually adjusted for each other, but not adjusted for covariates.

[b] Maternal smoking and the negative controls mutually adjusted for each other and for the following covariates: 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. χ^2 values were obtained from testing 3 null hypotheses that the association between maternal smoking and offspring ADHD diagnoses was equal to each of the 3 other associations (Wald tests). Degrees of freedom = 1 in all tests.

the association in the total sample. This was true both with and without imputed data on the ADHD measure.

The between-effects showed that unmeasured maternal characteristics were associated with child ADHD symptoms.

In families in which none of the parents smoked, 3334 mothers reported being exposed to passive smoking from another household member or at work. Maternal exposure to passive smoking was not associated with child ADHD (odds ratio = 0.94, SE = 0.12, *P* = .63).

Maternal smoking during pregnancy was more strongly related to offspring birth weight than the negative controls; see Supplemental Tables 6 and 7. An association between maternal smoking and offspring birth weight was found among siblings discordant for maternal smoking; see the Results section in the Supplemental Material.

TABLE 4 Results From Sibling Comparison Analyses of the Association Between Maternal Smoking During Pregnancy and Child ADHD Symptoms, With and Without Imputed Missing Values on the ADHD Measure

	b[a]	SE[a]	*P*[a]	b[b]	SE[b]	*P*[b]
Total sample	0.09	0.01	<.001	0.11	0.01	<.001
Within-effects: discordant siblings	−0.01	0.03	.58	−0.02	0.04	.65
Between- effects: maternal effects	0.11	0.03	<.001	0.13	0.04	<.001

[a] Missing values were imputed on the ADHD measure, and 530 sibling pairs discordant for maternal smoking were available for analysis.

[b] Missing values were not imputed on the ADHD measure, yielding 72 sibling pairs discordant for maternal smoking available for analysis. All analyses were controlled for parity, maternal age, and child's birth year.

DISCUSSION

In this large prospective birth cohort, we found that the association between maternal smoking during pregnancy and offspring ADHD diagnosis was very similar in magnitude to the associations with 3 negative controls (paternal smoking in the same period, grandmother's smoking when pregnant with the mother, and maternal smoking in previous pregnancies). The sibling control analyses showed an association between maternal smoking during pregnancy and maternally reported ADHD symptoms at 5 years in the whole sample, but not among siblings discordant for maternal smoking in pregnancy. The results suggest that the association between maternal smoking and offspring ADHD is due to unmeasured confounding factors. Maternal smoking during pregnancy was more strongly associated with offspring birth weight than the 3 negative control situations, and this association was also evident among siblings discordant for maternal smoking, indicating a causal relationship and giving credibility to our models.

These findings are in accordance with previous studies from the Avon Longitudinal Study of Parents and Children, in which maternal and paternal smoking were similarly associated with ADHD in the offspring.[15] Our results are, however, slightly different from those reported by Zhu and colleagues[16] from a similar study in the Danish birth cohort. They found that the association between maternal smoking during pregnancy and ADHD was stronger than the association with paternal smoking, providing indications of a causal effect.

The current study used an ADHD symptoms measure consisting mainly of items covering hyperactivity/impulsivity. Our findings are, however, not in accordance with results from a recent sibling control study, concluding that there may be a causal effect of maternal smoking during pregnancy on maternally reported ADHD symptoms, particularly regarding hyperactivity/impulsivity.[5] Our findings are more in line with other previous studies using sibling control designs concluding that the association between maternal smoking during pregnancy and offspring ADHD seems to be primarily confounded by genetic and/or environmental factors,[9–12] and also consistent with several other studies reporting that the associations between maternal smoking during pregnancy and different child outcomes (eg intelligence, conduct problems) are due to unmeasured confounding.[22–24]

Thapar and colleagues[25] were able to separate confounding due to genetic versus environmental factors by using a novel design. They compared offspring conceived through in vitro fertilization by using eggs from the mother or from genetically unrelated women. The results indicated that the magnitude of the association between maternal smoking during pregnancy and offspring ADHD was stronger in the genetically related mother-offspring pairs than in the unrelated, suggesting that the association between maternal smoking during pregnancy and offspring ADHD reflects genetic confounding.

The current findings are in accordance with the fact that ADHD rates in the population have been stable across several decades[26] even though smoking rates have decreased, both in general and during pregnancy.[27,28] Nevertheless, conclusions from the current study must be made with caution, as we have used observational data. For example, Yerushalmy observed that the association between maternal smoking during pregnancy and child birth weight was similar to the association with paternal smoking in a California birth cohort (results from his 1962 article are reprinted in Keyes et al, 2014[29]). He thus concluded that maternal smoking during pregnancy was unlikely to be causally linked to birth weight. He also observed that women had increased risk of having small children even if they started smoking after pregnancy,[30] which supported his conclusion. In light of the later evidence, his conclusion seems to be wrong even though it was based on legitimate reasoning.[29] This example illustrates the importance of basing conclusions on results from different samples as well as different designs.[29,31]

The current study has several strengths, such as a large sample size, prospective assessment of exposure, and diagnoses obtained from linkage to a national registry. However, the following limitations need to be taken into consideration. First, ADHD may not have been identified in some children. This may be particularly relevant for the youngest children, as ADHD diagnoses are seldom given to preschool children.[32] Prevalence of ADHD diagnoses in the NPR increases considerably each year from age 5 to age 11.[32] Cox proportional hazard regression was used to ensure that participants who were censored at the end of the study period without an ADHD diagnosis were compared with children with an ADHD diagnosis at the same age. Hence, the effect of age on the likelihood of having been registered with an ADHD diagnosis was controlled for. Some may have been diagnosed before 2008 without having contact with in- or outpatient clinics thereafter. However, the young age of the participants suggests that this is unlikely to have caused high numbers of false negatives. There may potentially also be some false positives (ie, incorrect ADHD diagnoses). Sensitivity analyses excluding children with only 1 registration of ADHD in the NPR were performed. This did not change the conclusions. The prevalence of ADHD in MoBa was 2.8% among boys and 1.1% among girls. This boy/girl ratio (~2.5) is similar to what is found for children and adolescents in the whole NPR. All ADHD medication use in Norway is registered in the Norwegian Prescription Database. More than 80% of children registered with ADHD in NPR also use medication for ADHD, according to the Norwegian Prescription Database. This also applies to MoBa participants with ADHD diagnoses. These findings further strengthen the notion of valid ADHD data in the current study. Second, as there may be stigma related to smoking, and particularly to smoking during pregnancy, participants may have underreported smoking in the current study. However, this problem is likely to be small, as the participants provided information about smoking in questionnaires rather than to health care professionals. Among women who had participated in MoBa more than once, 95% of classifications of concurrent smoking (yes/no) given in 1 pregnancy, was consistent with classification of smoking in previous pregnancies (yes/no) given in a later pregnancy, thus supporting the notion of only minimal problems with self-reported smoking. Also, in families in which both mother and father provided information on paternal smoking, 98.5% of fathers reported smoking if the mother had reported that he did ($\kappa = 0.78$), indicating high quality of the self-reported smoking data. However, some differential misclassification of smoking status is likely and may have biased the estimates.[33] For example, if a mother who smoked in 2 pregnancies, erroneously reported to be a nonsmoker in 1 of them, sibling comparisons may be biased

toward the null. The sibling design also may be biased by potential epigenetic changes induced outside the pregnancy period. Further studies are needed to examine such epigenetic effects. Third, there was a higher proportion of women smoking in previous pregnancies than in the current pregnancy. This difference may be due to declining smoking trends.[28] The current analyses were adjusted for child's birth year to prevent results from being affected by this. Fourth, the results could be biased due to effects of passive smoking. However, our results indicated that passive smoking was not associated with increased risk of child ADHD. This is also in line with findings from Langley and colleagues.[15] Fifth, individuals with low educational level, young age, and smokers are underrepresented in MoBa,[34] which may reduce the generalizability of the findings. However, the previously well-documented association between maternal smoking during pregnancy and offspring ADHD was replicated in the current study despite some underrepresentation of smokers. Also, the additional analyses on the association between maternal smoking and offspring birth weight suggested that there were enough smokers in the sample to show the expected effects of smoking on fetal development.

CONCLUSIONS

The current study applied several different approaches, and they all concur in indicating that the association between maternal smoking during pregnancy and offspring ADHD is not directly causal, but confounded by unmeasured factors. Maternal smoking during pregnancy was not more strongly associated with offspring ADHD diagnosis than paternal smoking during pregnancy, grandmother's smoking when pregnant with mother, or maternal smoking in previous pregnancies. There was no association between maternal smoking during pregnancy and offspring ADHD symptoms in siblings discordant for maternal smoking. The current results underscore the usefulness of applying multiple methods, including natural experimental designs, to explore the causal relationships that may underlie the associations evident in observational studies.

ACKNOWLEDGMENTS

We are grateful to all the participating families in Norway who take part in this on-going cohort study.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
MoBa: Norwegian Mother and Child Cohort
NPR: Norwegian Patient Registry

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: The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, National Institutes of Health/National Institute of Environmental Health Sciences (contract N01-ES-75558), and National Institutes of Health/National Institute of Neurological Disorders and Stroke (grants U01 NS 047537-01 and U01 NS 047537-06A1). Funded by the National Institutes of Health (NIH).

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

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Pediatrics 2017;139;; originally published online January 30, 2017;
DOI: 10.1542/peds.2016-2509

PEDIATRICS®
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