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Original Contribution

Association of Maternal Exposure to Childhood Abuse With Elevated Risk for Attention Deficit Hyperactivity Disorder in Offspring

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Children whose mothers experienced childhood abuse are more likely to suffer various neurodevelopmental deficits. Whether an association exists specifically for attention deficit hyperactivity disorder (ADHD) is unknown. We examined the association of maternal experience of childhood abuse with ADHD in offspring, assessed by maternal report of diagnosis and validated with the ADHD Rating Scale-IV in a subsample, in the Nurses' Health Study II (n = 49,497 mothers; n = 7,607 case offspring; n = 102,151 control offspring). We examined whether 10 adverse perinatal circumstances (e.g., prematurity, smoking) or socioeconomic factors accounted for a possible association. Exposure to abuse was associated with greater prevalence of ADHD in offspring (8.7% of offspring of women exposed to severe abuse vs. 5.5% of offspring of women not abused, P = 0.0001) and with greater risk for ADHD when the model was adjusted for demographic factors (male offspring, risk ratio (RR) = 1.6, 95% confidence interval (CI): 1.3, 1.9; female offspring, RR = 2.3, 95% CI: 1.7, 3.0). After adjustment for perinatal factors, the association of maternal childhood abuse with ADHD in offspring was slightly attenuated (male offspring, RR = 1.5, 95% CI: 1.2, 1.8; female offspring, RR = 2.1, 95% CI: 1.6, 2.8). We identified an association between maternal experience of childhood abuse and risk for ADHD in offspring, which was not explained by several important perinatal risk factors or socioeconomic status.

attention deficit hyperactivity disorder; childhood abuse; longitudinal study; maternal factors; neurodevelopment; violence

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; CI, confidence interval; RR, risk ratio; SES, socioeconomic status.

Accumulating evidence suggests that maternal experience of childhood abuse may affect offspring neurodevelopment. Offspring of women exposed to childhood abuse exhibit elevated risk for internalizing (1–5), externalizing (1, 3, 4, 6–8), and social problems (4, 6), as well as autism spectrum disorder (9). In animal studies, maternal exposure to stressors is associated with anxiety (10, 11), depressive symptoms, attention problems (12), and hyperactivity (13) in offspring, with evidence for mediation through effects of maternal stress hormones on offspring hormonal and neurological stress reactivity (10, 11, 13). Thus, it is possible that maternal exposure to childhood abuse may be associated with elevated risk of attention deficit hyperactivity disorder (ADHD) in offspring.

In addition, women who experience childhood abuse are at elevated risk of many adverse perinatal circumstances that have been associated with offspring ADHD and other neurodevelopmental deficits (9, 14–30). Elevated risk of ADHD has been associated with maternal prenatal tobacco (21, 31), alcohol (20), and antidepressant use (18), prepregnancy body mass index (BMI) (26), gestational diabetes (32), preeclampsia (30), experience of stress during pregnancy (19, 23, 33), prematurity (34), and low birth weight (20, 29). It is possible that increased exposure to these circumstances may be a pathway by which offspring of women who experienced childhood abuse are at elevated risk of ADHD.

In addition, low socioeconomic status (SES) is both a risk factor for childhood abuse (35, 36) and a consequence of childhood abuse (37, 38). Low SES has been associated with increased risk of ADHD in offspring. According to a recent systematic review and meta-analysis, low maternal education, low paternal education, residence in a single-parent family, low income, and low overall SES were all associated with substantially greater risk for ADHD in children (39). However, in the largest study

(n > 800,000 children), there was markedly higher ADHD risk among children living in US Census tracts with higher median household income (40), suggesting differential ascertainment by community wealth. Thus, low SES among women who experienced abuse might account for a possible increased risk of ADHD in their children.

One in 10 US children is diagnosed with ADHD, and ADHD is responsible for an estimated $143 billion to $266 billion in excess costs in the United States annually (41). Thus, identification of ADHD risk factors that could offer potential for interventions is of crucial public health significance. In this study, we examined whether maternal exposure to childhood physical, emotional, and sexual abuse is associated with offspring ADHD in a large, longitudinal cohort of women. We also examined whether 1) increased exposure to adverse perinatal circumstances, including maternal smoking, alcohol and antidepressant use, preeclampsia, gestational diabetes, pregestational BMI, prior abortion, intimate partner violence victimization, and suboptimal offspring birth weight and gestation length; and 2) lower SES might account for possible elevated risk of ADHD in offspring of women exposed to childhood abuse.

METHODS

Sample

Nurses' Health Study II is an ongoing cohort of 116,429 US nurses enrolled in 1989 and followed biennially. Nurses were originally from 14 states and now reside in all 50 states. We included parous women who responded to a supplemental 2001 questionnaire querying about childhood abuse and who later reported in 2013 whether they had ever had a child diagnosed with ADHD (n = 49,497).

Maternal exposure to childhood abuse

Exposure to childhood abuse was assessed in a supplemental 2001 questionnaire. Physical and emotional abuse was assessed with 5 questions from the Physical and Emotional Abuse Subscale of the Childhood Trauma Questionnaire (42). Women were asked whether any of the following had happened to them up to age 11 years: 1) "people in my family hit me so hard it left bruises"; 2) "punishments I received seemed cruel"; 3) "I was punished with a belt, a board, a cord, or some other hard object"; 4) "someone in my family yelled and screamed at me"; 5) "people in my family said hurtful or insulting things to me." Response options were given point scores as follows: 0, never; 1, rarely; 2, sometimes; 3, often; or 4, very often true. Response options were summed per scoring recommendations. The resulting scale was divided into quartiles to calculate risk ratios and to assess a possible dose-response relationship between maternal abuse and offspring ADHD.

Sexual abuse was assessed with the 2-item Sexual Maltreatment Scale of the Parent-Child Conflict Tactics Scales (43) for each of 2 time periods: up to age 11 years and ages 11–17 years. The questions were 1) "Were you ever touched in a sexual way by an adult or older child, or were you forced to touch an adult or older child in a sexual way when you did not want to?" and 2) "Did an adult or older child ever force you or attempt to force you into any sexual activity by threatening you, holding you down, or hurting you in some way?" Response options were given point scores as follows: never, 0; once, 1; and more than once, 2. Reponses were summed across all 4 questions to create a variable in 4 levels: none, mild (1–2 points), moderate (3–4 points), or severe (≥5 points) sexual abuse. Exposure to high levels of physical, emotional, or sexual abuse may be associated with increased risk of ADHD in offspring; therefore, we created a combined measure of physical, emotional, and sexual abuse by summing the categories (0–3) of each of the 2 measures (range, 0–6).

In addition, 4 items adapted from the Physical Assault Scale of the Conflict Tactics Scales (43) were asked regarding the 2 time periods, before age 11 years and ages 11–17 years. The items asked about the frequency a parent or step-parent did the following: 1) pushed, grabbed, or shoved you; 2) kick, bit, or punched you; 3) hit you with something that hurt; or 4) choked or burned you; and an additional item queried whether the respondent was attacked in some other way. Response options were given point scores as follows: never, 0; once, 1; a few times, 2; and more than a few times, 3. After scoring recommendations, a scale was created by summing these items. Because only part of this scale was queried, we examined its association with offspring ADHD in sensitivity analyses.

ADHD ascertainment

In 2005 and 2013, we asked women whether any of their children had been diagnosed with ADHD; in 2013, women were also asked the birth year of the affected child or children. After the 2005 questionnaire was returned, we randomly selected 200 women who reported having a child with ADHD to participate in a validation study; 137 women responded (68.5%). Of these, 20 women declined to participate and 9 women said their child did not have ADHD, leaving 108 participants. In the validation study, we asked women, "Who made your child's diagnosis?", "Has your child been evaluated by a specialist?", and "Is your child currently taking any medications?" In addition, women were asked to return the ADHD Rating Scale-IV questionnaire. Nearly half the children were diagnosed by a neurologist or psychiatrist (48.8%), with the remainder diagnosed by a pediatrician (38.1%) or another health care provider (13.1%). Most children were currently taking medication (86.9%) and had seen a specialist (85.5%).

Eighty-six women (81.1%) completed the ADHD Rating Scale-IV regarding their child. The ADHD Rating Scale-IV is an 18-item questionnaire assessing the 2 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* factors comprising ADHD: inattention (e.g., "does not seem to listen when spoken to directly") and hyperactivity-impulsivity (e.g., "has difficulty awaiting turn") (44). Each response option, ranging from 0 for never to 3 for very often, was summed to create a total score. The ADHD Rating Scale-IV has been validated against the Conners Teacher Rating Scale-39 and the Conners Parent Rating Scale-48 with good correlations (45), has been found to be stable over a 4-week span, and correlates significantly with classroom behavior and task accuracy (46). Although different percentile cutoffs have been used, scores at least in the 80th, 85th, and 90th percentiles are commonly the basis for recommending ADHD diagnostic screening (44, 47). In our validation sample, all girls scored above the 90th percentile, 63.8% of boys scored above the 90th percentile, and 81.1% of boys

scored above the 80th percentile. Scores on the ADHD Rating Scale among children diagnosed with ADHD did not differ by maternal abuse exposure ($P = 0.88$).

Selection of case and control offspring

We included as ADHD cases affected children of women who had indicated the child's birth year in 2013 and who responded to childhood abuse questions. The ADHD control group comprised children of women who indicated in 2013 that they did not have a child with ADHD and unaffected children of women who reported they had a child with ADHD.

Adverse perinatal circumstances, SES indicators, and demographic factors

In the 2001 questionnaire, women were asked about each of their pregnancies, including the year the pregnancy ended, the outcome (e.g., live birth, miscarriage), whether they smoked or drank alcohol during the pregnancy, whether they were physically hurt by their spouse at any time during the pregnancy (response options were never, once, or more than once), the length of gestation (response options were in 7 intervals from 12–20 weeks to ≥43 weeks), and the resulting child's sex and birth weight (response options were in 6 intervals from <5 to ≥10 lb). (One pound is equal to 0.45 kg.) Based on their association with offspring ADHD, we coded gestation length, in weeks, as follows: shorter than 37, 37–42, or longer than 42. Birth weight, in pounds, was coded as follows: less than 5.5, 5.5–9.9, or 10 or more. Because birth year was a strong predictor of offspring ADHD, we examined the association of ADHD with birth year, birth year squared, and birth year cubed (e.g., for birth year = 1990, 1990^2, 1990^3). The best-fitting model by Akaike Information Criterion included all 3 terms. Lifetime history of induced abortions and age at occurrence were assessed in 1993 and updated biennially.

History of gestational diabetes and year of diagnosis were assessed retrospectively in 1989 and updated biennially. Pregestational BMI (calculated as weight in kilograms divided by height in meters squared) was defined as BMI in the year prior to the child's birth year. BMI at each age from 18–55 years was calculated from self-reported height in 1989; biennially reported weight, 1989–2013; retrospectively reported weight at age 18 years; and retrospectively reported somatograms for ages 20, 30, and 40 years. For ages at which weight was not reported, BMI was interpolated. Lifetime history and age at occurrence of toxemia or preeclampsia during pregnancy were assessed in 1989 and updated biennially. Mother's age at child's birth was categorized in 5 levels (<25, 25–29, 30–34, 35–39, and ≥40 years). Educational attainment of nurses' parents, queried about in 2005, was used as an indicator of maternal childhood SES.

Beginning in 1989, and biennially thereafter, US Census tract data on median income and percentage college educated were obtained from nurses' geocoded residential addresses. Marital status was queried in 1989 and every subsequent 4 years. In 1999, nurses' husbands' educational attainment was queried (responses were coded as less than high school, high school, some college, 4 years college, and postgraduate). In 2001, nurses reported their standing in the community and the United States by indicating where on two 10-rung ladders they would place themselves (the top rung indicating the highest standing), which are validated measures of subjective social status previously associated with health outcomes (48). Finally, pretax household income was queried in 2001.

Analyses

We first calculated prevalence of ADHD in offspring, adverse perinatal circumstances, socioeconomic indicators, and demographic factors by maternal exposure to combined childhood physical, emotional, and sexual abuse. Next, to examine risk of ADHD in offspring by maternal exposure to childhood abuse, adjusted for demographic factors, we calculated risk ratios for ADHD case status with maternal exposure to 1) childhood physical and emotional abuse, and 2) childhood sexual abuse as the independent variable in separate models. To ascertain whether joint exposure to physical, emotional, and sexual abuse was associated with offspring ADHD, we calculated risk ratios for ADHD case status with the joint measure of physical, emotional, and sexual abuse as the independent variable. To ascertain the extent to which higher prevalence of adverse perinatal circumstances in women who experienced childhood abuse might account for increased risk of ADHD in their offspring, we further adjusted this model for maternal smoking, alcohol use, antidepressant use, prior abortion, gestational diabetes, pregestational BMI, preeclampsia, gestation length, exposure to intimate partner violence, and offspring birth weight.

To ascertain whether family SES might account for an association between maternal abuse and ADHD in offspring, we further adjusted for socioeconomic indicators. Because many women chose not to report household income ($n = 19{,}169$, 17.5%), we separately examined the association of abuse with ADHD additionally adjusted for household income in the subsample with income data. For children born substantially before cohort enrollment in 1989, socioeconomic indicators may not have reflected circumstances during early childhood, when such factors might affect risk of ADHD. Therefore, we conducted additional analyses restricted to births in 1986 and later ($n = 5{,}135$ case offspring; $n = 55{,}891$ control offspring), and we adjusted for all socioeconomic indicators, using marital status, median income according to the US Census tract, and percentage college educated in the year the child was 3–4 years old. To determine whether associations of maternal abuse and ADHD differed by child's sex, we included models a term for maternal abuse by child's sex. This term was statistically significant in all models; therefore, we present results stratified by child's sex.

We then assessed the extent to which adverse perinatal factors and socioeconomic indicators accounted for possible increased risk of ADHD in offspring of women exposed to childhood abuse. We first calculated the mediation percentage for each level of abuse separately (% mediation = (β estimate $\text{abuse}_{\text{base model}} - \beta$ estimate $\text{abuse}_{\text{adjusted for perinatal factors or socioeconomic indicators}}$)/$\beta$ estimate $\text{abuse}_{\text{base model}}$), then calculated the total mediation percentage by taking a weighted average using the mediation percentage at each level weighted by the number of women exposed at that level.

We conducted sensitivity analyses examining the association of offspring ADHD with maternal experience of physical abuse measured by the Physical Assault Scale of the Conflict

Table 1. Offspring Attention Deficit Hyperactivity Disorder, Demographic Factors, and Hypothesized Mediators by Maternal Exposure to Childhood Abuse (n = 49,497 Mothers; n = 109,758 Offspring), Nurses' Health Study II, 1989–2013

Variable	Maternal Exposure to Childhood Abuse													
	0 (No Abuse)		1		2		3		4		5		6 (Severe Abuse)	
	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Maternal and child characteristics														
Mothers		13,208		10,936		9,436		9,181		4,145		1,575		1,016
Offspring[a]		29,324		24,576		20,918		20,265		9,047		3,467		2,161
Offspring with ADHD	5.5	1,606	6.5	1,608	7.0	1,461	8.0	1,626	8.9	803	9.1	315	8.7	188
Offspring per mother[b]	2.2 (0.9)		2.2 (0.9)		2.2 (0.9)		2.2 (0.9)		2.2 (0.9)		2.2 (0.9)		2.1 (0.9)	
Maternal parents' education, ≤high school	44.4	5,861	46.8	5,114	48.6	4,582	50.7	4,658	53.2	2,207	55.4	873	54.1	550
Male offspring	52.1	15,265	52.0	12,767	51.9	10,848	51.7	10,467	51.7	4,673	52.8	1,830	51.6	1,114
Perinatal factors														
Maternal age at child's birth, years[b]	28.9 (4.7)		28.8 (4.9)		28.7 (4.9)		28.5 (5.0)		28.1 (5.1)		27.5 (5.4)		27.0 (5.5)	
Birth weight (pounds)														
<5.5	3.1	918	3.0	737	3.2	675	3.1	638	3.5	315	3.6	124	3.6	78
≥10	2.3	689	2.4	595	2.4	502	2.6	519	2.8	251	3.1	106	3.4	73
Pregnancy length, weeks														
<37	6.7	1,954	6.8	1,672	7.0	1,472	6.9	1,392	7.8	702	7.7	266	8.7	188
≥43	6.3	1,845	6.9	1,703	7.1	1,493	7.9	1,596	8.3	750	10.0	345	10.6	229
Smoking during pregnancy	7.9	2,319	9.2	2,270	10.5	2,186	12.1	2,450	13.7	1,235	15.8	547	15.1	326
Gestational diabetes	2.5	743	2.9	704	2.8	580	3.8	761	4.0	361	4.1	142	4.5	98
Pregestational BMI[c]														
25.0–29.9 (overweight)	10.4	3,040	11.9	2,926	12.3	2,577	13.6	2,758	13.7	1,242	14.4	498	15.4	333
≥30.0 (obese)	3.0	875	3.2	796	3.8	799	4.1	836	4.6	418	4.9	171	5.9	127
Antidepressant use	0.5	138	0.7	161	0.9	195	1.1	223	1.5	134	1.4	47	2.0	44
Intimate partner violence														
Once	0.7	194	0.9	220	1.0	216	1.6	324	2.1	194	2.6	91	3.2	70
More than once	0.4	113	0.6	153	0.8	173	1.4	279	2.2	199	2.7	94	5.2	112
Preeclampsia	3.3	969	3.7	901	3.8	797	4.7	958	5.4	484	5.1	177	7.1	154
Prior induced abortion	9.5	2,785	11.4	2,795	11.7	2,456	13.0	2,626	15.5	1,406	14.6	506	14.7	318
Alcohol use during pregnancy	11.8	3,470	13.0	3,189	14.2	2,971	14.4	2,913	14.3	1,297	14.5	501	14.5	314
Socioeconomic indicators														
Husband's education, 1999, <4 years college	33.1	9,701	34.6	8,503	34.1	7,114	34.6	7,018	35.6	3,220	37.2	1,288	38.9	840
Maternal self-reported social standing in United States, 2001[b,d]	3.8 (1.2)		3.8 (1.3)		3.8 (1.3)		3.9 (1.3)		4.0 (1.3)		4.1 (1.4)		4.2 (1.5)	
Maternal self-reported social standing in community, 2001[b,d]	3.9 (1.5)		4.0 (1.5)		4.0 (1.5)		4.1 (1.6)		4.2 (1.7)		4.2 (1.7)		4.4 (1.8)	
Census tract median family income, 1989, $1000s[b]	61.9 (22.5)		61.3 (22.2)		61.3 (22.4)		61.5 (21.7)		59.5 (21.6)		60.2 (22.6)		57.8 (20.0)	
Census tract college educated, 1989, %[b]	30.0 (17.1)		29.7 (17.0)		29.6 (17.1)		29.5 (16.8)		28.3 (16.7)		28.6 (17.2)		26.8 (15.9)	
Income, 2001, <$50,000	10.3	3,033	10.8	2,656	11.6	2,427	12.4	2,508	13.8	1,249	15.7	543	18.7	404
Marital status, 1989, divorced or separated	5.5	1,609	5.9	1,443	6.2	1,304	7.4	1,493	9.5	859	11.5	397	13.0	281

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index.

[a] Offspring birth year by maternal exposure to childhood abuse, median (interquartile range): None: 1984 (1978–1989); 1: 1984 (1979–1989); 2: 1984 (1978–1989); 3: 1984 (1978–1989); 4: 1983 (1977–1988); 5: 1982 (1976–1987); 6: 1981 (1975–1987).

[b] Values are expressed as mean (standard deviation).

[c] Weight (kg)/height $(m)^2$.

[d] Lower number = higher standing.

Table 2. Maternal Exposure to Childhood Sexual or Physical and Emotional Abuse and Risk of Attention Deficit Hyperactivity Disorder in Offspring, Nurses' Health Study II, 1989–2013[a]

Exposure	Female Offspring				Male Offspring			
	No. of Offspring	No. of Case Offspring	Risk Ratio	95% CI	No. of Offspring	No. of Case Offspring	Risk Ratio	95% CI
Model 1								
Maternal childhood physical and emotional abuse, quartile								
First (none)	18,380	606	1.00	Referent	20,200	1,576	1.00	Referent
Second	11,842	432	1.04	0.91, 1.19	12,395	1,208	1.24	1.15, 1.35[b]
Third	10,492	447	1.27	1.12, 1.46[b]	11,402	1,154	1.33	1.23, 1.45[b]
Fourth	12,080	651	1.70	1.51, 1.92[b]	12,967	1,533	1.55	1.44, 1.67[b]
Model 2								
Maternal childhood sexual abuse								
None	35,220	1,357	1.00	Referent	37,863	3,466	1.00	Referent
Mild	12,606	514	1.15	1.03, 1.28[c]	13,702	1,411	1.20	1.12, 1.28[b]
Moderate	3,270	166	1.40	1.17, 1.66[d]	3,609	407	1.35	1.21, 1.50[b]
Severe	1,698	99	1.69	1.35, 2.11[d]	1,790	187	1.24	1.06, 1.45[d]

Abbreviation: CI, confidence interval.

[a] The study population included 49,683 mothers, 7,607 case offspring, and 102,151 control offspring. Models were adjusted for maternal age at birth, child's birth year, and maternal parents' level of education.

[b] Wald χ^2 significant at $P < 0.001$.

[c] Wald χ^2 significant at $P < 0.05$.

[d] Wald χ^2 significant at $P < 0.01$.

Tactics Scales (49). Maternal childhood abuse has been associated with offspring autism spectrum disorder in this cohort (9), so to ascertain whether associations between maternal childhood abuse and offspring ADHD were independent of offspring autism, we conducted an analysis excluding all children whose mothers reported having a child with autism ($n = 414$ ADHD case offspring; $n = 1,603$ ADHD control offspring). Participants in the Nurses' Health Study II are predominantly non-Hispanic white (95.4%); therefore, to examine whether associations were similar among racial or ethnic minorities ($n = 4,995$), we conducted an analysis excluding non-Hispanic whites.

All analyses were conducted using SAS (SAS Institute, Inc., Cary, North Carolina). We calculated risk ratios using cluster-weighted generalized estimating equations implemented in PROC GENMOD to account for family clustering, using the inverse of the number of children as a weight to account for potential informative clustering; a Poisson distribution; and a log link (50). All models were adjusted for offspring birth year, the maximum of maternal parents' education, and mother's age at child's birth.

RESULTS

Nearly 50,000 mothers responded to questions about childhood abuse and responded to the 2013 questionnaire querying child's ADHD ($n = 49,497$ mothers; $n = 7,607$ ADHD case offspring; $n = 102,151$ control offspring). Offspring ADHD and all adverse perinatal factors were more prevalent in women exposed to severe abuse than they were in unexposed women (Table 1). For each indicator of SES, women who experienced abuse had lower status than women who did not (Table 1).

Risk of ADHD was higher in male and female offspring of mothers exposed to either childhood physical and emotional abuse or childhood sexual abuse (Table 2). At the highest levels of maternal abuse, the association with offspring ADHD was stronger among female versus male offspring. In models examining combined exposure to physical, emotional, and sexual abuse, risk of offspring ADHD was higher at each level of abuse compared with women who did not experience abuse, except the lowest level of abuse for female offspring (for severe abuse in female offspring, relative risk (RR) = 2.29, 95% confidence interval (CI): 1.73, 3.04 (Figure 1A); in male offspring, RR = 1.57, 95% CI: 1.28, 1.92 (Figure 1B). After adjustment for adverse perinatal factors, risk of ADHD remained elevated at all except the lowest level of abuse for female offspring (for female offspring, $RR_{\text{severe abuse}} = 2.05$, 95% CI: 1.54, 2.72 (Figure 1C); for male offspring, $RR_{\text{severe abuse}} = 1.46$, 95% CI: 1.19, 1.79 (Figure 1D)). Adverse perinatal factors statistically accounted for 8.6% of the increased risk of ADHD in offspring of women exposed to childhood abuse (11.6% in female and 5.5% in male offspring).

Adjustment for socioeconomic indicators only slightly attenuated the association of maternal abuse with ADHD risk in offspring (Table 3). Socioeconomic factors statistically accounted

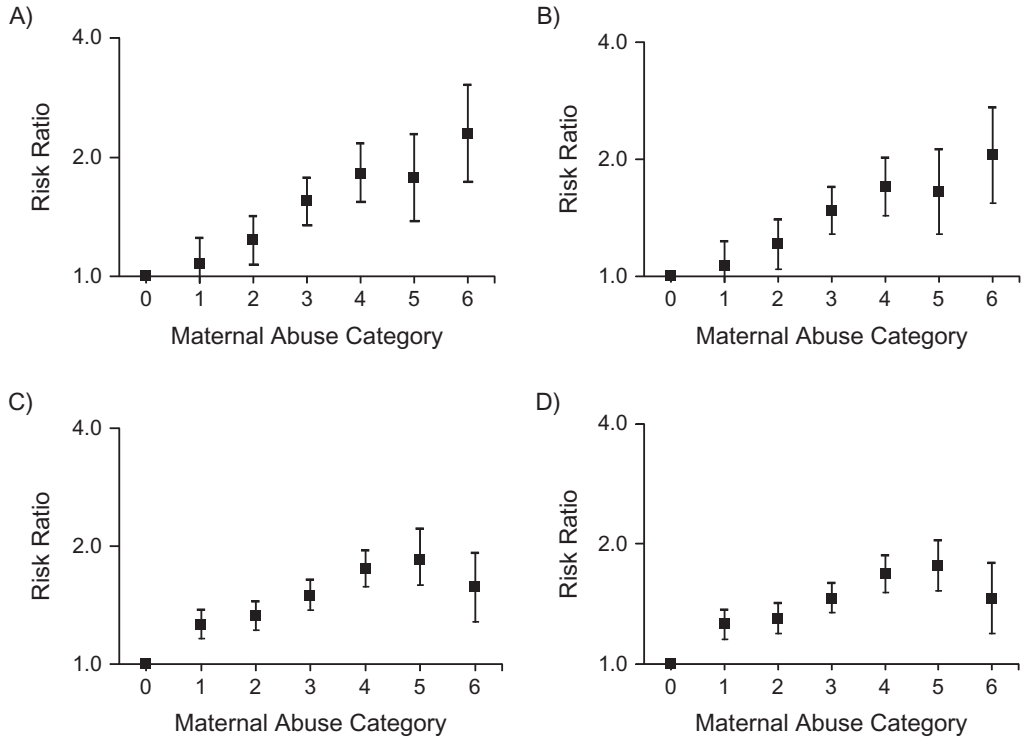

Figure 1. Maternal exposure to combined physical, emotional, and sexual childhood abuse and risk of attention deficit hyperactivity disorder (ADHD) in offspring (n = 49,683 mothers; n = 7,607 ADHD case offspring; n = 102,151 control offspring), Nurses' Health Study II, 1989–2013. A) Female offspring and B) male offspring (both models were adjusted for maternal age at child's birth, birth year, birth year squared, birth year cubed, and maternal parents' education). C) Female offspring and D) male offspring (both models were additionally adjusted for the following perinatal risk factors: birth weight; gestation length; preeclampsia; gestational diabetes; maternal pregestational body mass index (weight (kg)/height (m)^2); maternal perinatal exposure to intimate partner violence; maternal alcohol, tobacco, and antidepressant use; and maternal prior abortion.

for 3.2% of the increased risk of ADHD in offspring of women exposed to childhood abuse (3.4% in female and 3.0% in male offspring). Further adjustment for household income in addition to other socioeconomic indicators in the subsample with income data did not notably change mediation percentage, nor did mediation differ meaningfully in analyses restricted to children born in or after 1986.

In sensitivity analyses excluding women who reported having a child with an autism spectrum disorder and all their children (n = 414 ADHD case offspring; n = 1,603 ADHD control offspring), results were nearly identical. Offspring ADHD was strongly associated with maternal physical abuse as measured by the Conflict Tactics Scales (girls, $RR_{\text{severe abuse}} = 1.64$, 95% CI: 1.44, 1.87; boys, $RR_{\text{severe abuse}} = 1.37$, 95% CI: 1.26, 1.49; $P < 0.0001$ for both; Web Table 1, available at https://academic.oup.com/aje). In analyses restricted to racial and ethnic minorities, maternal exposure to abuse remained associated with offspring ADHD, though this did not reach statistical significance (girls, $RR_{\text{severe abuse}} = 1.95$, 95% CI: 0.71, 5.41; boys, $RR_{\text{severe abuse}} = 1.14$, 95% CI: 0.51, 2.56).

DISCUSSION

In this large, nonclinical sample, maternal experience of childhood abuse was strongly associated with risk of ADHD in offspring. At the highest level of maternal abuse, we found higher risk of ADHD in female offspring, compared with male offspring, although risk for male offspring was also significantly elevated compared with offspring of women who had not experienced abuse. Given that relatively few women were exposed to this highest level of abuse and that confidence intervals for effect estimate for each sex were highly overlapping, these results should be considered tentative.

Higher prevalence of 10 adverse perinatal circumstances in pregnancies of women exposed to abuse versus those unexposed to abuse accounted for only a small portion of elevated risk of ADHD in the offspring of the former. In addition, lower SES among women who experienced abuse accounted for very little of the higher risk of ADHD in their children. Two other important pathways could account for the association between maternal exposure to childhood abuse and offspring ADHD. First, it is possible that maternal childhood abuse affects the mother's biology during gestation in ways that increase risk of offspring ADHD. Second, it is possible that experience of childhood abuse is associated with elevated genetic risk for ADHD in mothers or their partners.

Adults who experienced childhood abuse exhibit dysregulation in the hypothalamic-pituitary-adrenal axis (51–55), the hypothalamic-pituitary-thyroid (HPT)-axis (56–61), and immune function (62–69), findings supported by animal studies (70–73).

Table 3. Association of Maternal Childhood Abuse With Attention Deficit Hyperactivity Disorder in Offspring, Base Model and Further Adjusted for Indicators of Socioeconomic Status, Nurses' Health Study II, 1989–2013

Category of Maternal Exposure to Childhood Abuse	Female Offspring				Male Offspring			
	Base Model[a]		Further Adjusted for Indicators of Socioeconomic Status[b]		Base Model[a]		Further Adjusted for Indicators of Socioeconomic Status[b]	
	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI
0 (No abuse)	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
1	1.08	0.93, 1.25	1.08	0.93, 1.25	1.27	1.16, 1.38[c]	1.26	1.16, 1.38[c]
2	1.24	1.07, 1.43[d]	1.23	1.06, 1.42[c]	1.33	1.22, 1.45[c]	1.32	1.20, 1.44[c]
3	1.55	1.35, 1.78[d]	1.52	1.32, 1.75[c]	1.50	1.37, 1.64[c]	1.48	1.35, 1.61[c]
4	1.83	1.54, 2.17[c]	1.78	1.50, 2.11[c]	1.75	1.57, 1.95[c]	1.71	1.54, 1.90[c]
5	1.78	1.39, 2.29[c]	1.71	1.33, 2.20[c]	1.85	1.59, 2.14[c]	1.79	1.55, 2.08[c]
6 (Severe abuse)	2.29	1.73, 3.04[c]	2.19	1.66, 2.90[c]	1.57	1.28, 1.92[c]	1.54	1.26, 1.88[c]

Abbreviation: CI, confidence interval.

[a] Adjusted for child's birth year, maternal age at birth, and educational attainment of mother's parents.

[b] Further adjusted for paternal educational attainment, maternal subjective social standing in the United States, maternal subjective social standing in the community, maternal marital status, US Census tract household median income, and US Census tract percentage college educated data.

[c] $P < 0.001$.

[d] $P < 0.01$.

Maternal biological dysregulation of the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid axis, and immune function has been associated with adverse offspring neurodevelopment. In human studies, dysregulation of these systems has been linked to ADHD (74–76) as well as to delay in expressive language, poorer cognitive functioning, and externalizing behavior (74, 77–85). In animal experiments, dysregulation of these biological systems harms neurodevelopment, causes memory deficits, and induces autistic-like behavior in offspring (86–92). Thus, maternal biological dysregulation during pregnancy may be an important mechanism by which offspring of women abused are at elevated risk of ADHD.

In addition, findings from twin and adoption studies indicate that ADHD is heritable with a strong genetic component (29), and it is possible that maternal experience of childhood abuse indicates genetic loading for ADHD that increases the risk of ADHD for her child. Children with ADHD are more likely to experience abuse (in this case, perhaps the respondent) (93–96), and parents with ADHD may be more likely to perpetrate abuse (perhaps the parents of the respondent), as was found in multiple studies in which impaired parenting in persons with ADHD was reported (93, 97–104). If either of these scenarios were present between the respondent and her parents, the scenario could constitute a genetic contribution to the association between the respondent's experience of abuse and her child's risk of ADHD. In addition, we have shown that maternal experience of abuse is associated with mate selection, with greater maternal abuse history predicting greater autistic traits in her spouse (105). If a similar selection occurs for ADHD traits, then an association between maternal experience of abuse and child ADHD could be explained by paternal genetics as well.

Our study has important limitations. As is common in large epidemiologic studies, to limit respondent burden and due to financial constraints, we relied on maternal report of ADHD diagnosis. ADHD, like other childhood neuropsychiatric disorders, may be misdiagnosed fairly often (106–109), which may have biased our results. However, in this cohort of medical professionals, self-report of medical conditions has had good validity (111–113). In addition, women who were strongly affected by their experiences of abuse may not have finished their education and, therefore, would not be eligible for participation in this cohort, which may have biased effect estimates toward the null hypothesis.

It is of public health relevance that we did not find elevated risk of ADHD only among women exposed to severe abuse. Rather, risk was elevated at each level of abuse compared with risk in situations of no abuse. Even offspring of women who experienced the mildest level of abuse were at increased risk of ADHD. Most women in this group (82%) had had hurtful or insulting thing said to them sometimes or more often, and a large minority (31%) had 1 unwanted sexual experience. Only 3.6% of these women were ever hit hard enough to cause bruising. More than 70% of women were exposed to a level of childhood abuse that was associated with increased risk of ADHD in their offspring. Because ADHD is associated in adulthood with lower educational attainment and increased job insecurity, social isolation, criminality, and premature death (113–117), it is important to identify causal factors driving the association between maternal childhood abuse and offspring ADHD. Identifying causal factors could suggest potential interventions for alleviating this risk.

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