



Association between Maternal Adverse Childhood Experiences and Attention-Deficit/Hyperactivity Disorder in the Offspring: The Mediating Role of Antepartum Health Risks

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Objectives: This study aimed to examine the effect of maternal adverse childhood experiences (ACEs) on the attention-deficit/hyperactivity disorder (ADHD) symptoms in the offspring and to examine the mediating role of antepartum health risk on the intergenerational transmission of maternal ACEs.

Methods: The participants consisted of 461 mother-child dyads. Mothers completed the ACEs questionnaire and Diagnostic Predictive Scales. Multivariate logistic regression analysis was used to estimate the risk of ADHD symptoms in the offspring of mothers with ACEs and the mediating effect of antepartum health risks by path analysis.

Results: In all, 35.4% (n=163) had at least one maternal ACE, and 11.1% (n=51) had three or more. Compared to the non-ADHD symptom group, the group of offspring with ADHD symptoms showed a significant association with maternal ACE score ($p<0.001$) and antepartum health risks ($p<0.001$). Multivariate analysis further showed a significant association between the sum of maternal ACEs [odds ratio (OR)=1.264, 95% confidence interval (CI)= 1.060–1.516, $p=0.009$], antepartum health risks (OR=1.236, 95% CI=1.036–1.475, $p=0.019$), and ADHD symptoms in the offspring. In the mediation model in which the mother's ACE score affected the offspring's ADHD symptoms, partial mediation through antepartum health risks was found to be significant ($B=0.041$, 95% CI=0.011–0.124).

Conclusion: Maternal ACEs are significantly related to the incidence of ADHD symptoms in the offspring and antepartum health risks exert an indirect effect. These findings suggest that maternal ACEs have a negative impact on the offspring's brain development through intergenerational transmission, resulting in neurodevelopmental disorders such as ADHD.

Key Words: Adverse childhood experiences; Attention-deficit/hyperactivity disorder; Antepartum health risks.

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INTRODUCTION

Adverse childhood experiences (ACEs) are known to affect neurodevelopment and the endocrine and immune systems, thus increasing cognitive, social, and emotional dysfunctions [1-3]. Furthermore, people with many ACEs have many physical or mental problems and a high premature mortality rate [4]. A recent meta-analysis reported that the impact of ACEs is transmitted down to generations and is closely linked to the risk of ACEs (violence, mental illness, substance abuse) in the next generation [3], and parents' ACEs have an adverse im-

act on the socioemotional growth of their children [5]. In particular, the presence of four or more ACEs in parents was associated with hyperactivity in their offspring [6].

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is understood as a brain maturational delay caused by an interaction among various factors, including, biological, environmental, and psychosocial risk factors [7]. Because antepartum health risks can have a detrimental impact on fetal brain development, studies have investigated antepartum health risks associated with ADHD. Currently, the identified antepartum health risks associated with ADHD include maternal smoking, antepartum stress, preterm birth, low birth weight, and pregnancy-related complications [8,9].

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According to previous studies, ACEs are positively correlated with antepartum health risks, and people with ACEs have difficulty controlling their emotions and seek strong compensatory strategies to mitigate negative emotions during pregnancy. This alters the neurobiological circuit and increases the risk of binge drinking during pregnancy [10], and mothers with a high number of ACEs exhibited a high risk for pregnancy diabetes, preeclampsia, low birth weight infants, and short gestation period [5]. Furthermore, chronic stress caused by ACEs elevates risky health behaviors, such as smoking, drinking, and binge eating, which are likely to lead to adverse birth outcomes, such as miscarriage and preterm birth [11].

While studies on the mediators of the impact of maternal ACEs on offspring's ADHD are lacking, based on previous findings, maternal ACEs are likely to increase antepartum health risks and thus have an adverse impact on children's neural development. Thus, this study aimed to investigate the effects of maternal ACEs and antepartum health risks on the incidence of ADHD in the offspring and the mediating role of antepartum health risks in the intergenerational transmission of maternal ACEs in the form of ADHD.

METHODS

Participants and methods

This study involved mothers and their children aged 6–18 years who had continuously been attending school for at least 6 months in Jeju Island. Data were collected using a questionnaire, which was distributed and retrieved by mental health staff trained on the background of the study and contents of the questionnaire. A total of 461 participants were enrolled, and written informed consent was obtained from the mothers and their offspring. Data were collected from September to December 2017. This study was approved by the Institutional Review Board of Jeju National University Hospital (2018-08-004).

Instruments

Adverse childhood experiences questionnaire

The ACEs questionnaire retrospectively surveys adverse experiences in childhood before the age of 18 years, including child abuse (emotional abuse, physical abuse, sexual abuse), child neglect (physical neglect, emotional neglect), and dysfunctional family environment (domestic violence, parents' divorce or separation, family member's substance abuse, mental illness, and incarceration) [12]. A "yes" response is scored 1 point, and "no" response, 0. The total score is used to indicate the degree of ACE exposure [3]. ACEs are ana-

lyzed in various ways, but the total score is used in most cases [13]. In the present study, the cumulative total score was classified into 0, 1, 2, and ≥ 3 , and to examine the impact of each type of ACE on children's mental health problems, the scores for 3 domains of child abuse, child neglect, and household dysfunction were used.

Diagnostic Interview Schedule for Children Diagnostic Predictive Scales

In this study, ADHD symptoms were assessed using the Diagnostic Predictive Scales (DPS). It is the primary screening tool of the Diagnostic Interview Schedule for Children (DISC)-IV, a structured interview tool based on the DSM-IV criteria. The DPS for parents is a self-reported tool that consists of 92 questions about the symptoms of a mental disorder of the child in the past year and eight questions about mood or behavioral problems the child has at home, school, or with friends. DPS is a brief scale but can be effectively used for DISC-IV diagnosis, with a high reliability [14].

A previous epidemiological survey on Korean children and adolescents [15] added 33 items to the DISC-IV but not the DPS (selective mutism, eating disorder, elimination disorder, posttraumatic stress disorder, tic disorder, cigarette, pica, and trichotillomania) and removed eight items related to general mood and behavior problems. The same tool was used in this study. We used the cutoff proposed in the study by Cubo for each disorder [16].

Assessment of antepartum health risks

The following 12 items pertaining to antepartum health risks are examined: physical problems, namely problems with fetal location, premature rupture of membranes, severe vaginal bleeding, and mild vaginal bleeding; rubella; preeclampsia; seizures in pregnancy; emotional problems requiring treatment, serious family problems; accidents or injuries requiring treatment; constipation; low back pain; perineal infection; heartburn; and severe psychological stress. These items about antepartum health risks were drawn from obstetric evaluation tools [17,18]. In this study, a "yes" response was given 1 point, and the total score was used to represent antepartum health risks.

Statistical analysis

Participants' demographic factors were analyzed using descriptive statistics and frequency analysis according to the total ACE score. The differences in maternal demographic factors, maternal antepartum health risk, and maternal ACEs according to the offspring's ADHD symptoms were analyzed using independent sample t-tests and chi-squared tests. Multiple logistic regression was performed for two models (ante-

partum health risk and ACE; Model 1: ACE total score, Model 2: ACE score for three domains) to identify the significant predictors of ADHD. The mediating effects were analyzed using Model 4, which is used to test simple mediation models, from the 76 statistical models in the PROCESS macro for SPSS proposed by Hayes [19]. The significance of the indirect effects, direct effects, and total effects were analyzed using bootstrapping, with 5000 samples and 95% confidence intervals (CIs). The mediating effects were deemed statistically significant if 0 was not included in the 95% CI. Data were analyzed using SPSS v.18 (SPSS Inc., Chicago, IL, USA) and Process Macro for SPSS v.3.4 software, and statistical significance was set at $p < 0.05$.

RESULTS

Participants' general characteristics

The mean age of the 461 participants was 42.79 ± 5.68 years; further, 275 participants had graduated from high school or higher (59.7%), and 258 (56.0%) were in the middle class in terms of their socioeconomic status; 35.4% ($n=163$) had at least one ACE, and 11.1% ($n=51$) had at least three ACEs. The mean antepartum health risk score was $0.77 (\pm 1.30)$. The mean age of the children was 13.26 years (± 3.91), with 38.6% ($n=178$) male and 61.4% ($n=283$) female. A total of 205 children were in elementary school (44.5%), while 256 were in middle school or high school (55.5%) (Table 1).

Comparison of sociodemographic factors, maternal ACE, and antepartum health risks nonbetween the ADHD symptom group and control group

Among the offspring, 13.7% ($n=64$) had ADHD symptoms. The ADHD symptom group was younger than the control group ($p=0.001$). The maternal antepartum health risk score was higher in the ADHD symptom group ($p < 0.001$), with a greater percentage of mothers who had ACEs ($p < 0.001$) (Table 2). In the ADHD symptom group, 27 were male (42.2%) and 37 were female (57.8%), and there were no significant differences in the ACEs and antepartum health risk scores according to the child's sex.

Maternal ACEs and antepartum health risks and child's ADHD symptoms

Multiple logistic regression was performed to examine the impact of total maternal ACE score and maternal antepartum health risk on the incidence of ADHD symptoms (Model 1) and the impact of three types of maternal ACEs and antepartum health risk on the incidence of ADHD symptoms (Model 2). In Model 1, the odds ratio (OR) of the incidence of ADHD symptoms in the presence of antepartum health risks

Table 1. Demographic characteristics of the study sample ($n=461$)

Mother related variables	
Maternal age	42.79 (± 5.68)
Maternal education level	
High (> high school)	275 (59.7)
Middle (high school)	158 (34.3)
Low (< middle school)	16 (3.5)
Missing value	12 (2.6)
Socioeconomic status	
High	135 (29.3)
Middle	258 (56.0)
Low	59 (12.8)
Missing value	9 (2.0)
Total ACE score (0–10)	
0	298 (64.6)
1	66 (14.3)
2	46 (10.0)
≥ 3 (3–8)	51 (11.1)
Antepartum health risks	0.77 (± 1.30)
Children related variables	
Sex	
Male	178 (38.6)
Female	283 (61.4)
Age	13.26 (± 3.91)
Education level	
Elementary school	205 (44.5)
Middle school and above	256 (55.5)

Data are presented as mean \pm standard deviation or n (%). SD: standard deviation, ACEs: adverse childhood experiences

after adjusting for socioeconomic status, maternal age and education level, and child's sex and age was 1.264 (95% CI= 1.060–1.516, $p=0.009$) and the OR of total maternal ACE score predicting the incidence of ADHD symptoms was 1.236 (95% CI=1.036–1.475, $p=0.019$). In Model 2, the OR of antepartum health risks in predicting incidence of ADHD symptoms was significant (OR: 1.275, 95% CI=1.069–1.520, $p=0.007$), but when the maternal ACE score was divided into three domains (child abuse, child neglect, household dysfunction), the ORs were not significant (Table 3).

Effects of maternal ACEs on incidence of ADHD symptoms through antepartum health risks

The effects of total maternal ACE score on the incidence of ADHD symptoms in the offspring through antepartum health risks were analyzed using mediation analysis ($R^2=0.197$, $F=18.431$, $p < 0.001$). The total maternal ACE score was significantly associated with the incidence of ADHD symptoms in the offspring ($B=0.312$, $p < 0.001$) and antepartum health risks ($B=0.186$, $p < 0.001$), and antepartum health risk was significantly associated with the incidence of ADHD symptoms ($B=$

Table 2. Comparison of psychosocial variables between ADHD symptom group and non-ADHD symptom group

	ADHD symptom (n=64)	Non-ADHD symptom (n=397)	p-value
Maternal age	41.70 (6.68)	42.98 (5.48)	0.154
Maternal education level			0.130
High (>high school)	45 (72.6)	230 (59.4)	
Middle (high school)	16 (25.8)	142 (36.7)	
Low (<middle school)	1 (1.6)	15 (3.9)	
Socioeconomic status			0.442
High	9 (14.1)	50 (12.9)	
Middle	32 (50.0)	226 (58.2)	
Low	23 (35.9)	112 (28.9)	
Children's sex (male)	27 (42.2)	151 (38.0)	0.527
Children's age	11.69 (3.85)	13.52 (3.87)	0.001
Children's education level			0.002
Elementary school	40 (62.5)	165 (41.6)	
Above middle school	24 (37.5)	232 (58.4)	
Antepartum health risks	1.30 (1.19)	0.69 (1.30)	<0.001
Total ACE score			<0.001
0	26 (40.6)	272 (68.5)	
1	11 (17.2)	55 (13.9)	
2	12 (18.8)	34 (8.6)	
+3	15 (23.4)	36 (9.1)	

Data are presented as mean \pm standard deviation or n (%). ADHD: attention-deficit/hyperactivity disorder, ACEs: adverse childhood experiences

Table 3. Multivariable logistic regression analysis for offspring' ADHD symptoms by maternal ACEs and antepartum health risks

	B	SE	OR	95% CI	p-value
Model 1					
Antepartum health risks	0.234	0.090	1.264	1.060–1.516	0.009
Total sum of maternal ACEs	0.212	0.090	1.236	1.036–1.475	0.019
Model 2					
Antepartum health risks	0.243	0.090	1.275	1.069–1.520	0.007
Maternal ACE domains					
Child abuse	0.252	0.233	1.286	0.815–2.030	0.280
Child neglect	0.090	0.352	1.094	0.549–2.180	0.799
Household dysfunction	0.225	0.180	1.252	0.879–1.782	0.212

Adjusted socioeconomic status, maternal age, maternal education level, offspring's age and sex. Hosmer-Lemeshow goodness of fit ($p=0.969$). ADHD: attention-deficit/hyperactivity disorder, ACEs: adverse childhood experiences, B: regression coefficient, SE: standard error of B, OR: odds ratio, CI: confidence interval

0.220, $p=0.009$) (Fig. 1). In the bootstrapping analysis to determine the significance of the direct and indirect effects of the ACE score, the total maternal ACE score had a significant direct effect on incidence of ADHD symptoms ($B=0.312$, 95% CI=0.151–0.472) and indirect effect through antepartum health risks ($B=0.041$, 95% CI=0.011–0.124) (Table 4).

DISCUSSION

Maternal ACEs and antepartum health risk are factors associated with ADHD symptoms in the offspring. In particular, maternal ACEs had significant indirect effects on the risk

of ADHD symptoms in the offspring through antepartum health risks.

The antepartum health risks assessed in this study included not only major risk factors such as preeclampsia, premature rupture of membrane, and seizures, but also a wide range of physical symptoms, emotional problems, and stress during pregnancy. Our results showed that maternal antepartum health risks significantly affected the risk of ADHD symptoms in the offspring, similar to previous findings that ADHD diagnosis in children aged 6–12 years is associated with maternal stress life events during pregnancy [20] and that stressful life events during pregnancy were associated with the off-

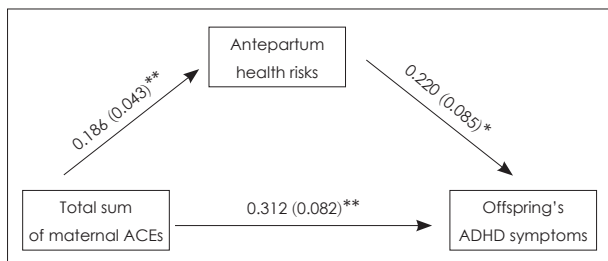


Fig. 1. Diagrams to test for mediation effect. Mediation model with a X (total sum of maternal ACEs), M (antepartum health risks), and Y (offspring's ADHD symptoms). Standardized path coefficients and standard errors are presented. * $p < 0.05$, ** $p < 0.01$. ADHD: attention-deficit/hyperactivity disorder, ACEs: adverse childhood experiences.

Table 4. The bootstrap results for the indirect effect of maternal ACEs on offspring's ADHD symptoms via antepartum health risks

Path	B	SE	95% CI
Direct effect			
Total sum of maternal ACEs → Offspring's ADHD symptoms	0.312	0.082	0.151–0.472
Indirect effect			
Total sum of maternal ACEs → Antepartum health risks → Offspring's ADHD symptoms	0.041	0.028	0.011–0.124

ADHD: attention-deficit/hyperactivity disorder, ACEs: adverse childhood experiences, B: regression coefficient, SE: standard error of B, CI: confidence interval

spring's ADHD symptoms in a prospective cohort study of 2900 participants [21].

The result that the cumulative ACE score, as opposed to the domains of ACE, has an adverse impact on the offspring's ADHD symptoms suggests that there is a dose-response relationship in the intergenerational transmission of mental health problems from parents to offspring, as observed in a previous study where cumulative risk was detrimental to child development [22].

Maternal ACE is significantly associated with antepartum health risk [11], and mothers with four or more ACEs have a two-fold increased biomedical risk during pregnancy [5]. Similar to our study, a previous study reported that maternal health risks in pregnancy and maternal ACEs led to adverse development outcomes in 12-month-old children [23]. Further, compared to children of mothers without childhood abuse experience, those of mothers with childhood abuse experience ACE showed a significantly high prevalence of ADHD, and adverse perinatal factors increased the risk of ADHD by 8.6% [24].

Prenatal stress has a direct impact on fetal neurodevelopment, such as delay in progenitor migration and reduction in forebrain proliferation [25]. Moreover, adverse environmental factors during pregnancy, such as prenatal stress, exposure to toxic substances, and infection, contribute to neurodevel-

opmental impairment by inducing epigenetic changes related to gene expression in the fetus [26]. Genetic heritability accounts for 70–80% of ADHD cases [27], and such antepartum health risks are highly likely to contribute to the etiology of ADHD by increasing or facilitating the genetic liability of neurodevelopmental disorders [7,28]. In addition, ACEs, such as child abuse, lead to an imbalance in the hypothalamic-pituitary-thyroid axis and immune functions [1,2], which is in turn associated with ADHD, language and cognitive developmental delay, and externalizing behaviors in the offspring [29]. Therefore, maternal biological dysregulation during pregnancy is likely to serve as an important mechanism underlying the elevated risk of ADHD in the children.

The results of this study suggest that maternal ACEs can contribute to neurodevelopmental disorders such as ADHD by affecting fetal brain development through biological mediators during pregnancy. Similar to our findings, a prior study on autism reported that mothers with childhood abuse experience more commonly experienced gestational diabetes, preeclampsia, smoking and drinking behaviors during pregnancy, miscarriage, and preterm births, with a significantly higher risk of their children being autistic, than mothers without such experience [30].

This study has a few limitations. First, this study was conducted in a single center and considering that the prevalence of ACE varies across regions and cultures, the findings cannot be generalized, necessitating large-scale prospective studies. Second, we used a self-reported screening tool to diagnose ADHD instead of a clinical diagnostic or structured diagnostic tool based on the DSM-5. Third, we did not include all the possible antepartum health risks in our questionnaire. However, various antepartum physical and emotional problems were included in this study. Fourth, the ACE questionnaire asks the respondent whether he/she has undergone specific experiences and it is not a screening scale that determines the presence of clinical symptoms based on a cutoff. However, this scale is yet to be standardized for the South Korean population.

Nevertheless, this study is the first study to propose that maternal ACEs are associated with ADHD symptoms in their offspring through the mediation of antepartum health risks. Maternal ACEs can influence fetal neurodevelopmental, resulting in disorders such as ADHD via intergenerational transmission.

CONCLUSION

Maternal ACEs and antepartum health risks are both significant predictors of ADHD symptoms in the offspring, and maternal ACEs also indirectly influence the ADHD symp-

toms through antepartum health risks. This suggests that in addition to the well-known impact of maternal ACEs on the offspring's emotional development, maternal ACEs negatively influence fetal brain development, contributing to neurodevelopmental disorders such as ADHD through intergenerational transmission. Future studies should examine the mediators and mechanisms through which maternal ACEs contribute to various neurodevelopment disorders other than ADHD in the offspring through intergenerational transmission.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Na Ri Kang, Duk-Soo Moon, Bung-Nyun Kim. Formal analysis: Na Ri Kang, Su-Jeong Bong. Investigation: Na Ri Kang, Duk-Soo Moon, Bung-Nyun Kim. Writing—original draft: Su-Jeong Bong, Duk-Soo Moon. Writing—review & editing: Duk-Soo Moon, Na Ri Kang.

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