Prenatal Exposure to Acetaminophen and the Risk of Attention-Deficit/Hyperactivity Disorder: A Nationwide Study in Taiwan

Mu-Hong Chen, MD, PhD[a,b,‡]; Tai-Long Pan, PhD[c,d,e,‡]; Pei-Wen Wang, PhD[f]; Ju-Wei Hsu, MD[a,b]; Kai-Lin Huang, MD[a,b]; Tung-Ping Su, MD[a,b,g]; Cheng-Ta Li, MD, PhD[a,b]; Wei-Chen Lin, MD[a,b]; Shih-Jen Tsai, MD[a,b]; Tzeng-Ji Chen, MD, PhD[h,i]; and Ya-Mei Bai, MD, PhD[a,b,*]

ABSTRACT

Background: Studies have suggested that a significant association exists between prenatal exposure to acetaminophen and the offspring's attention-deficit/hyperactivity disorder (ADHD) risk. However, this association has largely been unexplored among the Asian population, generally, and the Taiwanese population, specifically.

Methods: In our study, 950 study pairs (children with ADHD [*ICD-9-CM* code: 314] and their mothers) and 3,800 control pairs (children without ADHD and their mothers) matched by demographic characteristics were identified between 1998 and 2008 from the Taiwan Longitudinal Health Insurance Database. Maternal use of acetaminophen was assessed in the first trimester, second trimester, and third trimester of pregnancy and over the period from 3 months before pregnancy to the date of last menstrual cycle.

Results: Logistic regression analysis with adjustments for demographic data, gestational infections, comorbid perinatal conditions, and maternal mental health disorders indicated that exposure to acetaminophen in the second trimester (odds ratio [OR] = 1.19; 95% CI, 1.00–1.40), both the first and second trimesters (OR = 1.28; 95% CI, 1.00–1.64), or in any trimester (OR = 1.20; 95% CI, 1.01–1.42) was associated with an increased risk of ADHD in offspring. Sensitivity analysis excluding gestational infections and maternal mental health disorders confirmed this association (OR = 1.33; 95% CI, 1.04–1.69).

Conclusion: Prenatal exposure to acetaminophen was associated with an increased risk of ADHD in offspring, regardless of gestational infections and maternal mental health disorders. Additional studies are necessary to clarify the underlying mechanisms by which prenatal exposure to acetaminophen leads to neurodevelopmental risks.

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[a]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

[b]Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan

[c]School of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan

[d]Research Center for Chinese Herbal Medicine and Research Center for Food and Cosmetic Safety, College of Human Ecology, Chang Gung University of Science and Technology, Taoyuan, Taiwan

[e]Liver Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan

[f]Department of Medical Research, China Medical University Hospital, Taichung City, Taiwan

[g]Department of Psychiatry, Cheng Hsin General Hospital, Taipei, Taiwan

[h]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

[i]Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan

‡Drs M-H Chen and Pan contributed equally to this article.

**Corresponding author:* Ya-Mei Bai, MD, PhD, Department of Psychiatry, No. 201, Shih-Pai Rd, Sec. 2, 11217, Taipei, Taiwan (ymbi@mail2000.com.tw).

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in children and adolescents and affects approximately 10% of primary-school–aged children, 7.5% of seventh-grade teenagers, 6.1% of eighth-grade teenagers, and 3.3% of ninth-grade teenagers in Taiwan, with a male-to-female ratio in the range of 3:1–4:1.[1,2] ADHD manifests as the inability to marshal and sustain attention, modulate activity levels, and control impulses.[3] However, the specific pathophysiology of ADHD remains unclear, and its etiology appears to be complex. Multiple genetic and environmental factors induce a spectrum of neurobiological susceptibilities.[3–5]

An increasing body of evidence[6–11] compiled this decade suggests a possible association between prenatal exposure to acetaminophen and the offspring's ADHD risk. A study[12] estimated that up to 65% of American women and over 50% of European women used acetaminophen during their pregnancies. In 1987, Streissguth et al[13] first investigated the association between acetaminophen use during pregnancy and the child's subsequent intelligence and attention decrements and determined that maternal acetaminophen use was not related to a child's intelligence or attention. In 2013, Brandlistuen et al[11] first reported the relationship between prenatal exposure to acetaminophen and neurodevelopmental risks such as impaired gross motor development, internalizing and externalizing behaviors, and excessive activity levels in offspring. In 2014, Liew et al[7] identified a significant association between maternal acetaminophen use during pregnancy and the offspring's ADHD risk. They analyzed 64,322 live-born children and mothers included in the Danish National Birth Cohort and determined that 56% of mothers had used acetaminophen during pregnancy; children whose mothers had used acetaminophen during pregnancy were more likely to have ADHD-like behaviors at the age of 7 years (risk ratio [RR] = 1.13; 95% CI, 1.01–1.27) or receive an ADHD diagnosis (hazard ratio [HR] = 1.37; 95% CI, 1.19–1.59) compared with

Clinical Points

- Prenatal exposure to acetaminophen, especially in the second trimester, was associated with an increased risk of ADHD in offspring.
- The association between acetaminophen exposure and ADHD risk was independent of gestational infections or maternal mental health disorders.
- Clinicians and pregnant women are reminded that the prescription and use of acetaminophen must be carefully evaluated during pregnancy.

those whose mothers did not.[7] This association remained significant even after carefully adjusting for confounding factors such as maternal infection during pregnancy and a mother's mental health problems.[7] Furthermore, a dose-dependent relationship was established: a longer duration of acetaminophen exposure during pregnancy was related to a greater likelihood of ADHD development in offspring.[7] However, the aforementioned studies assessed only white populations. Whether the association between prenatal exposure to acetaminophen and the risk of ADHD can be extended to the Asian population generally or the Taiwanese population specifically requires further investigation.

A preclinical study[14] failed to validate the association between prenatal exposure to acetaminophen and the offspring's ADHD risk. Zebrafish were used to investigate the potential effect of acetaminophen exposure on locomotor activity levels, and the results were compared with those obtained for the established zebrafish Latrophilin 3 (Lphn3) ADHD model; Reuter et al[14] demonstrated that exposure to acetaminophen from the embryonic to larval stages did not cause hyperactivity in zebrafish larvae. Moreover, they reported that no additive or synergistic effects from acetaminophen exposure were evident in the *lphn3.1*-knockdown–susceptible zebrafish model.[14] The conflicting findings from preclinical and clinical studies suggest the need for further investigation of the possible association between prenatal acetaminophen use and the subsequent risk of ADHD.

In our retrospective study, a matched mother-child pair sample identified from the Taiwan Longitudinal Health Insurance Database was used to investigate the relationship between prenatal exposure to acetaminophen and the offspring's ADHD risk in the Taiwanese population. We hypothesized that children whose mothers were exposed to acetaminophen during pregnancy are at a higher risk of receiving a childhood ADHD diagnosis from a psychiatrist than those whose mothers were not.

METHODS

Data Source

In 1995, Taiwan implemented the National Health Insurance program, a compulsory and universal health insurance program offering comprehensive medical care coverage to all residents of Taiwan. The Taiwan Longitudinal Health Insurance Database is audited and released by the Taiwan National Health Research Institutes for academic research (https://nhird.nhri.org.tw/en/). To protect patient privacy, when individual medical records are extracted from the database, the information is deidentified, and patient anonymity is guaranteed. The database contains comprehensive data on insured individuals, including demographic characteristics, clinical visit dates, disease diagnoses, and prescriptions. In this study, using each individual's unique personal identification number, all of the information is linked. Subsequently, following the method of Kuo et al[15] and Cheng et al,[16] family kinships in the database are used for genealogy reconstruction. The codes of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) are used for disease diagnosis. The Taiwan Longitudinal Health Insurance Database has been used extensively in many epidemiologic studies in Taiwan.[16–19] The present study was initiated after approval from the Institutional Review Board of Taipei Veterans General Hospital.

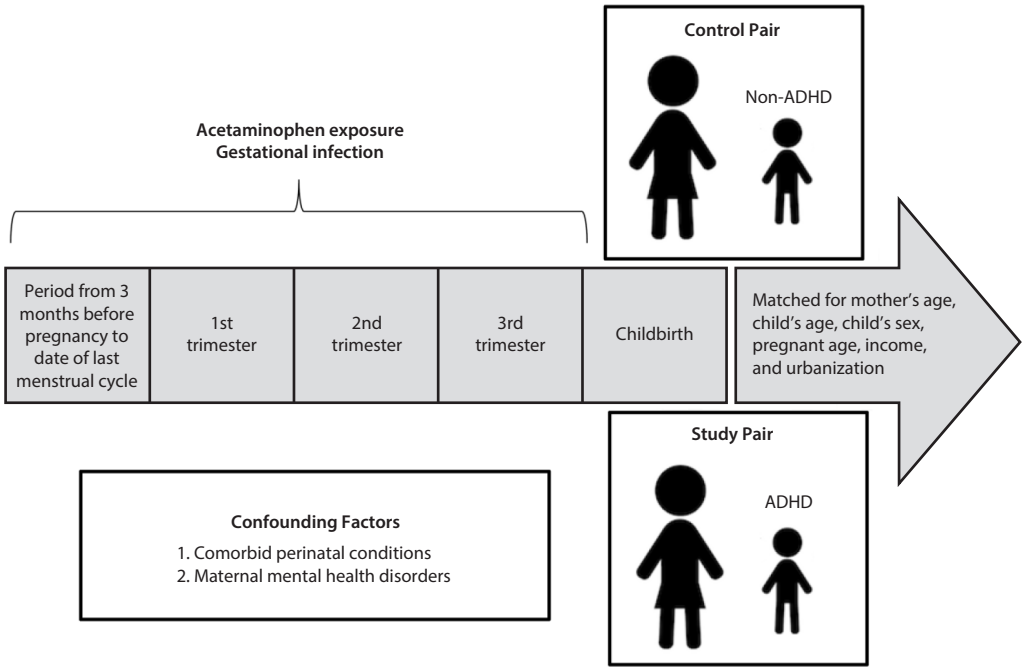
Inclusion Criteria for the Pairs of Mothers and Their Children With or Without ADHD

Children born between January 1, 1998, and December 31, 2008, who received diagnoses of ADHD (*ICD-9-CM* code: 314) by board-certified psychiatrists on the basis of diagnostic interviews and clinical judgement were identified and linked with their mothers as the mother–child-with-ADHD (study) pairs in the current study. Diagnoses of ADHD were received from 1998 to the study end date (December 31, 2013). The mother–child-without-ADHD (control) pairs were randomly (1:4) identified on the basis of the mothers' ages, children's sex and ages, mothers' age during pregnancy, income, and urbanization level. Acetaminophen use and gestational infections were assessed in the first trimester, second trimester, and third trimester and over the period from 3 months before pregnancy to the date of last menstrual cycle. Gestational infections included respiratory infections, urinary tract infections, gastrointestinal tract infections, and sexually transmitted infections. Cumulative doses (mg) of acetaminophen exposure were calculated in each trimester. Maternal mental health disorders, including schizophrenia, bipolar disorder, and major depressive disorder, and comorbid perinatal conditions, including preterm or low birth weight, birth trauma, and intrauterine hypoxia/birth asphyxia, were also assessed as the confounding factors. In addition, the prenatal exposure to psychotropic agents, such as antidepressants, mood stabilizers, atypical antipsychotics, ADHD medications, and benzodiazepines, was also identified in our study. Level of urbanization (levels 1 to 5, with level 1 the most urbanized region and level 5 the least) was also assessed for our study.[20] The study design is shown in Figure 1.

Statistical Analysis

For between-group comparisons, the F test was used for continuous variables and Pearson χ^2 test for nominal

Figure 1. Study Design to Explore the Risk of Prenatal Exposure to Acetaminophen on Attention-Deficit/Hyperactivity Disorder (ADHD) in Offspring



variables, where appropriate. Two logistic regression models were performed to investigate the relation between the exposure to acetaminophen in each trimester and the risk of ADHD. Model 1 adjusted for demographic data (age, sex, income, level of urbanization), gestational infections, and comorbid perinatal conditions. Model 2 additionally adjusted for maternal mental health disorders. Sensitivity analysis after excluding gestational infections and maternal mental health disorders was performed to further confirm the association between acetaminophen exposure and ADHD risk in the non-infectious and non-maternal mental health disorders condition. A 2-tailed *P* value of less than .05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc, Chicago, Illinois) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

In all, 950 study pairs (mothers–children-with-ADHD) and 3,800 control pairs (mothers–children-without-ADHD) were identified in our study. Mothers of children with ADHD had a higher prevalence of acetaminophen exposure in the second trimester (39.3% vs 35.3%, $P = .029$) and in any trimester (71.2% vs 67.4%, $P = .026$) and had a higher prevalence of psychiatric disorders, including bipolar disorder (2.2% vs 0.7%, $P < .001$) and major depressive disorder (5.7% vs 3.1%, $P < .001$), than did mothers of children without ADHD (Table 1). The acetaminophen exposure in the first and third trimesters and the comorbid perinatal conditions did not differ between study and control pairs (Table 1). Furthermore, prenatal exposure to mood stabilizers (n = 1 vs 3), atypical antipsychotics (n = 1 vs 1), ADHD medications (n = 0 vs 1), and benzodiazepines (4.5% vs 4.1%, $P = .526$) did not differ between the 2 groups. Only 6 mothers (0.6%) of children with ADHD and 2 mothers (0.1%) of children without ADHD were exposed to antidepressant during their pregnancy ($P = .001$).

Logistic regression analysis with adjustment for demographic data, gestational infections, comorbid perinatal conditions, and maternal mental health disorders showed that exposure to acetaminophen in the second trimester (OR = 1.19; 95% CI, 1.00–1.40) or in both first and second trimesters (OR = 1.28; 95% CI, 1.00–1.64) or in any trimester (OR = 1.20; 95% CI, 1.01–1.42) was associated with the increased risk of ADHD in offspring (Tables 2 and 3). However, the log-transformed cumulative doses of acetaminophen exposure in the second trimester (OR = 1.13; 95% CI, 0.76–1.69) or in both first and second trimesters (OR = 0.98; 95% CI, 0.50–1.91) were not related to the ADHD risk. Sensitivity analysis after excluding gestational infections and maternal mental health disorders confirmed the association between acetaminophen exposure in the second trimester (OR = 1.33; 95% CI, 1.04–1.69) or in both first and second trimesters (OR = 1.68; 95% CI, 1.18–2.40) and the likelihood of ADHD in offspring (Table 3). Furthermore, sensitivity analysis also found the significant association (OR = 1.27; 95% CI, 1.00–1.61) between acetaminophen exposure in the first trimester and offspring ADHD risk (Table 3).

Table 1. Demographic Data and Clinical Characteristics of Mothers of Children With and Without ADHD[a]

Characteristic	Mothers of Children With ADHD (n = 950)	Mothers of Children Without ADHD (n = 3,800)	*P* Value[b]
Age, y, mean (SD)			
Mother	39.59 (5.01)	39.61 (4.96)	.919
Mother at childbirth	28.74 (4.55)	28.83 (4.53)	.563
Children	10.86 (2.28)	10.78 (2.33)	.362
Children at ADHD diagnosis	3.71 (2.26)		
Male children	736 (77.5)	2,944 (77.5)	1.000
Acetaminophen exposure			
Period from 3 months before pregnancy to date of last menstrual cycle	334 (35.2)	1,270 (33.4)	.319
First trimester	374 (39.4)	1,421 (37.4)	.262
Second trimester	373 (39.3)	1,346 (35.4)	**.029**
Third trimester	535 (56.3)	2,144 (56.4)	.971
Any trimester	676 (71.2)	2,560 (67.4)	**.026**
Cumulative doses of acetaminophen exposure, mg, mean (SD)			
Period from 3 months before pregnancy to date of last menstrual cycle	3,118.05 (5,756.90)	2,845.48 (5,818.90)	.196
First trimester	3,319.95 (6,150.97)	3,159.00 (5,800.77)	.450
Second trimester	3,416.17 (5,972.90)	3,023.53 (5,631.16)	.058
Third trimester	5,971.69 (7,605.07)	5,844.09 (9,934.52)	.712
Gestational infections			
Period from 3 months before pregnancy to date of last menstrual cycle	190 (20.0)	732 (19.3)	.617
First trimester	244 (25.7)	969 (25.5)	.901
Second trimester	256 (26.9)	994 (26.2)	.621
Third trimester	268 (28.2)	1,032 (27.2)	.515
Any trimester	476 (50.1)	1,891 (49.8)	.856
Comorbid perinatal conditions			
Preterm or low birth weight	30 (3.2)	125 (3.3)	.919
Birth trauma	5 (0.5)	13 (0.3)	.382
Intrauterine hypoxia/birth asphyxia	2 (0.2)	20 (0.5)	.286
Maternal mental health disorders			
Major depressive disorder	54 (5.7)	119 (3.1)	**<.001**
Bipolar disorder	21 (2.2)	27 (0.7)	**<.001**
Schizophrenia	9 (0.9)	16 (0.4)	.073
Level of urbanization			1.000
1 (most urbanized)	270 (28.4)	1,080 (28.4)	
2	348 (36.6)	1,392 (36.6)	
3	129 (13.6)	516 (13.6)	
4	56 (5.9)	224 (5.9)	
5 (most rural)	147 (15.5)	588 (15.5)	
Income-related insured amount per month[c]			1.000
≤ NT$15,840	193 (20.3)	772 (20.3)	
NT$15,841–NT$25,000	416 (43.8)	1,664 (43.8)	
≥ NT$25,001	341 (35.9)	1,364 (35.9)	

[a]All values are n (%) unless otherwise noted.
[b]Boldface type indicates significant at $P < .05$.
[c]Multiply NT$ by 0.0324 for an approximate conversion to US dollars, eg, NT$15,841–NT$25,000 is approximately equivalent to $513–$810.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, NT$ = New Taiwan Dollar.

Finally, maternal bipolar disorder (OR = 2.25; 95% CI, 1.19–4.27) and major depressive disorder (OR = 1.57; 95% CI, 1.10–2.24) were significantly related to the increased risk of ADHD in offspring (Table 2).

DISCUSSION

Our findings supported the study hypothesis that prenatal exposure to acetaminophen, especially in the second trimester or in both the first and second trimesters, was associated with an increased risk of ADHD in offspring. This relationship remained significant even after carefully adjusting for or excluding gestational infections and maternal mental health disorders in the regression model. However, our study did not identify a dose-dependent relationship between prenatal acetaminophen use and the offspring's ADHD risk; the log-transformed maternal cumulative doses of acetaminophen were not related to ADHD risk in offspring.

Our findings suggest that the timing of prenatal exposure to acetaminophen is critical. Specifically, we determined that a significant relationship existed between maternal acetaminophen use in the first and second trimesters and the offspring's ADHD risk after adjusting for or excluding gestational infections and maternal mental health disorders. Neurogenesis and neural migration occur predominantly during the first and second trimesters, and synaptogenesis and gliogenesis begin in the second trimester and continue into childhood and adolescence.[21] These neurodevelopmental processes are significantly affected by many environmental factors such as maternal stress, abnormal maternal immune activation (ie, infections), and exposure to specific drugs or substances.[21] The Danish National Birth Cohort study[7] determined that maternal acetaminophen use in both the second and third trimesters was associated with ADHD-like behavioral problems in children at the age of 7 years (HR = 1.44; 95% CI, 1.12–1.87) and the use of ADHD medications (HR = 1.63; 95% CI, 1.28–2.07); exposure to acetaminophen in the first trimester was related to the risk (HR = 1.35; 95% CI, 1.07–1.72) of children's receiving an ADHD diagnosis in a hospital setting. Furthermore, Stergiakouli et al[10] determined that children with prenatal exposure to acetaminophen in the second and third trimesters exhibited an increased risk of multiple behavioral difficulties such as hyperactivity (RR = 1.31; 95% CI, 1.16–1.49) and conduct problems (RR = 1.42; 95% CI, 1.25–1.62). Integrating our findings with those of other studies, we suggest that the second trimester is the crucial period in which maternal acetaminophen use is associated with an increased risk of ADHD for offspring, which may imply that prenatal acetaminophen exposure affects neurogenesis and neural migration.

However, the definite pathophysiology of the relationship between prenatal exposure to acetaminophen and the offspring's ADHD risk remains

Table 2. Logistic Regression of Acetaminophen Exposure and ADHD Risk[a]

Variable	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)
Acetaminophen exposure		
Any trimester	**1.21 (1.02–1.43)**	**1.20 (1.01–1.42)**
Period from 3 months before pregnancy to date of last menstrual cycle	1.07 (0.91–1.26)	1.06 (0.90–1.25)
First trimester	1.10 (0.93–1.30)	1.09 (0.92–1.28)
Second trimester	**1.21 (1.02–1.43)**	**1.19 (1.00–1.40)**
Third trimester	0.98 (0.84–1.14)	0.97 (0.83–1.13)
Gestational infections		
Any trimester	0.96 (0.81–1.11)	0.94 (0.80–1.10)
Period from 3 months before pregnancy to date of last menstrual cycle	1.02 (0.83–1.24)	1.00 (1.82–1.23)
First trimester	0.96 (0.79–1.16)	0.97 (0.80–1.18)
Second trimester	0.93 (0.77–1.13)	0.93 (0.77–1.13)
Third trimester	1.05 (0.88–1.25)	1.05 (0.88–1.25)
Maternal mental health disorders		
Major depressive disorder		**1.57 (1.10–2.24)**
Bipolar disorder		**2.25 (1.19–4.27)**
Schizophrenia		1.35 (0.55–3.29)

[a]Boldface type indicates significant at $P < .05$.
[b]Adjusting for demographic data, gestational infections, and comorbid perinatal conditions.
[c]Adjusting for demographic data, gestational infections, maternal mental health disorders, and comorbid perinatal conditions.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, OR = odds ratio.

Table 3. Sensitivity Analysis of Acetaminophen Exposure and ADHD Risk[a]

Acetaminophen Exposure	Total OR (95% CI)	Excluding Gestational Infections and Maternal Mental Health Disorders OR (95% CI)
Any trimester	**1.20 (1.01–1.42)**	**1.40 (1.14–1.73)**
Period from 3 months before pregnancy to date of last menstrual cycle	1.06 (0.90–1.25)	1.23 (0.96–1.56)
First trimester	1.09 (0.92–1.28)	**1.27 (1.00–1.61)**
Second trimester	**1.19 (1.00–1.40)**	**1.33 (1.04–1.69)**
Third trimester	0.97 (0.83–1.13)	1.05 (0.85–1.29)
Both first and second trimesters	**1.28 (1.00–1.64)**	**1.68 (1.18–2.40)**
Both second and third trimesters	1.05 (0.93–1.119)	1.12 (0.95–1.32)
Both first and third trimesters	1.02 (0.90–1.15)	1.10 (0.93–1.29)
All 3 trimesters	1.04 (0.95–1.15)	1.12 (0.97–1.29)

[a]Boldface type indicates significant at $P < .05$.
Abbreviations: ADHD = attention-deficit hyperactivity disorder, OR = odds ratio.

unknown.[12,22] Several biologically plausible contentions regarding the effect of prenatal acetaminophen exposure on the risk of neurodevelopmental impairments, including ADHD, have been reported.[12,22,23] First, acetaminophen may alter the intrauterine immune system and increase the predisposition for oxidative stress and inflammation, which disrupts the normal development of microglia and their interaction with neurons.[12] Gervin et al[23] analyzed DNA methylation, which plays a major role in neurogenesis and gliogenesis,[24] in umbilical cord blood samples and identified significant differences in DNA methylation associated with prenatal exposure to acetaminophen between children with ADHD and controls. The human immune system is triggered and oxidative-stress–related gene responses occur even after exposure to a therapeutic dose of acetaminophen.[25] Exposure to acetaminophen in the fetal period produced major changes in serotonergic and dopaminergic neurotransmission in the prefrontal cortex and striatum, resulting in cognitive dysfunction and deficits in spatial working memory and motor performance in rat models.[26,27] The complex interactions between the immune system and neurotransmitters after prenatal exposure to acetaminophen and their role in ADHD risk in offspring require further investigation. Second, endocannabinoid system dysregulation is another possible mechanism for the association between prenatal acetaminophen use and ADHD risk in offspring.[12] The cannabinoid 1 receptor (CB1R) is crucial for neuron differentiation, neural migration, and the establishment of neuronal connectivity, and interference with its activity during critical times such as the first and second trimesters is suggested to adversely affect brain development.[12] Schultz et al[28] demonstrated a detrimental effect of the acetaminophen metabolite *p*-aminophenol on the viability of in vitro developing cortical neurons, which could act through CB1Rs. Furthermore, the cannabinoid 2 receptor (CB2R) is abundant in immune and microglial cells and primarily plays a role in immune system regulation.[12] Whether a possible association between acetaminophen-triggered maternal immune activation and *p*-aminophenol–related CB2R dysregulation increases the offspring's ADHD risk requires further investigation.

Finally, our study supported the significant association between maternal mental health disorders, especially major depression and bipolar disorder, and the risk of ADHD in offspring, in agreement with other studies of the mother-child coaggregation of major affective disorders and ADHD.[29,30] Maternal mental health disorders have been considered a major confounding factor of the relationship between maternal acetaminophen use and the offspring's ADHD risk.[10] Both our findings and those reported by Stergiakouli et al[10] supported that prenatal exposure to acetaminophen is an independent risk factor for the subsequent risk of ADHD in offspring, regardless of the presence of maternal mental health disorders.

Several study limitations should be mentioned. First, the prevalence of ADHD may be underestimated in the Taiwan Longitudinal Health Insurance Database because only those who sought medical consultation and help would be identified in our study. However, the diagnosis of ADHD was made by board-certified psychiatrists, thereby improving the diagnostic validity. In addition, because some subjects in the control group may actually have had ADHD that was not identified, the misclassification may exist, which may bias or even weaken the study findings. Second, acetaminophen is generally available without prescription in Taiwan. Pregnant women who purchased acetaminophen at their own expense cannot be identified in this study, which may partially explain the finding of no association

between cumulative doses of prenatal acetaminophen use and the offspring's ADHD risk. However, because the Taiwan National Health Insurance is low-cost and easily accessible, pregnant women are more likely to consult their physicians for the appropriate use of any drug. Furthermore, the under- or overestimation of acetaminophen use may exist because pregnant women may not comply with the medication doses that physicians prescribed, which may bias the results. Third, whether prenatal exposure to specific medications and substances may increase ADHD risk in offspring remained unclear. In Taiwan, pregnant women are more likely to avoid any medication and substance during the pregnancy period.[31,32] In our study, we focused on the association between acetaminophen exposure in pregnancy and ADHD risk in offspring. It was difficult to remove the bias confounded by every medication and substance in the current study. Face-to-face interviews would be necessary to further assess the complexity of medication and substance exposure during pregnancy with ADHD risk in offspring. Fourth, a cohort study would be necessary in the future to further investigate whether the maternal use of acetaminophen may have any effect on the age at which ADHD is diagnosed in offspring. Fifth, although we enrolled a large sample size of 950 study pairs and 3,800 control pairs, none of the mothers was diagnosed with ADHD and substance use disorders in our study, which may be underestimated based on the registered database study, because mothers who had ADHD and substance use problems but did not seek medical help and consultation would not be diagnosed with ADHD and substance use disorders and would not be identified in the National Health Insurance Research Database. Further studies may be required to investigate the potential roles of maternal ADHD and substance use disorders in the association of prenatal exposure to acetaminophen and ADHD risk in offspring.

In conclusion, prenatal exposure to acetaminophen, especially in the first and second trimesters, is associated with an increased risk of ADHD in offspring in the Taiwanese population, regardless of gestational infections or maternal mental health disorders. The US Food and Drug Administration identified and announced in 2015[33] the risk of ADHD in children of mothers who took acetaminophen in either over-the-counter or prescription products at any time during pregnancy. On the basis of our study results, clinicians and pregnant women are reminded that the prescription and use of acetaminophen must be carefully evaluated during pregnancy, especially in the first and second trimesters. Additional studies are necessary to clarify the definite pathophysiology of prenatal acetaminophen exposure and the offspring's ADHD risk.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.