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Prenatal exposure to acetaminophen increases the risk of atopic dermatitis in children: A nationwide nested case-control study in Taiwan

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51 This study was approved by the Institutional Review Board of Taipei Veterans General Hospital
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53

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66 **KEY MESSAGE**

67 Acetaminophen use has been identified as a risk factor for atopic diseases. However, the
68 association between prenatal acetaminophen exposure and atopic dermatitis in offspring remains
69 unclear. To investigate the association, we performed a nationwide nested case-control study in
70 Taiwan. In this study, prenatal exposure to acetaminophen is associated with an increased
71 incidence of offspring atopic dermatitis in a dose-response manner. Further research is needed to
72 elucidate the underlying mechanism.

74 **ABSTRACT**

75 **Background:** Acetaminophen (APAP) has been associated with the development of atopic
76 diseases. However, little is known about the relationship between prenatal APAP exposure and
77 atopic dermatitis (AD) in offspring. **Objective:** To investigate the association between prenatal
78 APAP exposure and AD risk in offspring. **Methods:** In this study, 2029 study pairs (AD-affected
79 children and their mothers) and 5,058 control pairs were identified between 1998 and 2008 from
80 the Taiwan Longitudinal Health Insurance Database. Maternal APAP exposure during pregnancy
81 were assessed. **Results:** After adjustment for potential confounders, there was a significant
82 association between risk of offspring AD and exposure to acetaminophen in the first trimester (OR
83 1.16; 95% CI 1.05-1.28), the second trimester (OR 1.14; 95% CI 1.03-1.27), both first and second
84 trimesters (OR 1.30; 95% CI 1.13-1.51), both first and third trimester (OR 1.20; 95% CI 1.04-
85 1.39), any trimester (OR 1.12; 95% CI 1.00-1.26), and all three trimesters (OR 1.32; 95% CI 1.08-
86 1.62) in a dose-response manner. **Conclusions:** Prenatal exposure to acetaminophen was
87 associated with an increased incidence of offspring AD.

88
89 **Keywords:** acetaminophen; atopic dermatitis; children; cohort study; epidemiology; prenatal;

1 Introduction

Atopic dermatitis (AD) is a chronically relapsing skin disease, affecting up to 20% of children worldwide.¹⁻³ The prevalence of AD has increased significantly over the past decades in developed countries.⁴ AD usually begins in early childhood and imposes a significant psychosocial burden on the patient and their family. The affected individuals often develop AD during infancy and subsequent allergic rhinitis and asthma in later life, this progression is known as the atopic march.⁵ Although there is no cure for AD, many treatments are effective in controlling the symptoms.^{6,7} While the exact cause of AD remains inconclusive, both genetic susceptibility to barrier dysfunction, immune dysfunction, and environmental factors contribute to the development of AD.^{8,9}

Acetaminophen (APAP) is one of the most widely used medications. APAP is generally well tolerated, even in pregnant woman, when used within the therapeutic range.^{10,11} Recent evidence has indicated that the use of APAP can exacerbate asthma and also increases the likelihood of developing asthma.¹² Increased asthma risk is associated with APAP exposure prenatally¹³⁻¹⁶ and in early and late childhood,^{17,18} adolescence,^{19,20} and adulthood.^{21,22} Additionally, APAP use may be a risk factor for developing other atopic diseases, including AD and allergic rhinitis.²³⁻²⁵ Lipiec *et al.* found a dose-dependent association between APAP use and symptoms of asthma, allergic rhinitis, and skin allergy in the Polish population.²⁶ Despite evidence supporting the link between APAP use and AD, the relationship between prenatal APAP exposure and AD risk is not known. Using the Taiwan's National Health Insurance Research Database with a large sample and a nested-cohort study design, this study aimed to examine the association of maternal exposure to APAP during pregnancy and offspring with AD. We hypothesized that maternal exposure to APAP during pregnancy was associated with an increased incidence of AD in the offspring.

2 Methods

2.1 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. Taiwan's Longitudinal Health Insurance Database is audited and released by the Taiwan National Health Research Institutes for academic research. 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. With each individual's unique personal identification number, family relationships were established by analyzing the birth certificate, insurance, and employment status of the dependent. The method of genealogical reconstruction using recorded family relationships in the NHIRD has been previously described.²⁷⁻³² The codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) are used for disease diagnosis. Taiwan's Longitudinal Health Insurance Database has been used extensively in many epidemiologic studies in Taiwan.³³⁻³⁷ The present study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2018-07-016AC).

2.2 Inclusion Criteria for The Mother-Child Pairs with or without AD

Children born between January 1, 1998, and December 31, 2008, who received diagnoses of AD (ICD-9-CM code: 691.8) by board-certified dermatologist at least twice were identified and linked with their mothers as the mother-child-with-AD (study) pairs in the current study. Diagnoses of AD were received from the childbirth to the study end date (December 31, 2011).

The mother-child-without-AD (control) pairs were randomly (1:2) selected after matching for the mothers' age, children's sex and age, pregnant age of mothers, income, and urbanization level.

APAP use and gestational infections were assessed in the first, second, and third trimesters.

Gestational infections included respiratory, urinary tract, gastrointestinal tract, and sexually transmitted infections. Cumulative doses of APAP exposure were calculated in each trimester.

Maternal atopic diseases (including asthma, atopic dermatitis, and allergic rhinitis), comorbid prenatal conditions (including preterm or low birth weight, birth trauma, and intrauterine hypoxia/birth asphyxia), maternal smoking and maternal mental disorder during the pregnancy were also assessed as the confounding factors. Level of urbanization (levels 1 to 5, with level 1 as the most urbanized region and level 5 as the least) was used to represent socioeconomic status.

The study design is shown in **Figure 1**.

2.3 Statistical Analysis

For between-group comparisons, the F-test was used for continuous variables and Pearson's χ^2 test was used for between-group comparisons, where appropriate. Logistic regression analysis was performed to investigate the relationship between the exposure to APAP in each trimester and the risk of AD. Demographic characteristics (age, sex, income, level of urbanization), gestational infections, and comorbid perinatal conditions were adjusted in model 1. Model 2 additionally included the presence of maternal atopic disorders in the adjusted covariates. Maternal smoking and maternal mental disorder during the pregnancy were additionally adjusted in the model 3. Additionally, logistic regression models with adjustment of demographic characteristics, gestational infections, comorbid perinatal conditions, maternal atopic disorders, maternal smoking and maternal mental disorder during the pregnancy were performed to examine the association between the cumulative doses (g) of APAP exposure and the risk of AD in

offspring. To assess the robustness of our results, we performed sensitivity analysis excluding pairs with gestational infections maternal atopic disorders, maternal smoking and maternal mantle disorder during the pregnancy. A two-tailed P value <0.05 was considered statistically significant. Data processing and 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).

3 Results

Overall, 2,529 study pairs (mothers and AD-affected children) and 5,058 control pairs (mothers–children pairs without AD) were identified in our study (**Table 1**). Mothers with AD-affected children had a higher prevalence of APAP exposure in the first trimester (42.9% vs 38.2%, $P < 0.001$), second trimester (39.2% vs 34.9%, $P < 0.001$), and any trimester (71.9% vs 67.9%, $P < 0.001$). Based on the APAP exposure in any trimester, the number-needed-to-treat was 25. In addition, based on the APAP exposure in the first, second, and third trimesters, the numbers-needed-to-treat were 21, 23, and 50, respectively. We also observed higher cumulative doses of APAP exposure (mg) in the first (4327.14 vs 3283.88, $P < 0.001$), second (3856.28 vs 3164.63, $P < 0.001$), and third (6651.92 vs 5820.87, $P < 0.001$) trimesters, among mothers of AD-affected children than those among mothers of children without AD. In addition, we found no association of the time (first, second, or third trimester) exposed to APAP with the age of AD diagnosis (all $p > 0.1$). Mothers of AD-affected children had higher prevalence of gestational infections in the first (31.3% vs 26.2%, $P < 0.001$), second, (31.4% vs 27.4%, $P < 0.001$), third (31.4% vs 29.1%, $P = 0.038$) trimesters, and in any trimester (57.4% vs 52.2%, $P < 0.001$), and a higher prevalence of maternal atopic diseases than mothers of children without AD.

The model 1 showed that APAP exposure in the first trimester (OR 1.17; 95% CI 1.05-1.29) and in the second trimester (OR 1.15; 95% CI 1.04-1.28) were related to the increased likelihood of offspring AD (**Table 2**). The dose-dependent analyses showed that the cumulative doses (per gram) of APAP exposure in the first (OR 1.02, 95% CI 1.01–1.02) and second (OR 1.01, 95% CI 1.00–1.02) trimesters were associated with the increased likelihood of AD in offspring. Gestational infections in the first trimester (OR 1.24; 95% CI 1.11–1.38) or second trimester (OR 1.15; 95% CI 1.03–1.29) or in any trimester (OR 1.17; 95% CI 1.05–1.31) were associated with an increased risk of AD in offspring. Furthermore, in the model 2, maternal asthma (OR 1.64; 95% CI 1.20–2.25) and allergic rhinitis (OR 1.24; 95% CI 1.03–1.49) were significantly related to the increased risk of AD in offspring. In the model 3, maternal mental disorder during the pregnancy (OR 1.90; 95% CI 1.17-3.10) was related to the offspring AD risk (**Table 2**).

After excluding pairs with gestational infections, maternal atopic disorders, maternal smoking and maternal mental disorder during the pregnancy, sensitivity analyses found that risk of AD in offspring was positively associated with APAP exposure in the first trimester (OR 1.23; 95% CI 1.04-1.46), second trimester (OR 1.24; 95% CI 1.03-1.49), both first and second trimesters (OR 1.50; 95% CI 1.16-1.94), both second and third trimesters (OR: 1.31; 95% CI 1.03-1.66), both first and third trimesters (OR 1.36; 95% CI 1.08-1.71), any trimester (OR 1.21; 95% CI 1.04-1.42), or all trimesters (OR 1.59; 95% CI 1.15-2.19) (**Table 3**).

4 Discussion

Our findings supported the hypothesis that prenatal exposure to APAP, especially in the first trimester or in the second trimester, both first and second trimesters, both first and third trimesters, any trimester, or in all trimesters, was associated with an increased risk of AD in offspring. These

associations remained significant after adjusting for or excluding gestational infections and maternal atopic disorders in the regression model. Furthermore, our study identified a mechanism by which APAP might result in dose-dependent relationship between prenatal APAP exposure and the AD risk in offspring; the maternal cumulative doses of APAP in the first and second trimesters were related to AD risk in offspring. To our knowledge, this is the first study investigating the association between prenatal APAP exposure and the risk of AD in offspring.

Embryonic skin development occurs mainly during the first trimester and almost completes by the second trimester, which might partially explain the association of prenatal APAP exposure in the first or second trimester, but not in the third trimester, with AD risk in offspring.³⁸ Although the exact pathogenesis linking prenatal exposure to APAP and the risk of AD in offspring remains elusive, some biological mechanisms may account for this association. Fetal immunological development is highly vulnerable to challenges, including psychological stress, infections, and metabolic stress.^{39,40} APAP crosses the placenta and can be traced in the infant's urine after prenatal exposure.⁴¹ APAP may trigger the intrauterine immune system, arouse oxidative stress-related gene responses, and increase the predisposition to oxidative stress and inflammation.^{42,43} In vitro and animal studies have revealed that N-acetyl-p-benzoquinone imine (NAPQI), one of the metabolites of APAP, leads to the depletion of glutathione, which acts as an important antioxidant in the skin⁴⁴. The depletion of glutathione resulted in reduced antioxidant capacity, inhibits T-helper 1-associated cytokine production, and favors T-helper 2 allergic immune responses.^{45,46} An open-labeled randomized control trial of prophylactic acetaminophen given at the time of vaccination illustrates that acetaminophen in routine antipyretic doses is capable of modulating immune responses.⁴⁷ Alternatively, APAP might influence COX-2 activity and production of prostaglandins E2,⁴⁸ which also in turn favor a T-helper 2 immune dominance.

Besides, in vivo research studies on humans suggest that oxidative stress has a significant role in atopic dermatitis, the APAP induced decreased antioxidant capacity may lead susceptibility to oxidative stress and development of atopic dermatitis⁴⁹. Thiele *et al.* have found evidence in mice supporting that prenatal APAP exposure affects maternal immune and endocrine adaptation to pregnancy, induces placental damage, and impairs fetal maturation and T-cell development.⁵⁰ The enhanced T-helper 2 allergic immune responses, susceptibility to oxidative stress, impaired fetal maturation, and T-cell development might subsequently increase the risk of AD. Studies have found glutathione-S-transferase gene polymorphisms to be significant associated with atopic dermatitis risks, which also suggest the important role of glutathione depletion in atopic dermatitis.⁵¹

With these possible biological mechanisms in mind, several cross-sectional and longitudinal epidemiological studies also support the association between the AD risks and APAP exposure in childhood and adult.^{23-25,52} One cohort study revealed APAP exposure during the 1st year of life is associated with subsequent allergic disease (atopic dermatitis, asthma, and allergic rhinitis).²³ From the multicenter, multicountry, cross-sectional, and Phase 3 study of the International Study of Allergy and Asthma in Childhood (ISAAC), in two age groups of 6- to 7-year olds and 13- to 14-year olds, APAP use represented an important risk factor for the development of asthma as well as for atopic dermatitis, no matter we analysis single country data, such as Poland²⁶, Mexico⁵³, Spanish, and Canada⁵⁴, or international datum together⁵⁵. To our knowledge, only one population-based Canadian birth cohort study investigated prenatal APAP exposure and atopy and allergic diseases at 1 year of age, which showed that prenatal APAP exposure is associated with decreased atopy.⁵⁶ The reason why it showed discrepancy result might be due to collecting questionnaires only at 1 year of age, too short to develop atopic dermatitis. Further randomized clinical trials,

which are not ethically feasible in this scenario, are needed to entangle whether the use of acetaminophen prenatally can lead to the development of atopic dermatitis in later childhood.

However, this association was confounded: (i) by indication (increased acute bacterial infection or fever that led to increases in both atopic dermatitis and APAP exposure); or (ii) by reverse causation (atopic dermatitis itself caused scratched wounds or pain resulting in increased APAP exposure).

Compared with previous studies, the strengths of our study include, first, the ability to examine the temporal relationship between atopic dermatitis and maternal APAP use in 2 case and control cohorts derived from the NHRID, which covers 98% of Taiwan's total population. As a result, this large sample size and retrospective design allowed us to assess the temporal relationship between children and maternal APAP exposure without ethically infeasibility. Second, to account for potential confounding factors, we performed further analyses by adjusting matching many factors, including gestational infections and maternal atopic disorders. Third, this study is one of few studies to simultaneously examine the temporal effect of maternal APAP exposure on the development of atopic dermatitis in an Asian population.

This study had several limitations. First, the prevalence of AD may be underestimated in the Taiwan Longitudinal Health Insurance Database because only those who sought medical consultation and help were identified in our study. Second, as with all studies based on this registry data, the possibility of misclassification of diagnoses may exist. However, the diagnosis of AD was made by board-certified dermatologists at least twice, therefore yielding an improved diagnostic validity and making misclassification bias unlikely. Third, APAP is generally available without prescription in Taiwan. Pregnant women who purchased APAP at their own expense

could not be identified in this study. These potential confounding factors might have occurred in both AD and non-AD groups, which might lead to a bias in the association between AD risk and prenatal acetaminophen use. In addition, the prevalence of APAP exposure during the pregnancy was about seventy percent in our study, which was compatible with the rate in the United State.⁴² The exact causes, such as fever or pain, of APAP exposure during the pregnancy would need further investigation. Fourth, a family association was identified according to the data on the insured patients and their dependents in the NHIRD. In Taiwan, only blood relatives or spouses qualify as the dependents of the insured patients. Therefore, children who were not dependent on the insurance of mothers were not identified as the mother-child pairs, which may be a selection bias in current study. Finally, the NHIRD lacks information on genetic, contact history, environmental factors, disease severity, diet, nutrition supplement (i.e., omega-3 long-chain polyunsaturated fatty acids, probiotics, vitamin D), farm living, climate, body mass index, lifestyle, bacterial endotoxin, microbiota in the gut or skin, or family history, which were possible uncontrolled confounders.

In conclusion, our study revealed a dose-response association between maternal prenatal APAP exposure, particularly in the first trimester, and AD risk in offspring. Further prospective studies are required to confirm our findings. Based on our results, physicians should be aware of this potential association when considering using APAP during pregnancy, especially in the first trimester, and should warn pregnant women of this possible association.

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Author Contributions

Cheng-Yuan Li: Formal analysis (Lead), Writing-original draft (Lead), Writing-review & editing (Equal); **Ying-Xiu Dai:** Conceptualization (Equal), Writing-original draft (Equal), Writing-review & editing (Equal); **Yun-Ting Chang:** Methodology (Equal), Software (Equal); **Ya-Mei Bai:** Methodology (Equal), Supervision (Equal); **Shin-Jen Tsai:** Methodology (Supporting), Writing-review & editing (Supporting); **Tzeng-Ji Chen:** Software (Equal), Writing-review & editing (Supporting); **Mu-Hong Chen:** Conceptualization (Lead), Formal analysis (Equal), Methodology (Lead), Writing-review & editing (Supporting)

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Table 1. Demographic data and clinical characteristics of mothers of children with and without AD

	Mothers of children with AD (n=2529)	Mothers of children without AD (n=5058)	p-value
Age of mother (years, SD)	38.88 (4.98)	38.84 (5.00)	0.743
Pregnant age of mother (years, SD)	28.93 (4.34)	28.78 (4.43)	0.183
Age of children (years, SD)	9.95 (2.70)	10.05 (2.75)	0.122
Age of AD diagnosis in children (years, SD)	8.07 (2.93)		
Males of children (n, %)	1327 (52.5)	2654 (52.5)	1.000
Acetaminophen exposure (n, %)			
First trimester	1086 (42.9)	1933 (38.2)	<0.001
Second trimester	991 (39.2)	1765 (34.9)	<0.001
Third trimester	1492 (59.0)	2883 (57.0)	0.099
Any trimester	1818 (71.9)	3434 (67.9)	<0.001
Cumulative doses of acetaminophen exposure (mg)			
First trimester	4327.14 (9079.23)	3283.88 (6037.95)	<0.001
Second trimester	3856.28 (7500.41)	3164.63 (6369.41)	<0.001
Third trimester	6651.92 (9074.41)	5820.87 (8050.20)	<0.001
Gestational infections (n, %)			
First trimester	792 (31.3)	1323 (26.2)	<0.001
Second trimester	793 (31.4)	1387 (27.4)	<0.001
Third trimester	795 (31.4)	1472 (29.1)	0.038
Any trimester	1451 (57.4)	2641 (52.2)	<0.001
Comorbid perinatal conditions (n, %)			
Preterm or low birth weight	80 (3.2)	125 (2.5)	0.084
Birth trauma	11 (0.4)	18 (0.4)	0.693
Intrauterine hypoxia/birth asphyxia	17 (0.7)	24 (0.5)	0.319

Maternal atopic disorders (n, %)			
Asthma	80 (3.2)	88 (1.7)	<0.001
AD	40 (1.6)	51 (1.0)	0.034
Allergic rhinitis	222 (8.8)	334 (6.6)	0.001
History of maternal smoking (n, %)	27 (1.1)	52 (1.0)	0.905
Maternal mental disorder during the pregnancy (n, %)	33 (1.3)	33 (0.7)	0.006
Level of urbanization (n, %)			1.000
1 (most urbanized)	657 (26.0)	1314 (26.0)	
2	900 (35.6)	1800 (35.6)	
3	264 (14.4)	728 (14.4)	
4	247 (9.8)	494 (9.8)	
5 (most rural)	361 (14.3)	722 (14.3)	
Income-related insured amount			1.000
≤ 15,840 NTD/month	423 (16.7)	846 (16.7)	
15,841~25,000NTD/month	1169 (46.2)	2338 (46.2)	
≥ 25,001NTD/month	937 (37.1)	1874 (37.1)	

Abbreviations: AD, atopic dermatitis; SD, standard deviation; NTD, New Taiwan Dollar.

Table 2. Logistical regression of acetaminophen exposure and AD risk

	Model 1 ^a	Model 2 ^b	Model 2 ^c
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Acetaminophen exposure			
Any trimester	1.14 (1.01-1.27)	1.13 (1.01-1.27)	1.12 (1.00-1.26)
First trimester	1.17 (1.05-1.29)	1.16 (1.05-1.29)	1.16 (1.05-1.28)
Second trimester	1.15 (1.04-1.28)	1.15 (1.03-1.27)	1.14 (1.03-1.27)
Third trimester	1.05 (0.95-1.26)	1.04 (0.95-1.15)	1.04 (0.94-1.15)
Gestational infections			
Any trimester	1.17 (1.05-1.31)	1.16 (1.04-1.30)	1.16 (1.04-1.29)
First trimester	1.24 (1.11-1.38)	1.23 (1.09-1.37)	1.20 (1.07-1.34)
Second trimester	1.15 (1.03-1.29)	1.14 (1.02-1.28)	1.11 (0.99-1.24)
Third trimester	1.06 (0.95-1.18)	1.05 (0.95-1.17)	1.01 (0.90-1.13)
Maternal atopic disorders			
Asthma		1.64 (1.20-2.25)	1.64 (1.20-2.25)
AD		1.43 (0.93-2.19)	1.43 (0.94-2.19)
Allergic rhinitis		1.24 (1.03-1.49)	1.24 (1.03-1.50)
Maternal smoking			1.00 (0.62-1.60)
Maternal mental disorder during the pregnancy			1.90 (1.17-3.10)

Abbreviations: AD, atopic dermatitis; OR, odds ratio; CI, confidence interval.

^aadjusting for demographic data, gestational infections and comorbid perinatal conditions.

^badjusting for demographic data, gestational infections, maternal atopic disorders and comorbid perinatal conditions.

^cadjusting for demographic data, gestational infections, maternal atopic disorders, comorbid perinatal conditions, maternal smoking and maternal mental disorder during the pregnancy.

Bold type indicated statistical significance.

Table 3. Sensitivity analysis of acetaminophen exposure and AD risk

	Total ^a	Excluding gestational infections, maternal atopic disorders, maternal smoking and maternal mental disorder during the pregnancy ^b
	OR (95% CI)	OR (95% CI)
Acetaminophen exposure		
Any trimester	1.12 (1.00-1.26)	1.21 (1.04-1.42)
First trimester	1.16 (1.05-1.28)	1.23 (1.04-1.46)
Second trimester	1.14 (1.03-1.27)	1.24 (1.03-1.49)
Third trimester	1.04 (0.94-1.15)	1.11 (0.95-1.29)
Both first and second trimesters	1.30 (1.13-1.51)	1.50 (1.16-1.94)
Both second and third trimesters	1.13 (0.98-1.31)	1.31 (1.03-1.66)
Both first and third trimesters	1.20 (1.04-1.39)	1.36 (1.08-1.71)
All three trimesters	1.32 (1.08-1.62)	1.59 (1.15-2.19)

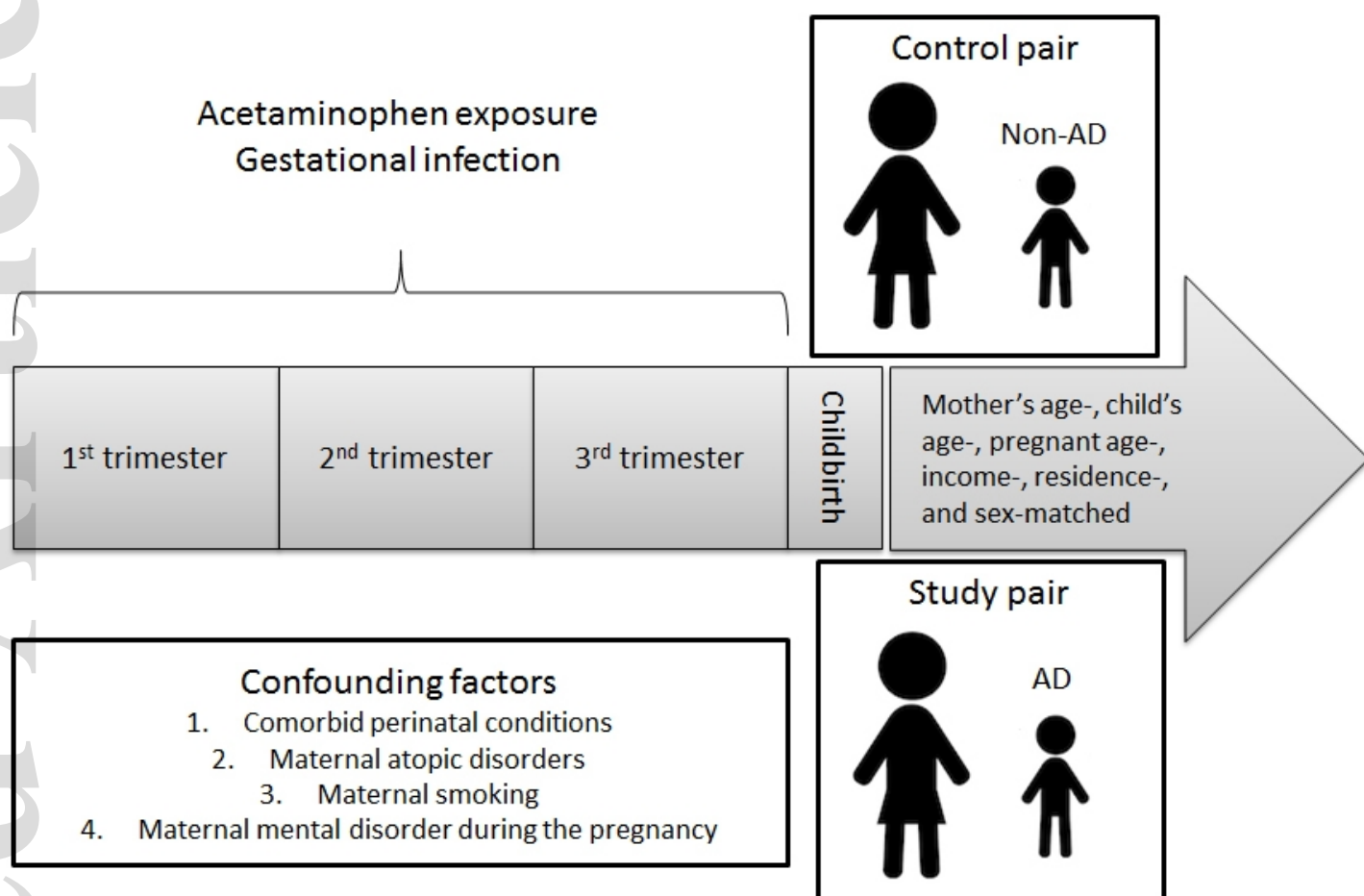
Abbreviations: AD, atopic dermatitis; OR, odds ratio; CI, confidence interval.

Bold type indicated statistical significance.

^aadjusting for demographic data, gestational infections, maternal atopic disorders, comorbid perinatal conditions, maternal smoking and maternal mental disorder during the pregnancy.

^badjusting for demographic data and comorbid perinatal conditions.

Figure 1. Study design illustration



Abbreviations: AD, atopic dermatitis.