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The Effect of Intrauterine Exposure of Antibiotics on The Risk of Atopic Dermatitis in Asian Children: A Systematic Review

rosalia soraya husna
universitas muhammadiyah malang, Indonesia
Email : rosaliacaca@gmail.com
Correspondence: rosaliacaca@gmail.com

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ABSTRACT
Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease with rising prevalence among Asian children, particularly as urbanization and environmental changes accelerate. While both genetic predisposition and environmental exposures are recognized contributors to AD pathogenesis, the influence of intrauterine antibiotic exposure remains insufficiently investigated, especially in Asian populations. This systematic review explores the association between maternal antibiotic use during pregnancy and the risk of AD in offspring, aiming to clarify a modifiable risk factor for this multifactorial condition. Following *PRISMA 2020* guidelines, a comprehensive literature search was performed using *PubMed* and *Cochrane Library*, targeting English-language studies (2000–2025) involving Asian cohorts. Six prospective cohort studies from China, Japan, South Korea, and Taiwan (n = 1,073,245 mother-child pairs) were included. Methods for determining antibiotic exposure varied, including maternal urine analysis, parent-reported data, and medical records. Results were inconsistent: two studies found a statistically significant increase in AD risk with prenatal antibiotic exposure (one reported a greater than threefold increase), while others found no association. This heterogeneity may reflect differences in genetic susceptibility, timing of exposure, or mechanisms related to microbiota disruption. The evidence suggests a possible but inconclusive link between prenatal antibiotics and AD, highlighting the need for standardized research methodologies and further investigation. Clinically, these findings underscore the importance of cautious antibiotic prescribing during pregnancy and support the development of targeted interventions to reduce AD risk in high-risk populations.

Introduction

Atopic dermatitis (*AD*) is a prevalent inflammatory skin condition marked by recurrent pruritus in pediatric patients (Frazier & Bhardwaj, 2020). AD is a chronic, pruritic inflammatory skin disorder that is rising in prevalence globally. The characteristic clinical manifestations of AD

include *xerosis*, *erythema*, papules, and exudation (Sroka-Tomaszewska & Trzeciak, 2021). Dermal damage and pruritus impact the physical well-being, emotional state, and sleep patterns of children, diminishing their quality of life (Torres et al., 2019). Furthermore, AD elevates a child's susceptibility to attention deficit hyperactivity disorder (*ADHD*) and autism spectrum disorder (*ASD*) (Schuler et al., 2023). A significant number of patients with AD subsequently develop asthma and/or allergic rhinitis later in life, a phenomenon known as the *atopic march*; asthma can result in considerable morbidity and potential fatality. The pathophysiology of AD is intricate, involving genetic factors, epidermal dysfunction, immunological disorders, lifestyle choices, climate, air pollution, reduced diversity of skin and intestinal bacteria, and psychological influences (Ramírez-Marín & Silverberg, 2022).

Although AD was formerly perceived as predominantly affecting children, adult-onset AD is increasingly recognized as a prevalent condition. AD prevalence varies across countries and ethnicities, and the demographics of AD continue to evolve. The epidemiology of AD in Asian communities has significantly changed in recent years. Globally, 15%–30% of children are impacted by AD, a prevalent chronic dermatological condition (Weidinger & Novak, 2016). AD imposes significant economic, psychological, and social burdens on children and their families, with insomnia resulting from pruritus being a critical issue for both children and their relatives (Farrell & Westlund, 2018). Significantly, the frequency of AD in Asian populations appears to be rising, potentially attributable to rapid urbanization in many large metropolitan regions; for instance, the urban population in China escalated from 11.8% in 1950 to 49.2% by 2010 (Avena-Woods, 2017). The current epidemiology of AD among various Asian cultures is ambiguous; nonetheless, an expanding body of information indicates that this condition is becoming increasingly frequent in many Asian nations with changing demographics. Challenges in data interpretation likely arise from discrepancies in research design, patients' understanding of the illness, and a complex interaction between a changing industrialized environment and disease patterns.

The incidence of AD rose in regions of Africa, East Asia, Western Europe, and Northern Europe from 1990 to 2010 (Bylund et al., 2020). A significant prevalence of AD has been documented in Sweden, Japan, New Zealand, the United Kingdom, Portugal, and Thailand (Flohr, 2011; Gu et al., 2004; Mallol et al., 2013). Research indicates that the incidence of AD in China is increasing. In 2004, a study involving 49,241 children from 10 provinces and cities revealed a prevalence rate of 2.8%.[13] A follow-up study in 2016 with 13,989 children across 12 provinces and cities in China indicated a prevalence rate of 12.9% (Wang et al., 2022). With ongoing economic development and urbanization, the incidence of AD in children may continue to rise, influenced by genetic and environmental factors, though the precise cause and pathophysiology remain unclear. Consequently, ongoing epidemiological research on AD in Asian populations is essential.

Over the past decade, clinicians have focused on finding modifiable risk factors for AD to decrease its prevalence. Maternal exposure to antibiotics has been associated with many allergic disorders (Cait et al., 2022; Huang et al., 2020; Zhong et al., 2021). Women's vulnerability to

infections escalates during pregnancy, with over 40% of women receiving antibiotics prior to delivery. Recent meta-analyses indicate that maternal antibiotic exposure may elevate the incidence of asthma and food allergies in children. Multiple studies suggest that antibiotic exposure modifies the maternal microbiome, thereby affecting newborn immunology and increasing the incidence of allergies (Al Alam et al., 2020; Francino, 2016; Prescott et al., 2021). However, no systematic review has synthesized the currently published data regarding the correlation between maternal antibiotic exposure and the risk of AD in offspring specifically in Asian populations, considering that AD is a multifactorial disease highly affected by environmental and genetic factors. Therefore, this paper will discuss the effect of maternal antibiotic exposure on the risk of AD in offspring in Asian populations.

Previous research by Cait et al. (2022) and Huang et al. (2020) has provided important grounding regarding the relationship between prenatal antibiotic exposure and atopic diseases. Cait et al. (2022) conducted a comprehensive meta-analysis of the risk of asthma and allergies due to antibiotic exposure, but this study was limited to Western populations and did not specifically address AD in Asian children. In addition, the study did not explore potential mechanisms such as disruption of the gut microbiome that might link antibiotics and AD. Meanwhile, Huang et al. (2020) focused on the relationship between prenatal antibiotics and eczema in infants, but the study only included data up to 2018 and did not consider Asia-specific factors, such as the impact of rapid urbanization or the region's unique genetic diversity.

This research aims to fill several important gaps. First, with a particular focus on the Asian population, the study highlights a unique epidemiological context, including the increased prevalence of AD associated with urbanization and environmental change, as shown in the Tai et al. (2024) study in Taiwan. Second, the study deepens our understanding of underlying mechanisms, specifically the role of gut microbiome dysbiosis due to antibiotic exposure, which was previously overlooked in the studies of Cait et al. (2022) and Huang et al. (2020). References such as Lee et al. (2014) and Francino (2016) reinforce this argument by showing how antibiotics can disrupt the balance of the microbiome and affect immune system development. Third, this study updates the current evidence by including large-scale prospective studies up to 2025, such as the study by Okoshi et al. (2023), thus providing a more up-to-date picture than the study by Huang et al. (2020).

The aim of this study is to consolidate the current evidence on the impact of intrauterine antibiotic exposure on the risk of AD in Asian children, taking into account the complex interactions between genetic, environmental, and microbiome factors. The results are expected to provide a scientific basis for clinical recommendations on prudent antibiotic use during pregnancy. In addition, these findings may encourage further research on microbiome-based interventions, such as the use of probiotics, to reduce the risk of AD in vulnerable populations. Thus, this research contributes to a deeper scientific understanding and has practical implications for public health.

Materials and Methods

The 2020 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were adhered to in the execution and documentation of this systematic review. A comprehensive literature search was conducted utilizing PubMed and Cochrane Library. The predetermined search string utilized was " (Antibiotic OR Antibiotics) AND (Mother OR Maternal OR Pregnancy OR Prenatal) AND "Atopic Dermatitis" During this stage, articles with relevant titles and abstracts were selected for further qualitative analysis and full-text examination. The studies included in this review were required to be published in English, released between 2000 and 2025, and have accessible full texts. The details of the research search strategy are illustrated in Figure 1.

The researchers include studies involving healthy mothers with no prior history of allergy and report the offspring's atopic dermatitis diagnosis. The following exclusion criteria were applied in order to ensure the reliability and authenticity of the findings: 1) studies that withheld important details; 2) publications that are not accessible in full text.

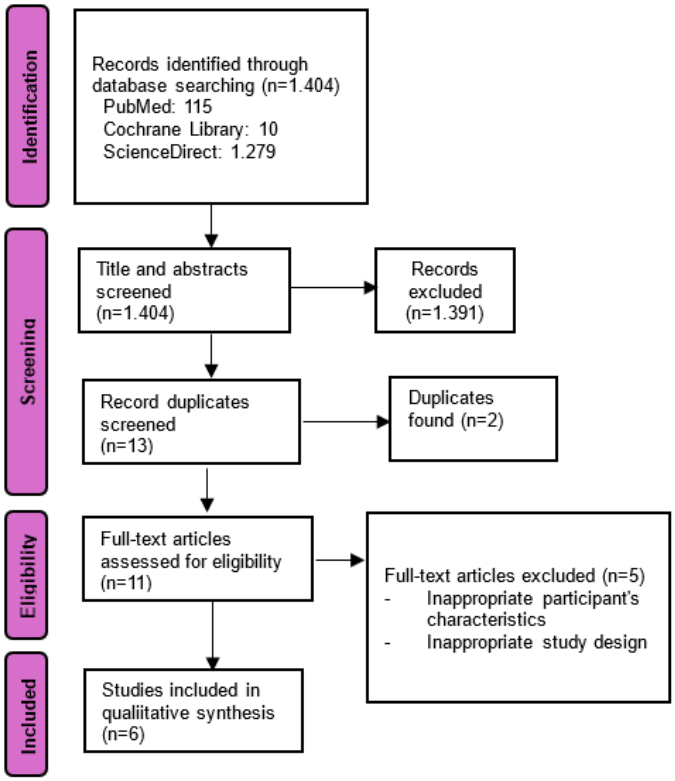

Figure 1. Diagram flow of literature search strategy for this systematic review

Results and Discussions

Table 1. Characteristics and results of the included studies.

Author, year	Location	Study design	Sample size	Measurement of antibiotic exposure	Timing of antibiotic exposure	Risk of atopic dermatitis

Geng, (2021)	China	Prospective cohort	2453	Maternal urine samples	All trimesters	Maternal exposure to antibiotics in different trimesters was associated with an increased risk of atopic dermatitis in 4-year-old children
Sasaki, (2020)	Japan	Prospective cohort	70408	Parent-reported	All trimesters	No association was found between prenatal antibiotic exposure and AD at age 1 year.
Gao, (2019)	China	Prospective cohort	976	Parent-reported	All trimesters	Prenatal exposure of antibiotics significantly increased the risk of atopic dermatitis by >3 times
Lee, (2014)	South Korea	Prospective cohort	412	Medical records	All trimesters	Exposure to prenatal antibiotics may impact the gut flora, potentially influencing the likelihood of atopic dermatitis in babies. These interactions may be influenced by genetic predisposition.
Tai, (2024)	Taiwan	Prospective cohort	900584	Medical records	All trimesters	Exposure to prenatal antibiotics may elevate the risk of juvenile atopic disorders in a dose-dependent fashion.
Okoshi, (2023)	Japan	Prospective cohort	98412	Interview during recruitments + Medical records	All trimesters	Antibiotics exposure during pregnancy was not associated with an increased risk of atopic dermatitis in their offspring

The results part of this systematic review offers a thorough examination of the features and conclusions of the included research, as outlined in Table 1. The research included many sites around Asia, specifically China, Japan, South Korea, and Taiwan, and was structured as prospective cohort studies. The total sample sizes of 1.073.245 mother-children pairs exhibited considerable variation, with the smallest research encompassing 412 individuals and the largest including 900,584 people. This variance in sample size underscores the broad scope and scale of research endeavors in this field.

The studies utilized several approaches to assess antibiotic exposure. For example, Geng (2021) employed maternal urine samples to evaluate antibiotic exposure, whereas Sasaki (2020) and Gao (2019) depended on parent-reported data. Lee (2014) and Tai (2024) utilized medical records, whereas Okoshi (2023) integrated interviews conducted during recruiting with medical records. All studies examined antibiotic exposure during all trimesters of pregnancy, guaranteeing a thorough evaluation of prenatal exposure.

The results concerning the risk of atopic dermatitis (AD) differed between the research. Geng (2021) and Gao (2019) both documented an elevated risk of ADlinked to maternal antibiotic exposure, with Gao observing a risk increase exceeding threefold. Lee (2014) proposed that prenatal antibiotic exposure could affect gut microbiota, potentially altering the incidence of atopic dermatitis, with genetic susceptibility being a contributing factor. Tai (2024) discovered that antibiotic exposure may increase the risk of juvenile atopic disorders in a dose-dependent fashion. Sasaki (2020) and Okoshi (2023) identified no significant correlation between prenatal antibiotic exposure and the likelihood of atopic dermatitis in their progeny.

The findings suggest a multifaceted association between maternal antibiotic exposure and the likelihood of atopic dermatitis in offspring. Some studies indicate a notable

correlation, while others do not, underscoring the multifarious characteristics of ADand the possible impact of genetic and environmental variables. These findings highlight the necessity for additional study to elucidate the processes behind these relationships and to uncover potential modifiable risk factors for ADin Asian populations.

Table 1 presents a detailed characteristics and results of the correlation between intrauterine antibiotic exposure and the incidence of atopic dermatitis (AD) in Asian children. This systematic review encompasses research undertaken in several Asian nations, namely China, Japan, South Korea, and Taiwan, all utilizing a prospective cohort design. This design choice is crucial as it facilitates the observation of outcomes throughout time, yielding a more comprehensive understanding of the potential long-term consequences of prenatal antibiotic exposure on the development of AD. The prospective design of these research guarantees that data on antibiotic exposure is gathered prior to the development of Alzheimer's disease, so minimizing recollection bias and augmenting the trustworthiness of the results.

The sample sizes of the studies exhibited considerable variation, from 412 participants in Lee's 2014 study in South Korea to a remarkable 900,584 participants in Tai's 2024 study in Taiwan. The difference in sample size is essential as it might affect the statistical power of the studies and the generalizability of their results. Extensive sample sizes, like those in Tai's and Okoshi's research, generally yield more dependable estimates of the correlation between antibiotic exposure and the likelihood of atopic dermatitis, but necessitating greater resources and time for execution. The variability in sample sizes indicates the differing capacities and resources present in various research environments, which can influence the breadth and profundity of the investigations.

Various approaches were employed to assess antibiotic exposure throughout the research. Geng (2021) in China employed maternal urine samples, which offer an objective assessment of antibiotic exposure. Conversely, Sasaki (2020) in Japan and Gao (2019) in China utilized parent-reported data, which may add recall bias but is frequently more practical in extensive investigations. Lee (2014) and Tai (2024) utilized medical records, providing a dependable data source, whereas Okoshi (2023) integrated interviews conducted during recruitment with medical records, potentially improving the precision of exposure assessment through information cross-verification. The diversity in measurement techniques emphasizes the difficulties in standardizing exposure assessment in epidemiological research and stresses the necessity for meticulous evaluation of potential biases and limitations in result interpretation.

All studies consistently evaluated the timing of antibiotic exposure, studying it during each trimester of pregnancy. This thorough approach is significant as it recognizes that the time of exposure may differentially impact the developmental processes of the fetus, potentially influencing the risk of AD. The continual evaluation of all trimesters guarantees that the research identifies any crucial periods of susceptibility throughout fetal development. This is especially pertinent considering the dynamic development of the fetal immune system,

which may be variably influenced by environmental exposures at different gestational periods.

The results concerning the risk of atopic dermatitis differed between the research. Geng (2021) and Gao (2019) both documented an elevated risk of AD linked to maternal antibiotic exposure, with Gao observing a risk increase exceeding threefold. The findings indicate that antibiotic exposure may interfere with the developing immune system or microbiota of the fetus, perhaps resulting in heightened susceptibility to AD. This supports the concept that changes in the microbiome can influence immune system development and function, a vital area of research in elucidating the genesis of AD. The potential influence of antibiotics on the maternal and fetal microbiota is a credible mechanism that requires additional exploration, since it may elucidate the pathophysiological mechanisms underlying AD.

Sasaki (2020) and Okoshi (2023) identified no significant correlation between prenatal antibiotic exposure and the development of atopic dermatitis (AD). Sasaki's study, encompassing a substantial sample of 70,408 participants, revealed no correlation at the age of 1 year. Okoshi's study, with 98,412 participants, also indicated no heightened risk. These findings suggest that additional factors, such as genetic predisposition or environmental impacts, may have a more substantial impact on the development of AD in these groups. The absence of relationship in these studies may stem from variations in study design, demographic characteristics, or measuring techniques. The lack of a consistent correlation among research underscores the complexity of ADas a multifaceted condition and indicates that the interaction of genetic, environmental, and microbial components may change among various populations.

Lee (2014) and Tai (2024) offer further elucidation on the putative processes connecting antibiotic exposure and AD. Lee's research in South Korea indicates that prenatal antibiotic exposure may affect gut microbiota, potentially influencing the risk of developing atopic dermatitis (AD). This corresponds with the increasing evidence indicating that the gut-skin axis contributes to the pathophysiology of atopic dermatitis (AD). Tai's research in Taiwan indicated that antibiotic exposure could increase the incidence of juvenile atopic disorders in a dose-dependent fashion, reinforcing the notion that the level of exposure may be a significant determinant. Tai's findings indicate that more antibiotic exposure correlates with a more significant effect on the developing immune system, thereby elevating the likelihood of atopic dermatitis (AD).

The clinical ramifications of these discoveries are substantial. If maternal antibiotic exposure is a modifiable risk factor for AD, it could influence antibiotic usage protocols throughout pregnancy. The inconsistency of outcomes among studies underscores the necessity for prudence in formulating treatment recommendations. Additional research is required to elucidate the processes via which antibiotics may affect ADrisk and to determine which populations may be most vulnerable. Comprehending the influence of antibiotics on the progression of ADmay provide significant ramifications for clinical practice and public

health. It may also facilitate the creation of targeted therapies designed to diminish the prevalence of AD in high-risk populations.

When juxtaposing these data with prior studies, it becomes apparent that the correlation between maternal antibiotic exposure and atopic dermatitis is intricate and not yet comprehensively elucidated. Prior studies indicate that antibiotics may modify the maternal microbiota, potentially influencing fetal immunological development. The inconsistency of findings among research suggests that additional factors, including genetic predisposition and environmental influences, may potentially be significant contributors. This underscores the complex characteristics of AD and the necessity for a holistic approach to comprehending its causation. The variations in study results highlight the necessity of examining the whole context of AD etiology, encompassing the possible interactions among genetic, environmental, and microbial variables.

A drawback of the research in this review is the dependence on varied methodologies for assessing antibiotic exposure, including maternal urine tests, parent-reported data, and medical records. These discrepancies may account for the variety in results and underscore the necessity for uniform methodologies in forthcoming research. The studies also differ in their follow-up durations, potentially influencing the detection of long-term effects of antibiotic exposure on the risk of Alzheimer's disease. Future research must focus on overcoming these limitations by utilizing standardized exposure assessment techniques and extending follow-up durations to enhance comprehension of the long-term effects of prenatal antibiotic exposure on the risk of atopic dermatitis. Standardizing exposure assessment methodologies would improve the comparability of results across research and aid in the synthesis of data in systematic reviews and meta-analyses.

Conclusion

This systematic review suggests a potential association between intrauterine antibiotic exposure and the development of atopic dermatitis (AD) in Asian children, though current evidence remains inconclusive due to heterogeneity in study designs and outcomes. The findings highlight the urgent need for further research to elucidate the underlying biological mechanisms and to identify modifiable risk factors that could inform prevention strategies. Understanding how antibiotics influence the onset and progression of AD could have important implications for clinical guidelines and public health interventions, particularly in high-risk populations. Future research should prioritize longitudinal, multicenter studies that integrate genetic, environmental, and microbiome data to provide a comprehensive understanding of AD pathogenesis and to support the development of targeted therapies aimed at reducing its incidence.

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