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A systematic review and meta-analysis of risk factors associated with atopic dermatitis in Asia

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic, inflammatory skin disorder characterised by intense itch and eczematous lesions. Rising prevalence of AD has been observed worldwide including in Asia. Understanding the risk factors associated with AD may explain its pathogenicity and identify new preventive strategies and treatments. However, AD-associated risk factors and comorbidities specific to Asia have not been systematically reviewed.

Methods: We performed a systematic review in accordance with the Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA) guidelines and summarised epidemiological studies investigating personal, family, and environmental factors and comorbidities associated with AD in Asia. Significant factors were assessed if they can be altered through lifestyle practices and further classified into non-modifiable and modifiable factors. Meta-analysis using the random-effect model was also conducted to provide an overall estimate for several significant factors.

Results: We identified a total of 162 epidemiological studies conducted in Asia. Among non-modifiable factors, a family history of atopic diseases was the most reported, suggesting the involvement of genetics in AD pathogenesis. Among modifiable factors, the results of meta-analyses revealed maternal smoking as the strongest risk factor with a pooled odds ratio (OR) of 2.95 (95% CI, 2.43–3.60), followed by active smoking (pooled OR, 1.91, 95% CI, 1.41–2.59).

Conclusion: While a family history may aid clinicians in identifying high-risk individuals, literature has long suggested the importance of gene-environment interaction. This review identified several modifiable factors including medical treatments, indoor and outdoor environmental exposure, and personal and family lifestyle specific to Asia. Based on the meta-analyses performed, prevention strategies against AD may start from changing personal and family lifestyle choices, especially smoking habits.

Keywords: Risk factors, Atopic dermatitis, Eczema, Asia

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INTRODUCTION

Background – symptoms and diagnosis of atopic dermatitis

Atopic dermtitis (AD) is a non-communicable skin disorder characterised by intense itch and eczematous lesions. It is relapsing in nature, often with repeated flares, and may negatively impact quality of life for patients and their family members.[1,2] AD is prevalent across all age groups but typically occurs during childhood.[3] According to the Phase III International Study of Asthma and Allergies in Childhood (ISAAC),[4] the prevalence of AD ranged from 2.0% to 22.3% among 6-7 years-old and 1.8%–19.0% among 13-14 years-old. While among adults, the prevalence ranged from 2.1 to 8.1%.[5] The clinical appearance of lesions also differs depending on age. Infants exhibit symptoms mainly at the cheeks of the face while children and adults are commonly observed to develop lesions on the extensor or flexural regions.[1] In diagnosing AD, there is no specific laboratory or histological test, and it entirely depends on clinical features.[1] Several clinical criteria have been proposed with the earliest being the Hanifin and Rajka criteria.[1] However, given its clinical heterogeneity which may resemble several disorders, making a correct diagnosis is a significant challenge for clinicians.[3]

Factors influencing atopic dermtitis development

The aetiology of AD is multifactorial involving genetics, immunological, and environmental factors. A family history of atopic diseases has been a strong predictor of AD, supporting the role of genetic factors in its development. Genetic predisposition such as the loss-of-function mutations in the filaggrin (FLG) gene contributes to epidermal barrier dysfunction[6] which increases epidermal permeability to environmental pollutants and allergens responsible for triggering immunologic responses and AD development. This suggests the important interplay between genetics and the environment, and understanding environmental factors may be crucial in preventing or reducing AD. With the establishment of the ISAAC consortium, ecological studies had reported several factors including demographic, socioeconomic, active and passive smoking, urbanisation, diet, breastfeeding and time of solid food introduction, obesity and physical exercise, and environmental air pollutants.[7,8] However, these factors are driven by geographical locations and cultural practices which may differ between Asian and Western countries. With the prevalence of AD increasing worldwide,[4] including Asia,[9] it would be of interest to identify risk factors associated with AD specific to Asia.

Aim of review

This review aims to present the current literature on epidemiological studies conducted in Asia. It provides a comprehensive overview of significant personal, family, and environmental factors through a qualitative discussion and quantitative meta-analyses.

METHODOLOGY

Search strategy and selection criteria

This review was conducted in accordance with the Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA) guidelines. The Web of Science and PubMed were searched in April 2020 and August 2020, respectively. The search was restricted to publications between 1990 and 2020. Key search terms included “epidemiology” or “risk”, together with a comprehensive repertoire of terms for the disease, namely “atopic dermatitis”, “eczema”, “allergic diseases”, “allergic disorders”, “atopic diseases” and “atopic disorders”. A list of 50 Asian countries and territories was also included. The full search terms were presented in Supplemental Appendix 1. No pre-existing search protocol was used.

The literature search generated 393 non-duplicated records. Fig. 1 illustrates the screening process. Epidemiological studies investigating personal, family, and environmental factors and comorbidities associated with AD in Asia were included. As this review aims to present a comprehensive overview of the topic, eligible studies were not restricted in terms of study characteristics including study design, population and size, and AD definition.

Studies on systematic review and meta-analysis, non-human subjects, other AD-related topics such as the efficacy of AD treatments, risk factors of non-

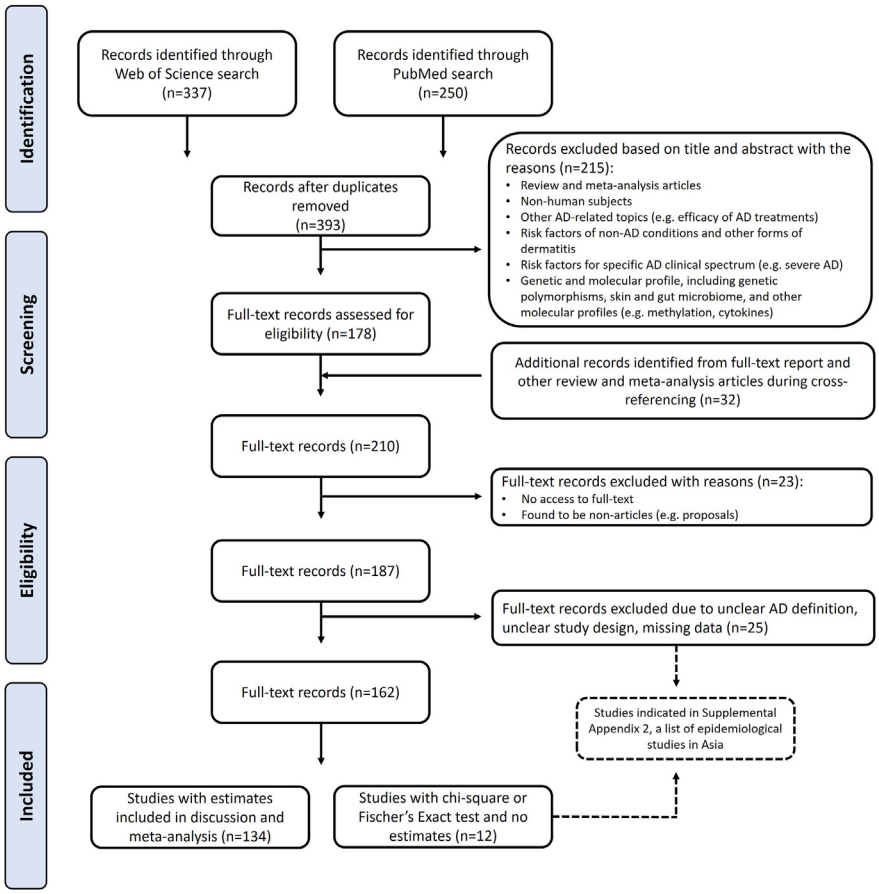

Fig. 1 PRISMA flow-diagram

AD conditions and other forms of dermatitis (eg, hand eczema or contact dermatitis), and risk factors of specific AD clinical spectrum (eg, severe AD) were excluded. Studies on genetic and molecular profiles associated with AD, including genetic polymorphisms, skin and gut microbiome, and immunological markers were further excluded as this review focuses on personal, family, and environmental factors and comorbidities.

Selected studies were further assessed using the full-text report. Additional studies identified from full-text reports and other systematic reviews and meta-analyses during cross-referencing were included. Studies which were inaccessible, identified as non-articles (eg, proposals), and had unclear study design, AD definition or missing in data were further excluded. Of the remaining 162 studies, 12 studies concluded significant factors based on Chi-square or Fisher Exact Test while 150 studies were based on estimates (eg, odds ratio [OR] and corresponding 95% confidence intervals [CI]). Fully adjusted (whenever possible) and significant estimates were recorded and summarised in Supplemental Appendix 3 for discussion and meta-analysis.

Statistical analysis

Meta-analysis was conducted using Stat/MP 11.0. The random-effects model was used to account for variations across studies. A meta-analysis was performed for risk factors with at least 3 independent studies reporting significant findings to estimate the overall risk. To avoid over-representation of results from the same study, each study was only represented once in each meta-analysis. When multiple results (eg, non-stratified and stratified populations, different AD definitions, and different quartiles of analysis) were significant, only one result was selected. Selection criteria and meta-analyses results containing the individual and pooled ORs were presented in Supplemental Appendix 4 Figs. 1-8. The pooled OR with its corresponding 95% CI, inconsistency index (I^2), and p-value for I^2 (p) were reported. I^2

represents the heterogeneity of studies included in the meta-analysis with a significance level of $p = 0.05$. $I^2 \leq 25\%$ corresponds to low, $I^2 \leq 50\%$ corresponds to moderate, and $I^2 \geq 75\%$ corresponds to high inconsistency.

RESULTS AND DISCUSSION

Prevalence and significant risk factors associated with AD

Based on the methodology described, 162 studies reporting personal, family, and environmental factors and comorbidities associated with AD were identified. They originated from 21 countries and regions. Eastern Asia had the highest number of studies and most studies reported a cross-sectional design (Table 1). Additionally, studies varied in their study population and size, and disease definition (Supplemental Appendix 2). While most studies investigated children (<18 years-old), some studies were interested in adults ($\geq$ 18 years-old). For instance, Kurt et al[10] studied individuals aged $\geq$ 18 years-old to investigate the risk of occupational exposure on adult-onset AD. As such, the prevalence estimates of AD varied, ranging from 0.8% in high school students in Turkey[11] to 37.6% in 6–7 and 13-14 years-old students in Iran[12] among cross-sectional studies.

Significant factors associated with AD were classified into non-modifiable and modifiable (Fig. 2). Non-modifiable factors are defined as factors which cannot be easily altered through lifestyle practices, and they include demographic factors, socioeconomic statuses, and personal and family medical history. Conversely, modifiable factors allow intervention, and they include medical treatments, outdoor and indoor environmental factors, and personal and family lifestyle factors. While non-modifiable factors would be discussed in this review, modifiable factors remain the focus of discussion. Significant factors were further stratified by study population of children ($\leq$12 years-old), adolescent ($\geq$13 years-old to <18 years-old), and adult ($\geq$ 18 years-old) (Supplemental Appendix 4 Figs. 10A, 11A, 12). Factors differed across the 3 age groups. For instance, children populations reported significant family lifestyle factors while adult populations did not. Active smoking was a significant factor for adolescent populations but was not applicable for children populations.

Asia is a geographical category with a diverse number of countries and regions. Factors investigated and reported may, therefore, vary depending on the cultural, socioeconomic, and climatic factors of the country or region. For instance, birth month was only significant among temperate countries and regions of Japan,[13] Taiwan,[14] and China.[15] The effect of specific air pollutants was most commonly reported as significant in China[16–19] which has a high air pollution index. The study of specific air pollutants may be further driven by resources such as meteorological stations in monitoring air quality. Diet also differs among Asian countries, and Cai et al[15] was the only study which investigated and identified a significant association of AD with organ meat which is likely to be a common food item in the Chinese diet. Therefore, when generalising risk factors across different countries or regions in Asia, it needs to be evaluated against the geographical locations, cultures, and ethnicities.

Non-modifiable factors

Demographics and socioeconomic status

In Supplemental Appendix 3 Table 1, multiple studies reported the importance of age, gender, socioeconomic statuses, and ethnicity in influencing the development of AD. These factors determine lifestyle practices which may trigger AD. Additionally, the association between ethnicity and AD suggests the role of genetics in AD development.[20] As these factors are non-modifiable, they are useful in identifying individuals at high-risk of AD development, but not in formulating preventive strategies against AD.

The pooled ORs for age, gender, sibling number, and various socioeconomic statuses were obtained (Fig. 3). The pooled OR of age was 0.88 (95% CI, 0.81–0.95; $I^2 = 96.0\%$, $p = 0.000$), suggesting a decreased odds of AD with increasing age. As AD has a male predominance during childhood and female predominance after adolescence,[21,22] the pooled OR for gender was based on 4 studies which exclusively investigated adult or adolescent populations and reported 0.67 (95% CI, 0.57–0.80; $I^2 = 63.2\%$, $p = 0.043$),

	Population (thousands) in 2019	Cross-sectional	Birth cohort	Prospective	Case-control	Total
Eastern Asia	**1,648,383**	**76**	**32**	**3**	**0**	**111**
China	1,439,324	21	3	0	0	24
Japan	126,476	25	16	0	0	41
Taiwan	23,817	15	13	3	0	31
South Korea	51,269	11	0	0	0	11
Hong Kong	7497	4	0	0	0	4
South-Eastern Asia	**453,788**	**11**	**5**	**0**	**0**	**16**
Singapore	5850	6	5	0	0	11
Vietnam	97,339	0	0	0	0	0
Indonesia	273,524	2	0	0	0	2
Lao	7276	1	0	0	0	1
Thailand	69,800	2	0	0	0	2
Southern Asia	**1,485,411**	**5**	**0**	**0**	**1**	**6**
Iran	83,993	4	0	0	1	5
India	1,380,004	1	0	0	0	1
Sri Lanka	21,413	0	0	0	0	0
Western Asia	**145,088**	**25**	**3**	**0**	**1**	**29**
Saudi Arabia	34,269	1	1	0	0	2
Turkey	83,430	11	1	0	0	12
Israel	8519	4	0	0	0	4
Armenia	2958	0	1	0	1	2
Kuwait	4207	2	0	0	0	2
Lebanon	6856	5	0	0	0	5
Oman	4975	1	0	0	0	1
Qatar	2832	1	0	0	0	1
Total		**117**	**40**	**3**	**2**	**162**

Table 1. 162 epidemiological studies categorised based on countries and territories and study design **Reference: United Nations 2019*[82]

suggesting a higher prevalence in females. According to the hygiene hypothesis, the risk of AD decreases with higher sibling number, and the pooled OR was 0.69 (95% CI, 0.62–0.78; I^2 = 82.8%, p = 0.000), supporting the hypothesis. The pooled ORs of various socioeconomic statuses were consistent in suggesting an increased odds of AD with higher status. Other demographic and socioeconomic factors were summarised in Fig. 2 with its

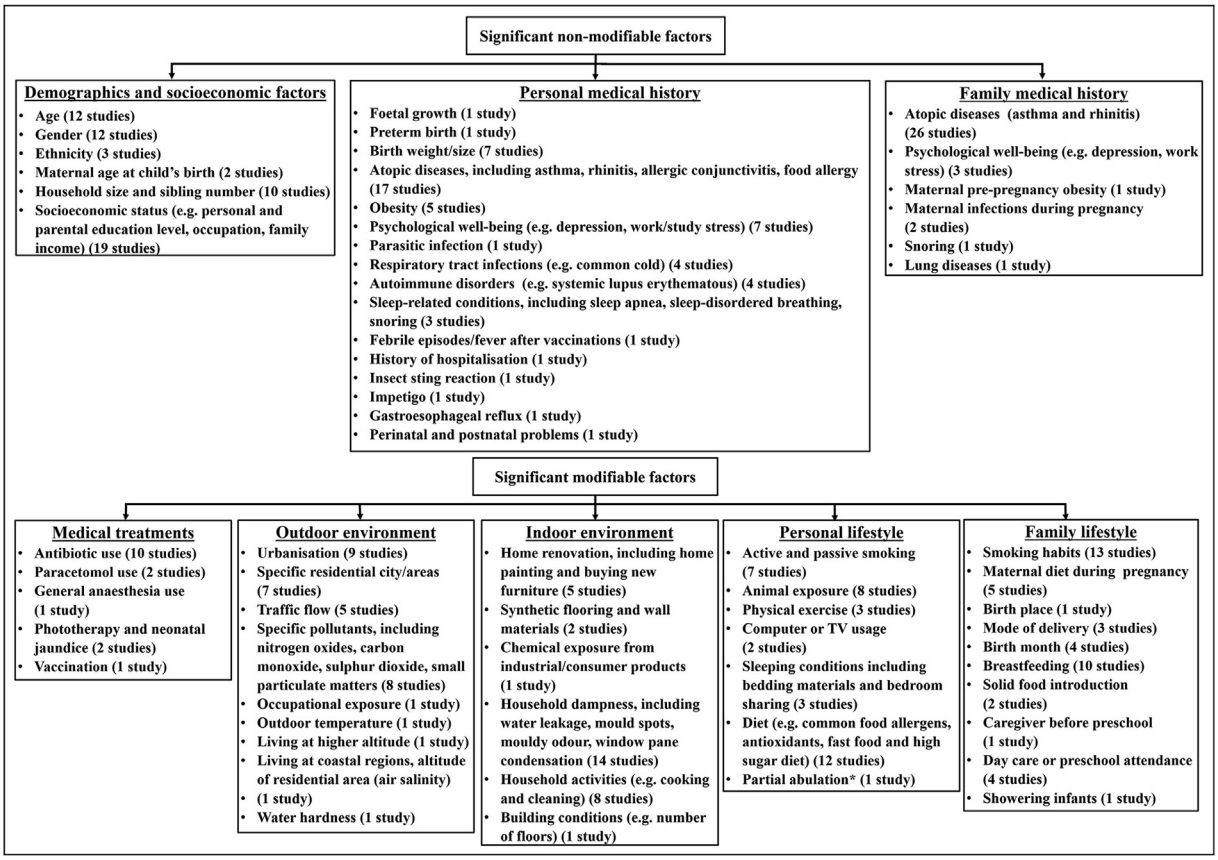

Fig. 2 Summary of significant factors classified into non-modifiable and modifiable factors with the number of studies reporting significant association indicated in brackets. *Factor is related to ethnicity; Refers to a ritual practice before prayers performed by the Muslim community which involves cleansing body surfaces exposed to the environment such as face, nose, ears, and hands and feet with clean running water without soap or chemicals[81]

estimates reported in Supplemental Appendix 3 Table 1.

Personal medical history

There may exist a bidirectional relationship between AD and other medical conditions in which AD triggers the development of other conditions or vice versa. Therefore, understanding comorbidities may allow clinicians to identify individuals at high-risk of AD development or those who may experience a deterioration of AD symptoms. In Supplemental Appendix 3 Table 2, these medical conditions include birth factors. Skin maturation occurs at approximately 36 weeks of gestation and a compromised skin barrier may predispose preterm neonates to AD development.[23] Conversely, the results for birth weight were inconsistent and the pooled OR was 0.93 (95% CI, 0.74–1.17; $I^2 = 86.3\%$, $p = 0.000$), suggesting an insignificant association with AD (Fig. 3).

Among comorbidities reported, atopic diseases, such as asthma, allergic rhinitis, allergic conjunctivitis, and food allergy, were most investigated. Among the pooled ORs for these atopic diseases (Fig. 3), food allergy reported the highest pooled OR of 6.34 (95% CI, 2.78–14.48; $I^2 = 88.6\%$, $p = 0.000$), supporting the hypothesis of epidermal skin barrier dysfunction leading to the introduction of food allergens into deeper epidermal layers.[24] The pooled ORs for asthma, allergic rhinitis and allergic conjunctivitis were 2.35 (95% CI, 2.13–2.60; $I^2 = 90.7\%$, $p = 0.000$), 2.66 (95% CI, 2.14–3.30; $I^2 = 94.1\%$, $p = 0.000$) and 2.03 (95% CI, 2.03, $I^2 = 98.6\%$, $p = 0.000$), respectively (Fig. 3). This confirms the atopic march theory in which AD leads to subsequent development of other atopic diseases.[25] Therefore, preventing the development of AD may be crucial in reducing the occurrence of other atopic diseases, and an AD diagnosis suggests more active health screening for early

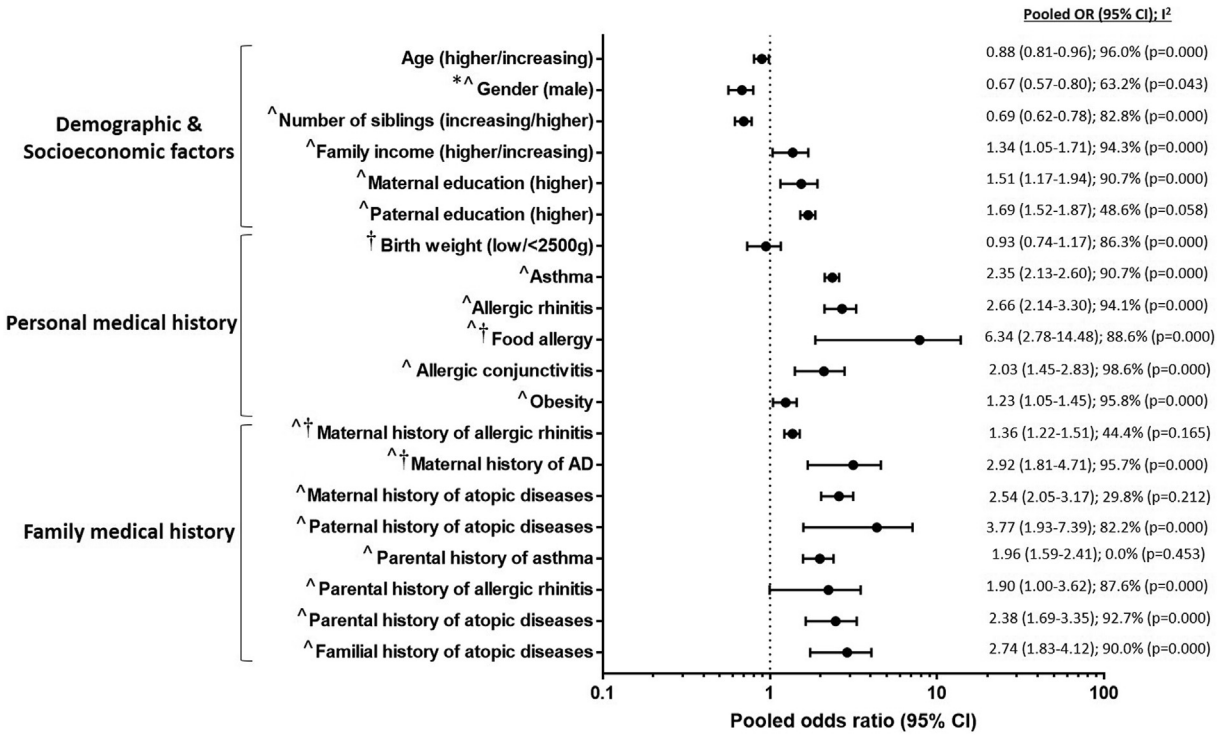

Fig. 3 Pooled ORs from meta-analyses of non-modifiable factors (demographic factors and socioeconomic statuses, personal and family medical history). Individual and pooled ORs of meta-analyses were presented in Supplemental Appendix 4 Figs. 1–3. ^ Factors which studies in meta-analysis demonstrated consistent trends in significance. † Factors which studies in meta-analysis involved only children population (≤12 years-old). *Based on studies which exclusively investigated an adult or adolescent population

detection. Other medical conditions including obesity with a pooled OR of 1.23 (95% CI, 1.05–1.46; I^2 = 95.8%, p = 0.000) (Fig. 3), were summarised in Fig. 2 with the estimates reported in Supplemental Appendix 3 Table 2.

Family medical history

A family medical history may be helpful for clinicians to identify individuals at high-risk of AD development. In Supplemental Appendix 3 Table 3, atopic diseases were the most common family medical condition investigated. The pooled ORs of various parameters for a family history of atopic diseases (Fig. 3) were consistent in demonstrating an increased odds of AD. A family history of atopic diseases is therefore a strong predictor of AD development, suggesting the involvement of genetic factors. The loss-of-function mutations in the FLG gene have been strongly associated with AD pathogenesis among Asian populations.[26,27] FLG functions in keratin aggregation which contributes to epidermal skin barrier integrity.[6] FLG is also proteolyzed into organic acids which maintain the pH gradient and antimicrobial activity of the epidermis.[6] FLG deficiency has been associated with higher pH which favours *Staphylococcus aureus* (*S. aureus*) growth,[28] and higher *S. aureus* colonisation has been observed among AD patients.[29] However, a family history of atopic diseases may also suggest shared environmental and lifestyle factors. As such, it may be important to consider gene-environment interaction in which the influence of environmental factors depends on the host's genetic susceptibility. Nonetheless, a family history of atopic diseases is a prominent risk factor which may help clinicians identify high-risk children and provide more intensive parental counselling on early interventions, such as changing family lifestyle, as early as the prenatal stage. Other medical conditions including depression were summarised in Fig. 2 with the estimates reported in Supplemental Appendix 3 Table 3.

Modifiable factors

Medical treatments

In Supplemental Appendix 3 Table 4, medical treatments during pregnancy and early childhood were shown to influence AD development.

Antibiotic use during pregnancy was reported by Gao et al[30] to be associated with an increased odds of AD in offspring. However, more research is needed to validate this finding among other Asian populations.

According to the hygiene hypothesis, early-life antibiotic use reduces the diversity of microbial exposure and increases the risk of developing AD.[31] Majority of the studies were consistent with this hypothesis, except Gao et al[30] Nevertheless, a pooled OR of 1.40 (95% CI, 1.17–1.68; $I^2 = 87.2\%$, $p = 0.000$) for early-life antibiotic use was obtained, suggesting its adverse effect on AD development (Fig. 4). Similarly, early-life paracetamol use was shown to increase the odds of AD in several reviewed studies. Conversely, general anaesthesia use was only investigated and reported by Kuo et al[32] to adversely influence AD development, and more research is needed to elucidate its effect among the Asian population.

Additionally, given that neonatal jaundice is more prevalent among Asians than other ethnicities,[33] it may be important to understand the negative impact of phototherapy, a common treatment for neonatal jaundice. Prolonged exposure to ultraviolet rays from phototherapy may suppress the immunologic switch from T helper cell (Th) 2 to Th1 response of the cutaneous system,[34,35] and reviewed studies were consistent to report an increased odds of AD with phototherapy. Similarly, vaccination may shift the immunologic balance towards a Th2 response.[36] Haemophilus influenza type b vaccination was reported by Wang et al[36] to be associated with an increased odds of AD.

Understanding the association between AD and various medical treatments may change clinical practice. For instance, clinicians may need to re-evaluate the duration of phototherapy for neonates and exercise additional counselling on antibiotics and paracetamol use for pregnant mothers and young children. As most developed countries have a well-planned vaccination programme for young children, revision of policies may be needed if future research consistently suggests an adverse effect of certain vaccinations on AD development.

Outdoor environmental factors

The skin constitutes the first line of physical and immunological defence against environmental factors. It is directly in contact with a variety of air

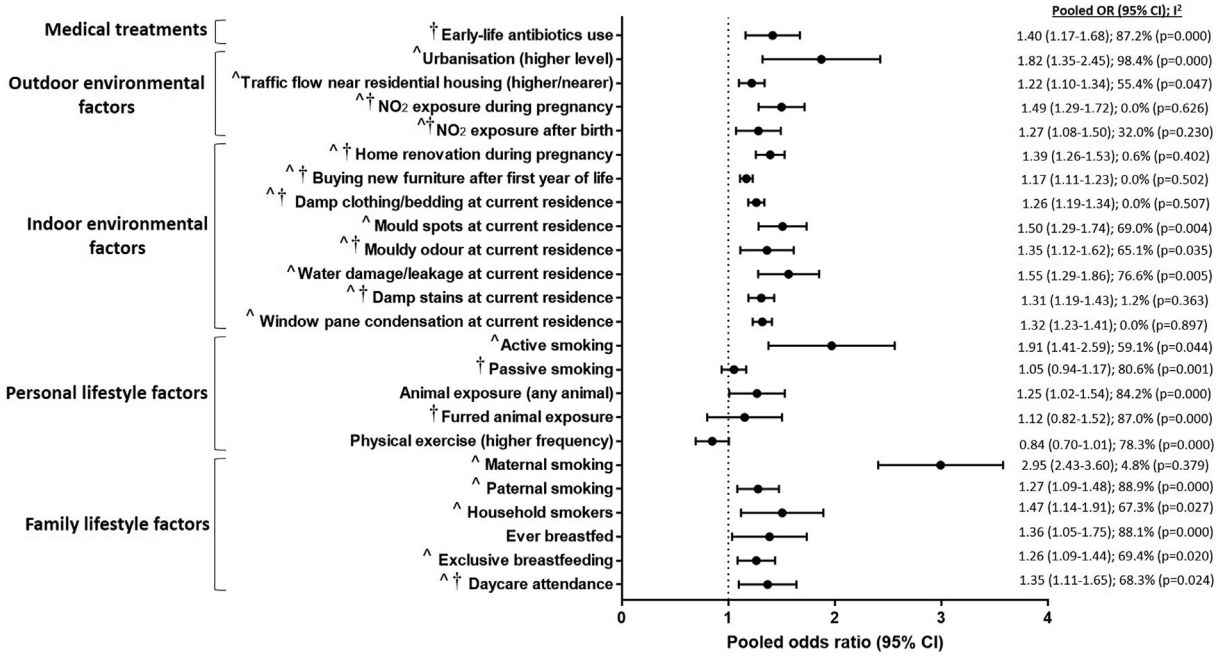

Fig. 4 Pooled ORs from meta-analyses of modifiable factors (medical treatments, outdoor and indoor environmental factors, personal and family lifestyle factors). Individual and pooled ORs of meta-analyses were presented in Supplemental Appendix 4 Figs. 4–8. ^ Factors which studies in meta-analysis demonstrated consistent trends in significance. † Factors which studies in meta-analysis involved only children population (≤12 years-old)

pollutants which produce reactive oxidative and nitrogen species.[37] These reactive species induce oxidative stress which damages proteins and lipids in the epidermis, leading to subsequent skin barrier dysfunction. In Supplemental Appendix 3 Table 5, multiple reviewed studies reported an adverse effect of outdoor pollutants on AD development. Air pollution can be a major problem for urbanised cities, and a pooled OR of 1.82 (95% CI, 1.35–2.45; $I^2 = 98.4\%$, $p = 0.000$) was obtained for urbanisation, suggesting an increased odds of AD with urban living (Fig. 4). A major source of air pollutants originates from the automobile. Diesel exhaust particles may induce alloknesis in which slight mechanical stimulation can sufficiently trigger pruritus, resulting in extensive scratching, skin barrier dysfunction, and AD development.[38] Living at residential housing near high traffic flow was consistently reported to be associated with increased odds of AD, and a pooled OR of 1.22 (95% CI, 1.10–1.34; $I^2 = 55.4.0\%$, $p = 0.047$) (Fig. 4) was obtained. Further, the influence of outdoor pollutants was reported to begin as early as during pregnancy. For instance, the pooled OR of 1.49 (95% CI, 1.27–1.72; $I^2 = 0.0\%$, $p = 0.626$) was obtained (Fig. 4) for nitrogen dioxide (NO_2) exposure during pregnancy, which was higher than that for NO_2 exposure after birth at 1.27 (95% CI, 1.08–1.50; $I^2 = 32.0\%$, $p = 0.230$) (Fig. 4). These findings potentially suggest the importance of government policies in combating air pollution. Individuals including pregnant mothers should also adopt personal and household precautions such as wearing covered clothes or masks and closing windows to reduce exposure to air pollutants, especially at urbanised locations. Other outdoor environmental factors include occupational exposure to chemicals, outdoor air temperature and living at high altitude, air salinity associated with living at coastal regions, and water hardness as summarised in Fig. 2 with the estimates in Supplemental Appendix 3 Table 5.

Indoor environmental factors

Similarly, the indoor environment contains pollutants and allergens capable of triggering AD development. In Supplemental Appendix 3 Table 6, household dampness promotes the growth of indoor allergens including dust mites and moulds.[39] The pooled ORs of various dampness indicators were consistent in reporting increased odds of AD (Fig. 4). Additionally, home renovation activities including buying new furniture and home painting, and the use of synthetic, modernised flooring and wall materials emit chemicals including volatile organic compounds (VOCs) which may trigger AD.[37,40,41] Further, the influence of indoor factors was reported to begin as early as during pregnancy. For instance, the pooled OR for home renovation during pregnancy was 1.39 (95% CI, 1.26–1.53; $I^2 = 0.6\%$, $p = 0.402$). Other daily household activities such as cooking or use of heating system further affect indoor air quality. Nonetheless, indoor factors may be controlled through household habits such as sunning mattresses and more frequent bedroom cleaning. Moreover, engaging in home renovation is often a choice and it may be advisable for individuals to minimise renovation work or seek temporary housing during the renovation period.

Personal lifestyle factors

In Supplemental Appendix 3 Table 7, personal lifestyle factors were shown to influence AD development. Tobacco smoke exposure was the most common personal lifestyle factor investigated. Smoke residues, when in contact with the skin, may degrade skin epidermal integrity, thus triggering AD. Reviewed studies were consistent in reporting increased odds of AD for active smoking. The pooled OR for active smoking of 1.91 (95% CI, 1.41–2.59; $I^2 = 59.1\%$, $p = 0.044$) was obtained, suggesting increased odds of AD with active smoking (Fig. 4). Conversely, reviewed studies were inconsistent for passive smoking with Lee et al[42] reporting a decreased odds possibly due to intentional avoidance by the individual or other household smokers. The pooled odds ratio for passive smoking was insignificant at 1.05 (95% CI, 0.94–1.17; $I^2 = 80.6\%$, $p = 0.001$) (Fig. 4).

Similarly, the results of animal exposure were inconsistent. While animal exposure is often considered a risk factor of atopic sensitisation, the hygiene hypothesis suggests animal contact to increase microbial exposure and decrease the risk of atopic diseases.[43] Based on the pooled ORs, "any animal" exposure (pooled OR, 1.25, 95% CI, 1.02–

1.54, $I^2 = 84.2\%$, p = 0.000, Fig. 4) was associated with an adverse effect while furred domestic pets was insignificant (pooled OR, 1.12, 95% CI, 0.82–1.52, $I^2 = 87.0\%$, p = 0.000, Fig. 4). However, the influence of animal exposure may differ depending on the type of animals. For instance, even among furred pets, the microbiota of dogs and cats is known to be highly diverse,[43] which may possibly explain the opposing effects of cats and dogs reported by 2 reviewed studies, Kurosaka et al[44] and Sriyaraj et al,[45] respectively. Moreover, the effects of animal exposure on AD may be modulated by genetics, for instance, polymorphisms at the promoter of CD14, a pattern recognition receptor responsible for recognising gram-negative bacteria and eliciting immune response.[46–49]

Additionally, daily lifestyle activities including computer/TV usage and physical exercise were reported to be associated with AD. A higher frequency of computer/TV usage was associated with an increased odds of AD. This may be due to more time spent indoors which increases exposure to indoor pollutants and allergens. Conversely, the results for physical exercise were inconsistent. While majority of the reviewed studies reported a protective effect against AD development, Al-Sahab et al[50] reported an increased odds of 1.46 times with higher exercise frequency, as its residents prefer to jog on the main roads, exposing themselves to outdoor air pollutants. The pooled OR of 0.84 (95% CI, 0.70–1.01; $I^2 = 78.3\%$, p = 0.000) for exercise suggests an insignificant role in triggering AD (Fig. 4).

Sleeping conditions may further contribute to AD development. In Supplemental Appendix 3 Table 7, Ergin et al[51] reported increased odds of AD with at least 4 people sleeping in the same room than sleeping alone. Although this refutes the hygiene hypothesis,[51] an alternative explanation may be that room-sharing introduces sleep disturbances,[52] affecting sleep quality and immunity.[53] The risk of AD may also depend on bedding materials. For instance, Waked & Salameh[54] reported increased odds of 1.46 for using spongy pillows which are likely to be made of synthetic materials. Synthetic materials are known to release chemical pollutants such as VOCs and trap more allergens due to their looser weaves.[55–57]

Additionally, eating habits may play an important role in AD development. However, eating habits may vary across different geographical regions, cultures, and ethnicities in Asia. In Supplemental Appendix 3 Table 7, among common food allergens, higher frequency of nut consumption was associated with an increased odds of AD. This is supported by the ISAAC Phase III study[58] which reported an increased odds of AD for consuming nuts at least once per week among 13-14 years-olds. Conversely, fish is a major source of n-3 polyunsaturated fatty acids (PUFAs) which has anti-inflammatory effects[59] and was shown to be protective against AD. Coincidentally, Miyake et al[60] reported decreased odds of AD with higher dietary levels of n-3 PUFAs including docosahexaenoic acid and eicosapentaenoic acid. This may suggest the importance of dietary supplements such as fish oil as AD preventive strategies. However, the effect of n-3 PUFAs may be influenced by other fatty acids such as n-6 PUFAs which is pro-inflammatory,[59] and it may be more crucial to consider multiple dietary components as opposed to a single component. Genetic polymorphisms of key mediators involved in fatty acid synthesis, catabolism, and utilisation may further influence the effects of PUFAs on AD development.[59]

With an increasingly westernised world, a high fat and sugar diet is a global concern. While a majority of the fast food or high-sugar items were associated with increased odds of AD, Cai et al[15] reported decreased odds for french fries, hamburgers, popcorn, and juice consumption. Cai et al[15] studied pre-schoolers in China and the protective effect reported may suggest parental knowledge on diet and AD or even obesity which is a comorbid of AD. This protective effect may also reflect the Chinese population to be more accustomed to a Chinese diet and consume less fast food and high-sugar items.

Gut microbiota and their metabolites may play a crucial role in B and T cell proliferation and differentiation to induce protective antibody responses.[61] Pro-, pre-, and syn-biotics have been hypothesised to normalise the gut microbiota which may serve as preventive strategies or treatments for AD. While Loo et al[62] reported increased odds of AD with probiotic consumption, the effect

of probiotic on AD development needs to be evaluated against the type of probiotic strains, together with dietary factors which may influence the bacterial metabolic activities.[63,64] Therefore, it may be crucial to investigate probiotics in tandem with common dietary habits in Asia.

Antioxidants including vitamins C, A, and E, and zinc and selenium protect against oxidative damage and inflammation.[65] Experimental models of vitamin A-deficient mice have demonstrated Th2 cells induction and subsequent skin allergy upon antigen administration in oral or skin challenge.[66,67] Several reviewed studies reported a protective effect of higher dietary vitamins and zinc levels against AD development. Conversely, serum vitamin D deficiency and lower levels of serum α-tocopherols, an anti-inflammatory isoform of vitamin E, were associated with increased odds of AD. A major source of antioxidants originates from vegetables and fruits, and their daily consumption may be crucial in AD development. However, Phathammavong et al[68] reported increased odds of AD with increased frequency of vegetable consumption. This highlights the possibility of food contaminants such as pesticides and insecticides on crops in triggering AD. Moreover, genetic polymorphisms of key mediators such as manganese superoxide dismutase and glutathione-S-transferase involved in the antioxidant defence system may confer individual variability in antioxidant metabolism and its protective effect.[69]

Family lifestyle

Family lifestyle refers to choices made by family members which may subsequently influence an individual's development of AD. In Supplemental Appendix 3 Table 8, smoking habits by family members were the most common family lifestyle investigated. The majority of the reviewed studies were consistent in reporting increased odds of AD as early as during pregnancy. Transplacental exposure to tobacco smoke may induce epigenetic changes, such as the hypomethylation of thymic stromal lymphopoietin gene 5′-CpG island region which was found to skew the immune system towards a predominantly Th2 response.[70] Among the pooled ORs of the various parameters for family smoking habits, maternal smoking reported a pooled OR of 2.95 (95% CI, 2.43–3.60; $I^2 = 4.8\%$, $p = 0.379$), demonstrating a more profound effect than that of paternal smoking at 1.27 (95% CI, 1.09–1.48; $I^2 = 88.9\%$, $p = 0.000$) (Fig. 4). This suggests the importance of maternal-related factors including *in utero* exposure, breastfeeding, and mothers spending more time with children after birth. Similarly, the pooled OR for household smoking of 1.47 (95% CI, 1.14–1.91; $I^2 = 67.3\%$, $p = 0.027$) was indicative of its role in triggering AD development (Fig. 4).

During pregnancy, mothers are likely to alter their diet due to morning sickness or enhance their nutritional intake to benefit foetal development. Therefore, maternal diet during pregnancy may play an important role in the child's subsequent health status. In Supplemental Appendix 3 Table 8, common food allergens identified include dairy products and eggs. The results of dairy products consumption were inconsistent across 2 reviewed studies which may have adopted different definitions of dairy products and timepoints of investigations. Conversely, egg consumption was reported to be associated with decreased odds of AD. This may highlight the practice of intentional avoidance of common food allergens in preventing foetal sensitisation. Moreover, higher consumption of green and yellow vegetables, apples, and citrus fruits are sources of antioxidants and were shown to be protective against AD. Conversely, meat, a major source of saturated fatty acid, was associated with increased odds of AD. Additionally, there were no reviewed studies investigating maternal diet during lactation which can affect breast milk contents and this may be a topic which warrants future research in Asia.

Parental choices on birth options including birthplace, mode of delivery, and birth months may further influence subsequent AD development in children. The importance of birthplace highlights the role of early allergen exposure in triggering AD. Reviewed studies were also consistent in demonstrating increased odds of AD with caesarean section. Compared to vaginal delivery, caesarean section does not provide an opportunity for the transfer of bacterial flora from mother to child which, according to the hygiene hypothesis, increases the risk of AD.[71] Conversely, the association of birth months with AD was

inconclusive as reviewed studies were inconsistent in their comparison and reference groups. While literature[72] suggested a higher prevalence of AD in cooler birth months due to drier climate resulting in drier skin type, it also depends on other environmental factors such as pollen counts with seasonal changes and sunlight exposure which varies with geographical latitudes.[73]

Further, the mother's choice to breastfeed may influence AD development. However, results from reviewed studies were inconsistent. Breast milk contains secretory IgA which enhances the infant's immunity against early-life infections.[66,74,75] However, this reduces microbial exposure which, according to the hygiene hypothesis, increases the susceptibility of developing AD.[76] The pooled OR for "ever breastfed" was 1.36 (95% CI, 1.05–1.75; $I^2 = 88.1\%$, $p = 0.000$), suggesting the adverse effect of breastfeeding on AD (Fig. 4). Similarly, for exclusive breastfeeding, a pooled OR of 1.26 (95% CI, 1.09–1.44; $I^2 = 69.4\%$, $p = 0.020$) was obtained, suggesting higher odds of AD for children who are exclusively breastfed (Fig. 4). Additionally, early solid food introduction is hypothesised to reduce AD through modulating the gut flora and developing oral tolerance.[77] However, reviewed studies reported otherwise. Moreover, as current literature[78] focused on investigating common food allergens in preventing food allergy, future research may emphasise on investigating its influence in AD development.

During early childhood, AD development may be further influenced by the choice of caregiver. In Supplemental Appendix 3 Table 8, children cared for by grandparents were reported to demonstrate increased odds of AD than those cared for by parents. Grandparents are possibly more conscientious in ensuring a hygienic environment which, according to the hygiene hypothesis, increases susceptibility towards AD. This finding may be associated with the socioeconomic status of parents. For instance, parents with white-collared jobs tend to have heavier career commitments and place their children under the care of the grandparents. Additionally, daycare or early preschool attendance were consistently associated with an increased odds of AD. This refutes the hygiene hypothesis which suggests that mingling with other children increases the likelihood of infections and decreases the susceptibility of AD. However, it also depends on other conditions in a daycare setting such as the types of activities which may induce stress and enhance immune reactivity.[72] The pooled OR for daycare or early preschool of 1.35 (95% CI, 1.11–1.65; $I^2 = 68.3\%$, $p = 0.024$) was obtained, suggesting its association with an increased odds of AD (Fig. 4).

STRENGTHS AND LIMITATIONS

Despite the strict methodology using the PRISMA guidelines, certain limitations should be considered. First, reviewed publications were epidemiological studies conducted in Asia. This limits the generalisability of the results and discussion to countries and regions outside Asia. Within Asia, it is important to consider the generalisability of factors across different geographical regions, ethnicities, and cultures. Moreover, genetics and molecular profiles such as genetic polymorphisms and skin microbiome, and risk factors associated with skin barrier dysfunction such as chemical irritants, were excluded as they are not identified in epidemiological studies. However, these topics are prominent risk factors of AD which may be reviewed separately. Similarly, risk factors associated with specific AD clinical phenotypes were excluded as it would be too extensive for the scope of discussion.

Second, the quality of studies was not assessed using the Newcastle-Ottawa Scale as this review aims to present a comprehensive overview of significant factors and comorbidities associated with AD in Asia. As such, there may have been personal bias and errors, such as misinterpretation of results. Additionally, publication bias which reflects the greater tendency to publish significant than insignificant results was not assessed. However, as this review focuses on summarising and *meta*-analysing only significant findings, assessing this bias may be less applicable. Although insignificant findings were excluded from the discussion of this review, they should not be deemed less important for future systematic reviews. For instance, Wang et al[79] investigated prenatal consumption of Traditional Chinese Medicine (TCM), and as TCM is widely used in Eastern Asia, it may be a factor for future investigation. Further, although fully

adjusted estimates were recorded whenever available, this does not exclude the possibility of confounding bias given that the associations between risk factors and disease are often not as straightforward.

Third, different study characteristics including AD definition, study design, and factor definition may introduce heterogeneity in the meta-analysis, and majority of the meta-analysis results (Figs. 3 and 4) reported a high heterogeneity (I^2>75%). This increases the risk of making erroneous inferences based on the results.[80] However, this methodological issue was to some extent accounted for by the random-effect model. A stringent set of selection criteria (Supplemental Appendix 4) to determine which analyses to be included in the meta-analysis was also applied to further reduce heterogeneity. Moreover, to determine if the excluded analyses influence the significance of results, a second meta-analysis with both the included and excluded analyses was performed and the same significance was obtained (Supplemental Appendix 4 Fig. 9). Subgroup analyses were also performed based on study population, namely, children (≤12 years-old), adolescents (≥13 to <18 years-old) and adults (≥18 years-old) (Supplemental Appendix 4 Fig. 10B, C, 11B). The pooled OR of age for child population (pooled OR, 0.97, 95% CI, 0.76–1.23; I2 = 96.0%, p = 0.000) differed from the overall risk estimate (Fig. 3).

However, the advantages of a large number of studies should also be considered. First, it increases the statistical power of meta-analysis to detect an effect, thus improving the precision and validity of estimates.[80] Second, the results of meta-analyses are useful in providing general trends on the effects of risk factors on AD development in Asia. Third, it allows the discussion of inconsistencies across studies which may highlight specific geographical locations, cultures, and ethnicities in influencing AD development. Moreover, despite the diverse study characteristics and factor definitions, several factors demonstrated a consistent effect across studies (indicated with ^ in Figs. 3 and 4), suggesting their importance in influencing AD.

CONCLUSION

The development of AD is strongly associated with a family history of atopic diseases. While a family history may aid clinicians in identifying high-risk individuals, literature has long suggested the importance of gene-environment interaction. This review identified several modifiable factors including medical treatments, indoor and outdoor environmental exposure, and personal and family lifestyle in the Asian population. Of these, maternal smoking reported the highest pooled odds of 2.95 (95% CI, 2.43–3.60), followed by active smoking with a pooled OR of 1.91 (95% CI, 1.41–2.59). It may be advisable for parents, especially mothers, and individuals to re-evaluate their smoking status. As several factors occur during pregnancy, counselling on AD preventive strategies may begin as early as during pregnancy.

Abbreviations

AD: atopic dermatitis; CI: Confidence interval; OR: Odds ratio; HR: Hazard ratio; RR: Relative risk; PR: Prevalence ratio; I^2: Inconsistency index; ISAAC: International Study of Asthma and Allergies in Childhood; FLG: Filaggrin; PRISMA: Preferred Reporting Item for Systematic Review and Meta-Analyses; p: p-value; Th: T helper cell; NO_2: nitrogen dioxide; VOCs: Volatile organic compounds; PUFAs: polyunsaturated fatty acids; TCM: traditional chinese medicine

Ethics approval and consent to participate

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Consent for publication

All authors give consent for publication.

Authors' contributions

F.T.C. supported and guided the literature review process. Y.T.N. performed the literature review and wrote the manuscript. Both authors read and approved the final version of the article.

Availability of data and materials

All data used and included in this review are available from the corresponding author (F.T.C.) and presented in Supplemental Appendix 1 to 3.

Declaration of competing interest

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Appendix A. Supplementary data

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