



An update on the prevalence, chronicity, and severity of atopic dermatitis and the associated epidemiological risk factors in the Singapore/Malaysia Chinese young adult population: A detailed description of the Singapore/Malaysia Cross-Sectional Genetics Epidemiology Study (SMCGES) cohort

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ABSTRACT

Background: Atopic Dermatitis (AD) is a highly pruritic, chronic-recurrent inflammatory skin condition associated with erythematous lesions that affect a significant proportion of the population. Although AD is a non-communicable disease, it can cause pain, unbearable itchiness, sleep disturbance, loss of work productivity, and reduced quality of life. As a heterogeneous disease, AD is influenced by multiple genes and environmental triggers. As such, it is imperative to gain a deeper insight into the intricate gene-environment relationship that results in the manifestation of AD.

Methods: There are 3 objectives in our study. We first aim to update the epidemiological status of AD amongst young adults in Singapore and Malaysia, in particular amongst the Chinese ethnic background. Next, we re-evaluated the possible associated risk factors, identified in our previous meta-analysis and review studies, on the current cohort. Finally, we described here a detailed disease presentation and symptoms profile of our Singapore and Malaysia Cross-Sectional Genetics Epidemiology Study (SMCGES) cohort, which forms the base population for the discovery of

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associated genetic factors in relation to asthma, allergic diseases and skin conditions. Based on a skin prick test (SPT) and investigator-administered medical history responses, we assessed the AD profiles of 11 494 participants and the significant modifiable and non-modifiable factors associated with disease presentation.

Results: The prevalence of AD in the combined population was 13.5%. Chronic and moderate/severe AD were observed in 35.5% and 40.5% of the individuals with AD, respectively. Family history of atopic diseases, prior history of drug allergies, a history of acne, increased household family monthly income, higher number of individuals in the shared household, parental education, sedentary lifestyle, physical activities, alcoholic consumption, and even quality of diet was significantly associated with AD presentation, chronicity, and severity. Among all the factors evaluated, family and personal history of atopic diseases imposed the strongest associated risk.

Conclusions: These findings supported our previous review studies and affirmed that familial history or genetic factors critically influence the development of AD in our population and environment. Environmental and other modifiable factors can also trigger AD throughout the lifetime of individuals who have especially inherited the atopic disease disposition. A better understanding of how these risk factors affect AD individuals in our population can facilitate disease surveillance, monitor disease control, and serve as a description for our future genetic epidemiology studies.

Keywords: Atopic dermatitis, Risk factors, Epidemiology, Ethnic Chinese, Singapore/Malaysia

INTRODUCTION

Background

Atopic dermatitis (AD) is a chronic inflammatory skin disease highly associated with xerosis and pruritus.¹ Although AD is non-communicable, it is often associated with other allergic conditions and is one of the earliest manifestations of the “atopic march”. Most AD patients usually have personal and/or family history of atopic diseases like asthma (AS) and allergic rhinitis (AR).^{2,3} Since its first description in the 1880s, AD prevalence has been rising steadily, and it affects up to 30.0% of children and 10.0% of adults in industrialized countries.⁴

Historically, the Hanifin-Rajka Criteria was the earliest AD diagnostic model and reported high sensitivity and specificity of up to 96.0% and 93.8%, respectively.⁵ The Millennium Criteria were proposed to further condense the Hanifin-Rajka Criteria for better AD diagnosis. For the first time, AD was associated with an elevated total serum immunoglobulin (Ig) E level. Importantly, the detection of allergen-specific IgE as a diagnostic feature for AD had a sensitivity of 81.8% and specificity of 98.8%.⁶ Thus, either a skin prick test

(SPT) or measurement of IgE could be performed to determine the atopic status of an individual.^{1,6} The use of SPT was not popular in some clinical settings, with the fear that the already-hypersensitive AD patients might react severely and have more unnecessary induced irritation to their compromised skin.⁷ However, SPT remained a relatively rapid, straightforward, and inexpensive manner to determine allergic susceptibility. In some cases, SPT had a higher sensitivity when compared to *in-vitro* serum IgE measurements.^{8,9} In some clinical settings, physicians or dermatologists typically diagnose and differentiate AD based on the presentation of clinical symptoms along with the patient’s history of atopic conditions, such as AS and/or AR, with or without SPT or any specific IgE measurements.^{1,4} The common clinical features include the presence of inflamed, patchy rashes, and their distribution at the flexural and dorsal locations.¹ The use of several clinical features remains heterogeneous in diagnosis as they varied with global areas, gender, age, and even environment.¹⁰ In recent years, newer features like conjunctivitis associated with AD were surfacing and made the diagnosis of AD to be even more specific for a particular group or

background.¹¹ There are no 100% effective preventive or prophylactic measures to counter against AD, and the available mainstream treatments for AD remains mainly moisturizers and topical corticosteroids to relieve AD-induced dryness and inflammation.¹² AD is not life-threatening but it harms the self-confidence, quality of life, and mental well-being of AD patients.¹³ Hence, there is a need for a set of standardized and reliable diagnostic criteria to assist contemporary epidemiology research settings and in clinical trials relating to AD treatment.

Although the pathogenesis of AD is not fully described, many studies attributed genetics, immunological, and environmental factors to be critical in promoting AD.^{3,4} Strong evidence suggested that a family history of atopic diseases has been a strong predictor of AD alongside genetic predisposition. The loss-of-function mutation in the filaggrin (FLG) genes led to a dysfunctional epidermal barrier and increased susceptibility to allergens and pollutants in the environment.¹⁴⁻¹⁶ This highlighted that AD is a highly complex disease that involves an intricate interplay of genetic and environmental factors in disease manifestation. It is imperative to understand the risk factors associated with AD with the ultimate goal of identifying new preventive strategies and treatments.

Objective of the epidemiological study

Recently, we reviewed the epidemiological AD-associated risk factors in Asia and revealed a comprehensive list of significant personal, family, and environmental factors. This includes non-modifiable factors such as a family history of atopic diseases, increasing age, and gender. With the modifiable factors assessed, the link between maternal smoking and active smoking with AD pathogenesis was the strongest.¹⁷ Hence, this study aims to conduct an epidemiological study to identify, compare, and evaluate the different AD-associated risk factors observed in our previous review. It also seeks to identify novel risk factors relating to AD presentation, severity, and chronicity. The novel insights can assist further AD research and the development of prophylactic strategies and targeted therapeutics.

With the increasing global prevalence of AD, including in Singapore and Malaysia, it would be paramount to identify potential AD risk factors specific to these regions. Past studies have shown that close to 21.5% of Singapore's adolescents suffered from AD, and the prevalence was higher among the Chinese (21.6%).¹⁸ The high prevalence of AD observed in Singapore was consistent with the global findings, especially in other developed countries.¹⁹ Thus, we want to understand the pattern of AD by updating the evolution of its risk factors in the Singapore and Malaysian environment. This approach may refine our understanding of AD and assist in future disease intervention and management.

Finally, we are also interested in understanding and studying the underlying basis of AD in relation to other atopic diseases (AS, AR) and skin conditions (acne, skin aging). As highlighted in our studies, many of these complex diseases (AS, AR, and acne) are highly associated with genetic components.^{17,19-22} This paper also serves to update and describe the Singapore and Malaysia cross-sectional cohort for our upcoming genetic studies.^{23,24}

MATERIALS AND METHODS

Participants and data collection

Altogether 16 336 participants were recruited on a voluntary basis from Singapore and Malaysia in an ongoing collection to investigate the epidemiology and genetics of allergic diseases. The collection was conducted in National University of Singapore, Singapore (2005 until 2019), Universiti Tunku Abdul Rahman (UTAR), Malaysia, in 2016 and 2018, and Sunway University, Malaysia, in 2019. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. Prior to their participation, all participants signed an informed consent form. The participants then completed a set of investigator-administered, validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires to obtain their sociodemographic, personal lifestyles, dietary habits, familial and personal medical history, and acne history profiles. Missing data sets, values, and invalid responses concerning age, gender, race, and eating habits were excluded from the analysis. Out of the remaining

participants, most (83.4%) belong to the Chinese ethnic. The Chinese individuals ($n = 11,494$) were selected to provide a representative overview of AD epidemiology in the combined Singapore and Malaysia ethnic Chinese young adult population. This avoids ascertainment bias that will affect the interpretation and quality of our results and prevent the loss of statistical power. The other ethnic race groups (of Malay and Indian backgrounds) were also ascertained in our study but would be analysed separately.

Disease classification and definitions

Using the ISAAC validated core questionnaire as a guideline, the study assessed the presentation and classification of AD in 11 494 participants. All participants were also tested for their atopic status by performing an SPT with 4 common aero-allergens. That includes 2 different species of common house dust mites (*Blomia tropicalis* and *Dermatophagoides pteronyssinus*), an oil palm pollen (*Elaeis guineensis*), and a fungus species (*Curvularia lunata*). *Blomia tropicalis* and *Dermatophagoides pteronyssinus* were highly sensitive and specific markers for allergic sensitization in Singapore.²⁵ Recently, sensitization to *Curvularia lunata* was also proven to be highly associated with allergic diseases.²⁶ An SPT response is positive when the wheal diameter of ≥ 3 mm appeared with either of the house dust mites when compared to positive (histamine) and negative (saline) controls. The absence of wheal of ≥ 3 mm and erythema for both house dust mites indicated the individual to be SPT negative.

In addition to their SPT reactivity, the study classified participants based on their responses to questions on AD clinical symptoms. An AD case is affirmative to "have you ever had an itchy rash which was coming and going for at least six months?" and "has this itchy rash at any time affected any of the following places: The folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, cheeks, ears or eyes?" along with being SPT positive. The participant is categorised as an AD non-atopic control if they are negative for both questions and being SPT negative. SPT positive participants who answered "No" to both questions on AD clinical symptoms are categorized as an atopic

control. Other combinations that differed from the above criteria were excluded.

We also further evaluated 2 AD phenotypes amongst the sample of 1550 AD cases. AD cases were stratified into either the non-chronic (intermediate) or chronic group based on their responses to "has this rash cleared completely at any time during the last 12 months." We classified AD cases into different degrees of severity (mild, moderate, and severe) based on the question, "in the past 12 months, how often, on average, have you been kept awake at night by this itchy rash." Lastly, we also cross-validated a smaller subset of our population that presented with "has this itchy rash at any time affected any of the following places: The folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, cheeks, ears or eyes?" to a doctor-diagnosed observation. High sensitivity (90.6%) and specificity (85.5%) were observed.

To ensure reliability and robustness in our study, we re-analysed the diagnosis in the clinical setting using the same risk factors and termed it AD⁺. Instead of incorporating the SPT findings, the same population was assessed for the presence of AD symptoms with either AS or AR. By excluding the criterion of SPT reaction, the participants were grouped either as a case or a control with no atopic controls.

Food scores

Quality of diet based on glycaemic index score (QDGIS) and Diet Quality based on dietary fats score (DQDFS) were constructed according to the participant's responses to the section that examined 16 kinds of foods. We determined foods of high glycaemic index (GI) levels to have a GI value ≥ 55 (burgers/fast food, cereals, rice, and potatoes) and low GI levels to have a GI value < 55 (fruits, vegetables, pulses, nuts, milk, and probiotic drinks).²⁷ The remaining 6 foods (meat, seafood, margarine, butter, eggs, and pasta) that have little or no carbohydrates were excluded from the QDGIS analysis. Similarly, foods were grouped into high (meat, seafood, margarine, butter, eggs, milk, and burgers/fast food) and low-fat content (fruits, vegetables, pulses, cereals, rice, and potatoes). The remaining three foods (pasta, nuts, and probiotic drinks) were excluded

from the DQDFS analysis. Thereafter, different GI and fat scores were assigned based on the rubric stated in Manousos et al.²⁷ Based on their intake frequency in a week and types of GI/fat, either a positive or negative score (7 for most or all days and 2 for once or twice per week) was assigned. No score was given to responses to never or only occasionally. A positive score was assigned for the consumption of low GI foods and high-fat foods in QDGIS and DQDFS, respectively. Participants were finally grouped into three main categories each for QDGIS: Poor (≤ 0), Moderate (0.01–8.99), and Good (≥ 9) and DQDFS: High Fat Score (≥ 0), Moderate Fat Score (–8.00 to –1.00) and Low Fat Score (≤ -9).

Statistical analysis

Microsoft Excel (<http://office.microsoft.com/en-us/excel/>) was used for data entry. The data was cleaned by removing invalid or inconsistent responses before analysing it with R program version 2021.09.0.351 (RStudio Team, 2021). Binary logistic regression was used to model the association between AD presentation and the potential risk factors. Univariate analyses were first conducted, followed by multivariate analyses that adjusted for age and gender. Significant factors identified were tested further with an additional multivariate analysis that adjusted for age, gender, and familial AD. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance of results was defined as $p < 0.05$, and the OR range did not cross 1.000.

RESULTS AND DISCUSSION

Population description

From the collective sampled population from Singapore and Malaysia, the total database consists of 11 494 Chinese subjects. Table 1 describes the distribution of the demographic characteristics. The Singapore population (91.6%), compared to the Malaysia population (8.44%), contributed more to the combined database. Most participants were undergraduate students aged around 22.19 (SD = 5.26). The male to female ratio was about 1:1.375, with more females (57.9%) outnumbering males (42.1%). According to Singapore's Ministry of Social and Family Development (MSF), Singapore has a higher

proportion of females, with only 957 males/1000 females.²⁸ The body mass index (BMI) ranged from 8.02 to 72.5 (mean = 20.87, SD = 3.15) with a mean height and weight of 165.5 cm and 57.48 kg, respectively. Most subjects (60.3%) were within the healthy BMI range (18.0–23.0), and less than 30% of them were unhealthy (underweight/overweight). Amongst the unhealthy population, there were slightly more overweight individuals with BMI >23.0 (16.8%) than underweight individuals with BMI <18.0 (12.4%). This was consistent with the reported increasing prevalence of higher body mass index and overall lower physical activities among Singaporeans between the age of 18–29, with 11.4% being obese.²⁹ Additionally, more than half of the combined population stayed in a household with ≥ 2 people, with 50.4% and 43.4% living with 2–4 and ≥ 4 people, respectively. The average household size in Singapore was about 3.22 in 2020.³⁰ The majority showed a positive SPT reaction (up to 69.0%) with a smaller proportion of participants showing a negative SPT reaction (30.4%). Similar to our previous studies on allergic sensitization, most individuals in Singapore would be reactive to house dust mites.³¹

Although the proportion of females (66.4%), overweight individuals (32.7%), and households with ≥ 4 people (63.6%) were higher in Malaysia than Singapore, it did not affect the overall population. Otherwise, no significant differences were observed in age, height, weight, and SPT reactivity between the Singapore and Malaysia population. These consistencies in the population comparison further add confidence to our analysis, making the results using the combined population more representative and reliable.

AD disease prevalence and presentation

Out of the 11 494 participants, more than half of them fell under the atopic control (55.6%) and around a quarter of them were classified as AD non-atopic control (25.9%) and with 1550 participants to be AD cases (13.5%) (Table 2).

The overall response rate was high (99.7%) for the main question that addressed the presence of an itchy rash in the last 12 months. As part of the disease classification criteria, all AD cases reported positive to "have you ever had an itchy rash which

Variables	Malaysia n (%)	Singapore n (%)	Overall n (%)
Total Participants (n)	970 (8.44%)	10,524 (91.6%)	11,494 (100%)
Mean Age (years) ± SD*	21.17 ± 4.10	22.29 ± 5.35	22.19 ± 5.26
Mean Height (cm) ± SD	162.60 ± 8.93	165.80 ± 8.98	165.50 ± 9.03
Mean Weight (kg) ± SD	59.29 ± 13.29	57.30 ± 11.41	57.48 ± 11.61
Mean BMI ± SD	22.47 ± 4.62	20.71 ± 2.91	20.87 ± 3.15
Gender			
• Male	326 (33.6%)	4518 (42.9%)	4844 (42.1%)
• Female	644 (66.4%)	6006 (57.1%)	6650 (57.9%)
Body Mass Index (BMI)**			
• Healthy (18.0–23.0)	530 (54.6%)	6404 (60.9%)	6934 (60.3%)
• Underweight (<18.0)	96 (9.90%)	1335 (12.7%)	1431 (12.4%)
• Overweight (>23.0)	317 (32.7%)	1617 (15.4%)	1934 (16.8%)
N/A***	287 (2.80%)	1168 (11.1%)	1195 (10.4%)
Number of People in the Household			
• <2	22 (2.30%)	472 (4.50%)	494 (4.30%)
• 2 to 4	314 (32.4%)	5481 (52.1%)	5795 (50.4%)
• ≥4	617 (63.6%)	4374 (41.6%)	4991 (43.4%)
N/A***	17 (1.80%)	197 (1.90%)	214 (1.86%)
Skin Prick Test (SPT)			
• Positive	640 (66.0%)	7296 (69.3%)	7936 (69.0%)
• Negative	328 (33.8%)	3161 (30.0%)	3489 (30.4%)
Not Done	2 (0.2%)	67 (0.6%)	69 (0.6%)

Table 1. The overall demographics and participant characteristics of the Singapore & Malaysia combined population * SD refers to standard deviation. ** BMI (kg/m²) was calculated by the division of body mass (weight) with the square of height. In this study, BMI was referenced to the Asian class. ***N/A (not applicable) refers to responses that are either left blank or invalid.

was coming and going for at least six months?" and "has this itchy rash at any time affected any of the following places: The folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, cheeks, ears or eyes?". Based on the question that investigates recent itchy rash, "have you had this itchy rash at any time in the last 12 months?", 88.9% of the 1550 AD cases still experienced the itchy rash in their flexural regions in the past year.

On the other hand, a small proportion of the AD non-atopic controls did experience an itchy rash in the past six months ($n = 176$), with only 118 of them having the same itchy rash persisting in the last 12 months. The atopic control groups, however, had more individuals positive to ever having a rash ($n = 421$), and 267 of these individuals had the same itchy rash ongoing in the past year. However, none of these individuals from the AD non-atopic control or atopic control group had

	AD case group n (%)	AD non-atopic control group n (%)	AD atopic control group n (%)
Total Participants (n)	1550 (13.5%)	2978 (25.9%)	6386 (55.6%)
Questions			
Have you ever had an itchy rash which was coming and going for at least six months? • Yes	1550 (100%)	176 (5.91%) ^a	421 (6.59%) ^b
Have you had this itchy rash at any time in the last 12 months? • Yes	1378 (88.9%)	118 (3.96%) ^c	267 (4.18%) ^d
Has this itchy rash at any time affected any of the following places: The folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, cheeks, ears or eyes? • Yes	1550 (100%)	0 (0.00%)	0 (0.00%)
Ever had an itchy rash & Itchy rash at flexural regions & Skin Prick Positive & Have you ever had eczema? • Yes	1550 (100%)	0 (0.00%)	0 (0.00%)
Has this rash cleared completely at any time during the last 12 months?			
• Yes	965 (62.3%)	-	-
• No	550 (35.5%)	-	-
NA	35 (2.26%)	-	-
In the past 12 months, how often, on average, have you been kept awake at night by this itchy rash?			
• Never	891 (57.5%)	-	-
• <1 night/week	460 (29.7%)	-	-
• ≥1 night/week	168 (10.8%)	-	-
N/A	31 (2.00%)	-	-
In the past 12 months, have you suffered from dry skin?			
• Yes	564 (36.5%)	-	-
• No	396 (25.5%)	-	-
N/A	590 (38.0%)	-	-

Table 2. Atopic dermatitis characteristics of the Singapore & Malaysia combined population. AD case is defined as a skin prick test (SPT) positive individual with AD symptoms of having an itchy flexural rash for at least 6 months ^aResponse to an itchy rash for ≥6 months but the participant may not have the rash on flexural areas and/or recovered in the last 12 months and/or SPT negative and/or answered no to doctor-diagnosed atopic dermatitis. ^bSame criteria as stated in ^a but participant is SPT positive. ^cThe participant had an itchy rash for ≥6 months and occurred in the past 12 months but the rash may not be on flexural areas and/or SPT negative and/or answered no to doctor-diagnosed atopic dermatitis. ^dSame criteria as stated in ^a but participant is SPT positive.

(A) Socioeconomic			Univariable logistic regression			Multivariable logistic regression ^a				
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Gender	<i>Female</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Male</i>	1.890	1.662	2.148	0.000	1.925	1.693	2.190	0.000
II.	Age group	>24	1.000	(REF)		-	1.000	(REF)		-
		20-24	1.089	0.906	1.312	0.368	1.070	0.888	1.293	0.477
		<19	1.079	0.873	1.337	0.483	1.262	1.016	1.570	0.036
III.	Total household income per capita (SGD)^b	<S\$2000	1.000	(REF)		-	1.000	(REF)		-
		S\$2000 to \$3999	1.581	1.318	1.899	0.000	1.592	1.325	1.918	0.000
		S\$4000 to \$5999	2.068	1.684	2.543	0.000	2.141	1.738	2.640	0.000
		≥S\$6000	2.328	1.916	2.833	0.000	2.366	1.941	2.887	0.000
IV.	Total household number	≤3	1.000	(REF)		-	1.000	(REF)		-
		4	2.087	1.761	2.479	0.000	2.140	1.802	2.547	0.000
		≥5	2.172	1.822	2.595	0.000	2.150	1.800	2.573	0.000
V.	Paternal education	<i>Primary</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Secondary</i>	0.823	0.681	0.995	0.044	0.833	0.687	1.011	0.063
		<i>Tertiary</i>	0.723	0.599	0.873	0.000	0.726	0.600	0.880	0.001
VI.	Maternal education	<i>Primary</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Secondary</i>	0.952	0.799	1.137	0.587	0.954	0.798	1.142	0.608
		<i>Tertiary</i>	0.800	0.665	0.964	0.019	0.807	0.669	0.976	0.026
XVII.	Birthplace	<i>Local</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Migrant</i>	0.205	0.169	0.247	0.000	0.200	0.165	0.242	0.000

<i>(B) Personal Lifestyles</i>			Univariable logistic regression			Multivariable logistic regression ^a				
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Alcohol	<i>Non-drinker</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Occasional</i>	1.280	1.126	1.457	0.000	1.182	1.036	1.347	0.013
		<i>Frequent</i>	1.530	0.945	2.444	0.078	1.358	0.834	2.181	0.210
		<i>Drinker</i>	1.288	1.134	1.464	0.000	1.187	1.042	1.352	0.010
II.	TV/computer (sedentary lifestyle)	<i><1 h</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>1 to 3 h</i>	1.306	1.091	1.567	0.004	1.347	1.121	1.621	0.002
		<i>>3 to 5 h</i>	1.277	1.054	1.548	0.013	1.266	1.042	1.540	0.018
		<i>>5 h</i>	1.331	1.088	1.629	0.005	1.346	1.098	1.652	0.004
III.	Physical Activities (outdoor lifestyle)	<i>> 5 h</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Never or only occasionally</i>	1.328	1.160	1.522	0.000	1.189	1.035	1.366	0.015
		<i>Once or twice per week</i>	1.590	1.291	1.956	0.000	1.301	1.050	1.611	0.016
		<i>Most or all days</i>	2.342	1.929	2.847	0.000	2.377	1.953	2.897	0.000

<i>(C) Familial History of Acne</i>			Univariable logistic regression			Multivariable logistic regression ^a				
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Acne ever	<i>No</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Yes</i>	1.235	1.001	1.526	0.050	1.276	1.031	1.583	0.026
II.	Maternal acne	<i>No</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Yes</i>	1.457	1.125	1.888	0.004	1.454	1.120	1.888	0.005
III.	Parental acne	<i>None</i>	1.000	(REF)		-	1.000	(REF)		-
		<i>Only 1 parent</i>	1.235	0.884	1.721	0.213	1.232	0.877	1.725	0.226
		<i>Both</i>	1.452	1.026	2.049	0.034	1.445	1.017	2.048	0.039

(D) Dietary Habits			Univariable logistic regression			Multivariable logistic regression ^a				
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Quality of Diet based on Glycaemic Index Score (QDGIS)	Poor	1.000	(REF)		-	1.000	(REF)		-
		Moderate	0.840	0.717	0.984	0.030	0.844	0.719	0.991	0.039
		Good	0.837	0.716	0.980	0.027	0.871	0.743	1.022	0.091
		Moderate/Good	0.838	0.729	0.966	0.014	0.858	0.744	0.990	0.035
II.	Dietary Quality based on Dietary Fat Score (DQDFS)	Low Fat Score	1.000	(REF)		-	1.000	(REF)		-
		Moderate Fat Score	1.282	1.098	1.497	0.000	1.215	1.039	1.422	0.015
		High Fat Score	1.662	1.427	1.938	0.000	1.554	1.331	1.816	0.000
		Moderate/High	1.461	1.277	1.674	0.000	1.375	1.199	1.578	0.000
(E) Co-morbidities			Univariable logistic regression			Multivariable logistic regression ^a				
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Asthma (AS)	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	7.773	6.234	9.766	0.000	7.428	5.942	9.353	0.000
II.	Allergic Rhinitis (AR)	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	6.295	5.499	7.214	0.000	6.278	5.474	7.208	0.000
III.	Personal drug allergy	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	1.856	1.524	2.259	0.000	1.842	1.508	2.250	0.000
IV.	Paternal drug allergy	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	1.473	0.835	2.564	0.173	1.419	0.797	2.493	0.226
V.	Maternal drug allergy	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	1.766	1.177	2.644	0.006	1.858	1.231	2.797	0.003
VI.	Parental drug allergy	No	1.000	(REF)		-	1.000	(REF)		-

		Yes	1.892	1.365	2.620	0.000	1.922	1.380	2.674	0.000
VII.	Body Mass Index (BMI)	Healthy (18.0-23.0)	1.000	(REF)		-	1.000	(REF)		-
		Underweight (<18.0)	1.057	0.875	1.274	0.564	1.103	0.909	1.336	0.317
		Overweight (>23.0)	1.365	1.155	1.613	0.000	1.202	1.011	1.428	0.037

<i>(F) Familial History of Atopic Dermatitis (AD)</i>			Univariable logistic regression				Multivariable logistic regression ^a			
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Paternal AD	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	4.719	3.625	6.186	0.000	4.868	3.725	6.405	0.000
II.	Maternal AD	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	2.540	2.038	3.167	0.000	2.759	2.205	3.456	0.000
III.	Parental AD	None	1.000	(REF)		-	1.000	(REF)		-
		Only 1 parent	3.624	2.944	4.468	0.000	3.910	3.162	4.844	0.000
		Both	4.219	2.307	7.932	0.000	4.597	2.492	8.711	0.000
IV.	Sibling AD	0	1.000	(REF)		-	1.000	(REF)		-
		1	2.110	1.757	2.535	0.000	2.226	1.847	2.684	0.000
		2	2.030	1.545	2.666	0.000	2.097	1.589	2.767	0.000
		≥ 3	2.751	1.672	4.573	0.000	2.966	1.781	4.989	0.000
V.	Familial AD	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	3.147	2.717	3.649	0.000	3.363	2.892	3.914	0.000

(G) Familial History of Allergic Rhinitis (AR)			Univariable logistic regression				Multivariable logistic regression^a			
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Paternal AR	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	3.969	2.625	6.097	0.000	3.758	2.467	5.812	0.000
II.	Maternal AR	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	3.461	2.426	4.982	0.000	3.271	2.278	4.736	0.000
III.	Parental AR	None	1.000	(REF)		-	1.000	(REF)		-
		Only 1 parent	4.016	2.881	5.647	0.000	3.858	2.750	5.457	0.000
		Both	3.672	1.441	10.00	0.007	3.111	1.197	8.618	0.002
IV.	Sibling AR	0	1.000	(REF)		-	1.000	(REF)		-
		1	1.270	0.998	1.611	0.049	1.283	1.004	1.634	0.044
		2	1.647	1.196	2.263	0.002	1.625	1.173	2.245	0.003
		≥ 3	2.293	1.405	3.767	0.001	2.471	1.493	4.121	0.000
V.	Familial AR	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	1.722	1.396	2.121	0.000	1.678	1.354	2.076	0.000

(H) Familial History of Asthma (AS)			Univariable logistic regression				Multivariable logistic regression^a			
AD presentation (case vs. non-atopic control)			OR	95% CI		P	OR	95% CI		P
I.	Paternal AS	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	2.463	1.742	3.491	0.000	2.565	1.805	3.657	0.000
II.	Maternal AS	No	1.000	(REF)		-	1.000	(REF)		-
		Yes	2.510	1.879	3.360	0.000	2.558	1.907	3.437	0.000
III.	Parental AS	None	1.000	(REF)		-	1.000	(REF)		-
		Only 1 parent	2.736	2.115	3.544	0.000	2.807	2.162	3.653	0.000
		Both	1.358	0.461	3.667	0.554	1.488	0.502	4.053	0.446

tertiary level conferred a lower OR of getting AD, suggesting a higher parental education to be protective against AD development (refer to [Table 3](#) section [AV, AVI]). Although participants whose fathers attained a secondary education were significant in the univariate analysis, the same association did not remain significant after age and gender adjustment. Migrants, as compared to locals, are significantly associated with a lower risk for AD (OR^a: 0.200) (refer to [Table 3](#) section [AVII]).

The frequency of alcohol consumption was classified as such, drinker (>4 days/week), frequent (1-4 days/week), and occasional (≤3 days a month). The risk of AD was higher amongst participants who drink alcohol frequently (OR^a: 1.358) when compared to occasional drinkers (OR^a: 1.182). Nonetheless, drinkers (frequent/occasional) had a higher significant risk of developing AD (OR^a: 1.187) (refer to [Table 3](#) section [BI]). Sedentary lifestyles, as characterized by frequent TV/computer usage/day, were identified to be positive with AD development, with the highest risk observed for 1-3 h (OR^a: 1.347) and >5 h (OR^a: 1.346) (refer to [Table 3](#) section [BII]). Similarly, an outdoor lifestyle measured by physical activities/week revealed a positive association with AD development. Correspondingly, the more time spent on physical activities/week had an increasing effect on the OR, with most or all days (OR^a: 1.301) higher than once or twice/week (OR^a: 1.189) (refer to [Table 3](#) section [BIII]).

While this study also assessed the influence of dietary factors and quality by deriving two novel dietary index scores constructed on the summation of the GI value, dietary fat, and intake frequency of various foods. Moderate QDGIS was to be significantly associated with AD (OR^a: 0.844). When compared to the poor QDGIS group, the combined moderate/good QDGIS group remained significant (OR^a: 0.858) (refer to [Table 3](#) section [DI]).

Increased fat scores were significantly associated with an increased AD presentation (OR^a: 1.554) (refer to [Table 3](#) section [DII]). Thus, our dietary indices suggest that the frequent consumption of a diet either high in GI or fat was positively associated with AD presentation.

The history of familial acne seems to affect the development of AD whereby either maternal acne (OR^a: 1.445) or both parents having acne (OR^a: 1.454) showed significant association to the participant's AD status. The odds of AD development were also higher in the participants who reported having acne (OR^a: 1.276) than those without acne. Overall, acne was positively associated with AD development (refer to [Table 3](#) section [CI-CIII]).

Significantly, individuals with co-morbidities such as AS, AR, and personal drug allergies were more likely to develop AD. Asthmatic participants had the highest risk amongst the other risk factors assessed in this study (OR^a: 7.428). The risk was equally prominent in participants with AR (OR^a: 6.278) (refer to [Table 3](#) section [DI, DII]). In this study, a cut-off value of BMI >23.0 (Asian Class) determines an individual being overweight and unhealthy. Participants with AD were only significantly associated with a higher BMI (OR^a: 1.202) compared to the non-atopic control group (refer to [Table 3](#) section [DVII]).

Interestingly, for individuals who had a history of personal drug allergy, their likelihood of AD development was high (OR^a: 1.842) (refer to [Table 3](#) section [DIII]). Individuals with maternal drug allergies were equally risky (OR^a: 1.858), and parental drug allergy imposed a slightly higher risk (OR^a: 1.922) (refer to [Table 3](#) section [DV, DVI]). Despite paternal drug allergy being positively related to AD as a risk factor, the effects were insignificant when comparing the AD cases with the AD non-atopic control. Personal drug allergies to non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics were at 73.0% and 13.0%, respectively. While the incidence of maternal drug allergy to NSAIDs and antibiotics was 19.0% and 34.0%, respectively (data not shown here).

Aside from the above factors, no significant association with AD presentation was observed for other evaluated factors, including paternal, siblings and familial acne, pets ownership, polycystic ovary syndrome (PCOS), menstrual cycle, and oral intake of contraceptive pills ([Supplemental Table 2](#)). Nonetheless, we did not report smoking as a potential risk factor to AD presentation as most participants surveyed were non-smokers, the analysis for smoking would be confounded

by the small sample-size effect and the lack of statistical power.

Familial history is the strongest predisposing risk factor for AD presentation

A positive family history of AD was significantly associated with an increased risk of AD presentation even with adjustment of age and gender (refer to [Table 3](#) section [EI-EIV]). AD prevalence was more frequent in participants whose mother had a history of AD (OR^a: 2.759) relative to participants whose mother had no AD. While compared to maternal AD, the likelihood of AD development was remarkably higher in participants with paternal AD (OR^a: 4.868). The association to AD in participants whose both parents had AD was significantly higher (OR^a: 4.597) than participants with only 1 parent having AD (OR^a: 3.910). The risk was higher for participants with siblings having AD than those without, with the effects at the strongest with ≥ 3 siblings (OR^a: 2.966).

AD is essentially the first manifestation of an atopic diathesis (AS and AR) that affects genetically predisposed individuals. Thus, this study also evaluates the association between family history of AS and AR to AD. Similar to the familial history of AD, both diseases were significantly associated with AD development. Akin to the analysis of the family history of AD, participants with paternal AR imposed a higher risk (OR^a: 3.758) than maternal AR (OR^a: 3.271). Parental AR, be it both parents or one parent having AR, presented a positive association to AD. Siblings AR, however, showed a significant additive effect, with the risk observed to be the highest in ≥ 3 siblings having AR (OR^a: 2.471) (refer to [Table 3](#) section [FI-FIV]). We recaptured the same significant association to AD development in the analysis for participants with a familial history of AS. The risk of AD development was similar in participants with paternal AS (OR^a: 2.565) and maternal AS (OR^a: 2.558). The association became weaker for participants with both asthmatic parents (OR^a: 1.488) when compared to only 1 asthmatic parent (OR^a: 2.807). Similarly, the history of sibling AS was significantly associated, and there was also an additive effect observed with the highest risk amongst ≥ 3 siblings having AS (OR^a: 2.085) (refer to [Table 3](#) section [GI-GIV]). When we combined paternal, maternal, and

sibling AD history, the association to AD development with family AD was the highest (OR^a: 3.363), followed by family AS (OR^a: 1.692), and then family AR (OR^a: 1.678) (refer to [Table 3](#) section [EV, FV, GV]).

Among all the non-modifiable factors, a positive history of familial AD disease was consistent in demonstrating an increased odds of AD. We used an additional multivariate analysis adjusted for familial AD (on top of the previous age and gender) to re-analyse the same significant factors ([Supplemental Table 3](#)). The criteria for familial AD requires an affirmative response from the participant to a positive AD status in either the biological father, mother or any of the siblings. Likewise, the following factors such as income, maternal education, alcoholic consumption, DQDFS, and drug allergy (personal, paternal, maternal, and parental) between AD presentation remained significantly associated. Additionally, participants with fathers attaining a secondary school education became significantly associated with AD presentation (refer to [Supplemental Table 3](#) section [AIII]). This suggested that all the risk factors identified were independent of familial AD. The risk of asthmatic participants developing AD remained the highest for an OR^a value above 7.200. The risk of AR participants for AD development was the second-highest for an OR^a value above 6.000 (refer to [Supplemental Table 3](#) section [DI, DII]). Remarkably, there was an increase in the OR^a values for total household numbers after familial AD was adjusted (refer to [Supplemental Table 3](#) section [AII]). On the other hand, factors like BMI, TV/computer usage, physical activities, QDGIS, and acne (personal, maternal, and parental) lost their significance after familial AD adjustment but, their association remained in the same direction. Despite decrement observed in the OR^a value for paternal, maternal, and parental AR, these factors were still significantly and strongly associated with AD presentation. The association for paternal AS, maternal AS, and parental AS were less affected, and they remained significant. Prominently, the association of siblings (≥ 2) with AR and siblings (≥ 1) with AS became insignificant (refer to [Supplemental Table 3](#) section [EIV, FIV]).

Risk factors associated between different forms of AD severity and AD chronicity

For AD severity, the association of personal AS and AR became stronger in moderate/severe AD cases with the respective ORs^a (refer to [Supplemental Table 4](#) section [DI, DII]) to be even higher than those observed in AD presentation. Interestingly, the OR^a for personal AS (OR^a: 8.323) for moderate/severe AD was the highest among all OR^a values identified in this study. Similarly, the association of a personal AS hit an OR^a value higher than 8.000 in participants with chronic AD (refer to [Supplemental Table 5](#) section [DI]). Compared to AD presentation, the association of familial history of AD became stronger with chronic AD (refer to [Supplemental Table 5](#) section [EI-EV]). The association of acne (personal, maternal, and parental) became insignificant with chronic AD (refer to [Supplemental Table 5](#) section [CI-CIII]). Otherwise, all other associations of significant risk factors identified for AD presentation remained unchanged (refer to [Supplemental Tables 4 and 5](#)). In conclusion, the identified risk factors significantly affect the overall development and progression of AD.

Consistent significant risk factors were identified between AD SPT-based and AD⁺

Though the population size for AD⁺ cases ($n = 2324$) and controls ($n = 9170$) became bigger, the overall population distribution remained similar to those in AD SPT-based (data not shown here). When analysed for the same set of risk factors in AD⁺, most of the association was highly consistent with those identified in AD SPT-based. Particularly gender, age, income, familial history of AD, AR, AS, personal and maternal drug allergies remained significantly associated even in AD⁺ (refer to [Supplemental Table 6](#)). Thus, this supported the use of an SPT-based AD definition in our study.

Risk factors and their association with atopic statuses

The effects of increased household people, parental education, alcohol consumption, physical activities, dietary quality, history of acne, and maternal drug allergies lost their significance when compared to the atopic controls. However, factors

such as increased household monthly income, increased TV/computer usage, overweight BMI, personal and family histories of atopic diseases, personal and parental drug allergies remained significantly associated with AD presentation. Interestingly, the comparison with atopic controls significantly associated paternal drug allergies with AD presentation (refer to [Supplementary Table 7](#)). Thus, these differences suggested that some factors may be independent of one's atopic status to SPT and may be implicit in affecting AD symptomatic development.

DISCUSSION

ISAAC can be utilized to obtain the baseline measurements to assess future trends and form a basis for future research on AD.³² The British dermatologists had established the UK Working Party Criteria to validate AD diagnosis based on questionnaire data.^{33,34} We integrated these questions into the core questions of the ISAAC questionnaire. The question on an itchy rash coming and going for the past 12 months helped to discriminate the usual mild-moderate AD from non-atopic AD (and other similar dermatological conditions). The UK working party validated this question to have high sensitivity (91.0%) and specificity (46.0%).^{33,34} Moreover, the additional question on flexural rash further improved the sensitivity to 94.0% and specificity to 81.0%.^{33,34} Similar validation studies using the ISAAC-diagnosis have high specificity and sensitivity within different populations and ethnic groups.^{35,36}

In our Singapore/Malaysia cohort, we further validated our use of SPT in AD diagnosis by comparing it to AD⁺ as a gold standard for clinical diagnosis. The sensitivity and specificity of using SPT and clinical presentations were high at 90.6% and 85.5%, respectively as compared to AD⁺. Furthermore, the sensitivity and specificity for "ever had an itchy rash" were 57.6% and 85.0%, respectively. For the question on the flexural rash, the sensitivity and specificity were 77.7% and 78.9%, respectively. The question for "itchy rash in the last 12 months" had a sensitivity and specificity of 63.9% and 78.4%, respectively. Thus, this indicates that our questionnaire is well-suited for use in the Singapore/Malaysia population.

As we defined our AD cases for this epidemiological study to be dependent on SPT reaction, it offered us the opportunities to evaluate the association of the risk factors concerning AD instead of non-atopic dermatitis. The current debate on AD pathogenesis is mainly around genetic predispositions but not all atopic individuals develop eczema.^{1,3,4} In our study, we have 6386 atopic controls who were SPT positive but not presented with symptoms for AD and not doctor-diagnosed for eczema. With that understanding, there could be other profound environmental and immune triggers to onset AD at any stage in life. Therefore, it is critical to analyse for novel risks that may affect the pathophysiology and development of skin disorders even in atopic individuals. As our Singapore and Malaysia combined database is large and still expanding, it formed a solid foundation for further research in our future genetic epidemiology studies.

Despite Singapore and Malaysia being countries with racial diversity, there is an unequal proportion and probability of sampling among some races. As a consequence, the results analysed may not be representative and accurate about a certain racial group in the population. Although we can stratify the sample population into different races, the group for other races like Indian and Malay may be too small ($n < 2000$) and be statistically underpowered. For this reason, we only selected the major racial group of Chinese to be included in our study. Chinese (75.9%) is the predominant ethnic group in Singapore.³⁷ Future analysis and description of AD epidemiology in other ethnicities such as Malay and Indian are possible when the database for these ethnicities become sufficiently larger in our subsequent collection.

Among the 11 494 Chinese participants, 60.3% are in a healthy BMI range of 18.0–23.0. The mean BMI amongst the population is 20.87. We associated an unhealthy BMI of >23.0 with an increased prevalence of AD presentation in our study. A higher mean BMI can be significantly higher in individuals with severe AD and especially at the age between 12 to 14.³⁸ Another recent study points to a higher risk of AD onset in children with higher total cholesterol level.³⁹ Very importantly, an unhealthy BMI associated with obesity had a higher tendency to develop complicated chronic diseases (heart diseases,

diabetes, cancers, anaemia etc) in addition to AD.⁴⁰ Thus, maintaining a healthy BMI is essential to reduce and prevent the development of comorbidities like AD and other diseases. As most participants are in the healthy BMI range, there would be a lower risk of AD development in these individuals. Further studies may be required to explore the effects of a higher BMI in influencing the presentation of AD.

The prevalence rate of AD stands at 13.5% based on our survey questions on AD symptoms and SPT results. Malaysia has the highest prevalence of AD among children across Asia (13.4%) in the same period and highlighted AD as a substantial challenge in the environment like Malaysia and Singapore. All the AD cases had an itchy rash that occurred at the flexural regions for at least six months. A large proportion (88.9%) of AD cases were continually affected by the same flexural rash in the last 12 months, indicating that they have not recovered. Although 11.1% of AD cases did not show any flexural rash in the last 12 months, it was not a clear indication of the recovery status as there might be fear of AD reoccurrence in the future. AD is commonly regarded as an early childhood disease, with many children reporting improvements in AD recovery as they grow older.⁴² A previous study in Singapore schools revealed an AD prevalence of 20.8% for school children (aged 7 to 12) and teenagers (aged 12 to 16).¹⁸ The prevalence was the highest among the 7 years old (22.7%), followed closely by those of 16 years old (21.5%). The study listed heat and sweating as one of the main aggravating factors for AD in Singapore.¹⁸ In another earlier study, 13.6% of AD patients in Singapore displayed late AD onset (after 21 years old), suggesting that environmental conditions may play a strong and active role in influencing AD development in adulthood.¹⁹

The prevalence of chronic rash in our AD cases was at 35.5% and was considerably high, given that AD is a childhood-associated disease. Although many affected patients grow out of mild childhood AD as they grow older, AD can reoccur at any point in their life after a prolonged environmental trigger.^{41,42} Likewise, multiple factors can trigger and worsen AD with various degrees of remission. More than half of our AD cases were mild (57.5%) and around 40.5% were

moderate/severe. Two studies conducted in Singapore reported increased severity of AD symptoms among the 12–15 year olds.^{18,19} Dry skin accompanied by cracks and sores is a characteristic symptom of AD and reflects a dysfunctional skin barrier. Among the AD cases, 36.5% had dry skin and 25.5% did not have dry skin. A recent cross-sectional study emphasized a positive association of dry skin with atopic disposition.⁴³ Individuals with genetic predispositions to atopic diseases and dry skin would be affected by AD to a larger extent. Hence, they should be extra cautious about its potential environmental hazards.

An individual with a higher family income has more financial ability to cope with AD clinical treatment costs and manage disease progression.⁴⁴ However, the increased ability and accessibility to medical care may result in a detection bias for the correlation between higher income and increased AD prevalence. These wealthier individuals may be more proactive and willing in seeking medical attention than those of a lower-income group. According to the National Healthy Interview Study (NHIS) in the United States, the high incidence of AD was associated with increased health care utilization and insurance coverage.⁴⁵ This finding was supported by another study that having a high socioeconomic status (SES) positively influenced the prevalence of allergic diseases among 75 963 Korean adolescents.⁴⁶

The established hygiene hypothesis suggested increased early life exposure to different non-pathogenic microbes can educate the immune system to react appropriately to foreign stimuli and thereby, decreasing the susceptibility for allergic diseases. Interestingly, we underscored a greater associated risk of AD development with more people living together in the same household. It is important to note that not all microbial exposures confer protection against AD. AD Patients show more frequent colonization by *Staphylococcus aureus* (*S. aureus*) and such bacterial infection can lead to the formation of severe eczematous lesions.⁴⁷ Furthermore, in the presence of epidermal barrier abnormality, other harmful microbes such as *Malassezia* may be easier to penetrate the skin to cause cutaneous inflammation and worsen AD.⁴⁸ In this regard, the increased interaction between those living in the same household

environment may propagate the development of AD. More research work is necessary to better determine the risks and opportunities associated with microbial exposure, especially in individuals with skin barrier deficiency.

AD prevalence in our study is higher in males rather than females. The current epidemiologic and experimental studies have no consistent conclusions on whether sex hormones and gender identity can impact AD presentation.⁴⁹ Since our population comprised more females and they were all Chinese, the observation may flip-flop when the population size increase or the ethnic change. Otherwise, we postulate that males may be frequently engaged in more physical activities (ie, contact sports, gym training and workouts) or manual laborious work (ie, painting, construction, firefighting, repair work) that exposed them to a higher risk of outdoor pollutants and occupational allergens.⁵⁰ In contrast, a higher parental education reduced the prevalence of AD presentation. When the parents receive higher education, they become more knowledgeable, aware, and resourceful in seeking proper disease treatments and management.⁵¹

As described by the atopic march theory, the presence of other atopic diseases positively interrelate to affect the development of one another.⁵² The results of our epidemiology study for AD were consistent with our review study that there was a high likelihood of AD presentation among patients with atopic comorbidities such as AS and AR. Our results also add to the findings of the Canadian Healthy Infant Longitudinal Development birth cohort study in which the combination of AD with allergic sensitization increased the risk of AS more than 7-fold.⁵³ It is not uncommon for children and adults with AD to have co-occurring AS and the burden of having both diseases can be deleterious. It was shown in a Swedish study that asthmatic patients with AD have a higher impaired quality of life compared to those with only AD.⁵⁴ Another UK cohort study demonstrated an increased risk of both cutaneous and systemic infections among individuals with AD and AS and/or AR.⁵⁵ In a United States study involving 27,175 adults, adults with AD had a significantly higher lifetime prevalence of AS and are associated with persistent AS disease and attacks.¹⁰ The

pathogenic role of increased total IgE is often implicated among patients with AD and AS across various races and ages.⁵⁶ Shared risk loci such as FLG, IL-4/KIF3A, and AP5B1/OVOL1 are also found to be associated with the subsequent manifestation and aggravation of allergic co-morbidities.⁴⁵ Given the high burden risks and common underlying pathology of AD and AS, an active and advanced health screening for early AD detection is highly recommended in these susceptible individuals.

The association of paternal AD was the strongest compared to maternal, siblings, and parental AD. Further research on the role of paternal AD status may be essential to understand such differences observed. Meanwhile, most of these participants and their family members reside together in the same household. They are likely exposed to the same environment and share a common lifestyle.^{17,46} As such, the effects of modifiable factors may be enhanced in hosts with genetic susceptibility to atopic diseases. For mild or moderate AD patients with 14 novel FLG null mutations, there was a greater risk of recurrent bacterial skin infection from environmental exposures.⁵⁷ With a better understanding of the personal and family atopic history, physicians can diagnose AD patients more accurately and especially useful for identifying infants and children with a high risk of developing AD. Physicians can also advise vulnerable individuals on better preventive therapies and early interventions that may hinder AD disease presentation.

TV/computer usage was directly proportional to the odds of AD development. The surrounding environment, indoor or outdoor, may have multiple sources of allergens and triggers to affect AD development. As most individuals tend to use TV or computer in an air-conditional room, especially for an office job or studying, the environment may become humid and cold. Low humidity was reported to reduce FLG production and was positively associated with AD prevalence.⁵⁸ There is an increased chance to encounter air pollutants for outdoor exposure, especially in a polluted urban setting. The air pollutants may generate harmful reactive oxygen and nitrogen species that damage epidermal proteins and lipids, leading to further skin impairment.^{15,59} Otherwise,

individuals participating in strenuous physical activities that involved sporting equipment, team sports, and close contacts may be exposed to more chemical irritants and bacterial skin pathogens that promote skin barrier dysfunction.^{15,60}

We revealed from the use of QDGIS that diet and eating habits do affect the development of AD. More investigations, however, are required to understand and determine the intricate relationship between the intake frequency of foods and AD. We also showed that drug allergies were a novel risk factor associated with AD. The use of antibacterial medications curbed the increased colonization of *S. aureus* to prevent further skin barrier damages induced on AD patients.⁶¹ In AD patients with antibiotic allergies, harmful skin bacteria such as *S. aureus* may proliferate uncontrollably to lead to a higher risk of skin infection and AD symptoms. Although the exact mechanism of NSAID intolerance exacerbating allergic diseases is unclear, there has been a study showing increased frequency of allergic diseases and NSAIDs sensitivity in young adults.⁶² Currently, no clear findings were underlying the association of acne presentation and AD presentation. We postulate that a similar set of environmental and genetic factors may be involved but more studies should be done to demonstrate such plausibility. Locals in our cohort were associated with a higher odds of AD than migrants. The present studies concerning the association between AD and birthplace are scarce in Singapore. In the future, a sub-population stratified by birthplace can be studied to better understand the possible roles of both modifiable (climate, diets) and non-modifiable (genetics) specific to the Singapore/Malaysia region in aggravating AD development.

Given the advancement of artificial intelligence (AI), AI can be integrated as a new, rapid, and improved approach in future AD diagnosis. Recent work has shown high sensitivity (94.4%) and specificity (95.8%) in differentiating inflammatory skin diseases through the use of an AI dermatology diagnosis assistant.⁶³ Machine learning-based studies have been conducted to analyse the association of 130 risk factors with severe AD in a cohort of 367 adult patients.⁶⁴ With our large quality datasets, it is possible to develop AI-

powered prediction models to assist us further in the identification and sub-typing of the various AD phenotypes and/or endotypes. As a highly heterogeneous skin disease, AD subtyping is necessary for enabling the development of personalized medicine approaches. For instance, the severity of AD is often assessed by scoring the extent of affected sites and intensity of clinical signs by clinicians. However, clinical assessments are highly prone to both interobserver and intraobserver variability. A recent pilot study introduced the use of an AI-facilitated scoring method in achieving reliable AD severity assessments that shorten diagnosis time and advance clinical practices.⁶⁵ This exciting field of AI research can lead to the individual prediction of AD disease evolution and refine individual treatment responses.

LIMITATIONS AND CONCLUSION

Firstly, the extrapolation of the analysed results may not be possible for other ethnicities as this study primarily focused on the Chinese in Singapore and Malaysia. Secondly, the study was conducted retrospectively to estimate the associative effects between AD and the risk factors. Thus, it cannot determine the causative effects of the risk factors conclusively. A recall study, however, can be conducted on the same population to better understand the disease progression. Lastly, there were some missing responses for the food section in the questionnaire which resulted in the removal of some data. However, the population database for our analysis remained large ($n = 11\,494$) and is reliable to be considered in an epidemiological study. We also ensured that the risk associations observed followed good strength of association, consistency, coherency, sensitivity, and specificity. Future work can follow up on the investigation of the association of foods, diet, and eating habits with AD.

In summary, this study provides an update on the prevalence, severity, and chronicity of AD and describe Singapore and Malaysia as our base to guide our future genetic pathology evaluation. We also re-evaluated the epidemiological status of AD and the potential risk factors acting independently upon the AD population in Singapore. Because the prevalence of AD among the Singapore and Malaysia Chinese population remained high over

time, more research is required to understand the pathogenesis of AD and its implication in atopic individuals. We hope that the identification of novel risk factors would better facilitate disease surveillance to monitor disease control and be critical to reducing the prevalence of AD, leading to better interventions to prevent disease aggravation and progression in Singapore and Malaysia.

Abbreviations

AD: Atopic dermatitis; AI: Artificial intelligence; AR: Allergic rhinitis; AS: Asthma; BMI: Body Mass Index; CI: Confidence intervals; DQDFS: Diet quality based on dietary fat score; FAD: Familial atopic dermatitis; FLG: Filaggrin; IgE: Immunoglobulin E; ISAAC: International study of asthma and allergies in childhood; GI: Glycaemic index; MSF: Ministry of social and family development; NHIS: National health interview survey; NSAID: Non-steroidal anti-inflammatory drugs; OR: Odds ratio; PCOS: Polycystic ovary syndrome; QDGIS: Quality of diet based on glycaemic index score; *S.aureus*: *Staphylococcus aureus*; SES: Socioeconomic status; SGD: Singapore Dollar; SPT: Skin prick test.

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Availability of data and materials

All data used and included in this study are available from the corresponding author (F.T.C.).

Authors contributions

F.T.C. conceived and supervised the current research study. J.J.L. conducted the literature review, analysed and interpreted the data, and wrote the manuscript. J.J.L., Y.Y.E.L., J.Y.N., P.M., Y.T.N., W.Y.T., Q.Y.A.W., S.R.M., Y.Y.S.,

Y.R.W., K.F.T., S.M.R.S., K.R., and Y.Y.S. assisted in the recruiting participants, and collated the data. All authors read and approved the final manuscript.

Ethics approval and consent

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices, and in compliance with local regulatory requirements. The cross-sectional studies in Singapore were conducted on the National University of Singapore (NUS) campus annually between 2005 and 2019 with the approval of the Institutional Review Board (NUS-IRB Reference Code: NUS-07-023, NUS-09-256, NUS-10-445, NUS-13-075, NUS-14-150, and NUS-18-036) and by the Helsinki declaration. The cross-sectional studies in Malaysia were held in the Universiti Tunku Abdul Rahman (UTAR), and Sunway University. Ethical approval was granted respectively from the Scientific and Ethical Review Committee (SERC) of UTAR (Ref. code: U/SERC/03/2016) and Sunway University Research Ethics Committee (Ref. code: SUREC 2019/029). Before the data collection, all participants involved signed an informed consent form.

Consent for publication

All authors have read and consented to the publication of this manuscript.

Competing interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2022.100722>.

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