Wong et al. World Allergy Organization Journal (2022) 15:100704
http://doi.org/10.1016/j.waojou.2022.100704

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Allergic rhinitis in Chinese young adults from the Singapore/Malaysia cross-sectional genetics epidemiology study (SMCGES) cohort: Prevalence, patterns, and epidemiology of allergic rhinitis

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ABSTRACT

Background: Allergic rhinitis (AR) is characterized by the occurrence of at least 2 symptoms of nasal itching, nasal blockage, rhinorrhea, and sneezing, when not afflicted with a cold or flu, with defined atopic sensitization demonstrated by skin prick test or specific IgE responses. Besides the detriment to standard of living and economic burden of AR, both multicentre and single-cohort studies have observed an increase in AR prevalence in Asia over time.

Methods: In total, 12 872 individuals, with mean age 22.1 years (SD = 4.8), were recruited from universities in Singapore and Malaysia. Each participant provided epidemiological data based on an investigator-administered questionnaire adapted from the validated International Study of Allergies and Asthma in Childhood (ISAAC) protocol, and atopy status was determined using a skin prick test (SPT) performed by qualified staff. AR was diagnosed according to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and a positive SPT result.

Results: Sensitization (determined by SPT) to either *Blomia tropicalis* or *Dermatophagoides pteronyssinus* was prevalent in 66.5% of the cohort. Current rhinitis (manifesting $\geq$2 rhinitis symptoms, within the past 12 months) was observed in 48.9% of our population, while AR, which included atopy status, was estimated at 39.4%. Sneezing and rhinorrhea were the most common symptoms among AR cases. AR prevalence decreased with increasing age (OR: 0.979; 95% CI: 0.969–0.989), while male gender (OR: 2.053; 95% CI: 1.839–2.294), and a parental history of allergic diseases (OR: 2.750; 95% CI: 2.284–3.316) were significant risk factors for AR. Upon adjustment for age, gender, and parental history, housing type (OR: 0.632; 95% CI: 0.543–0.736) and income level (>$6000 vs <$2000; OR: 2.461; 95% CI: 2.058–2.947) remained as significant

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http://doi.org/10.1016/j.waojou.2022.100704
Received 14 March 2022; Received in revised from 1 August 2022; Accepted 2 September 2022
Online publication date xxx

risk factors for AR, while ever having kept a pet (OR: 1.167; 95% CI: 1.025–1.328) emerged as a risk factor. Conflicting results were obtained for indicators of sedentary lifestyle: frequent physical activity (OR: 1.394; 95% CI: 1.150–1.694) and increased duration spent using the TV/computer (OR: 1.224; 95% CI: 1.006–1.489) both increased the risk of AR. Lastly, we used the Quality of Diet based on Glycaemic Index Score (QDGIS) to assess the Glycaemic Index (GI) level of overall diet. We identified lower GI level of overall diet as a protective factor against AR manifestation (OR: 0.682; 95% CI: 0.577–0.807).

Conclusion: While the previously established non-modifiable risk factors for AR were present in our study population, the identification of modifiable risk factors, such as TV/computer usage, and dietary habits, opens a new area for research, both in the areas of gene-environment interaction, and management of AR.

Keywords: Allergic rhinitis, Epidemiology, ISAAC, Prevalence, Risk factors

INTRODUCTION

Background of Allergic Rhinitis

Rhinitis arises due to the inflammation of the nasal mucosa which results in characteristic symptoms, such as nasal congestion, nasal pruritis, rhinorrhea, and sneezing.[1,2] While rhinitis may be categorized as allergic and non-allergic, allergic rhinitis (AR) is the most common form of rhinitis and is associated with type I IgE-mediated immune response to allergen stimuli.[1,3] Allergens frequently implicated in hypersensitivity reactions resulting in symptomatic manifestations include pollens, fungal spores, house dust mites, cockroaches, and animal dander.[4] In temperate regions, concentrations of allergens peak during conducive environmental conditions or seasons, triggering allergic responses in humans and resulting in a distinct temporal pattern in AR symptom emergence (previously known as seasonal AR).[1,4] Conversely, a tropical climate such as that of Singapore results in the perennial presence of allergens, with important examples including the house dust mite *Blomia tropicalis*, which is highly prevalent in homes and has high sensitization rates.[4–6] Further assessment of allergen sensitization in Singapore and Malaysia, through IgE response tests, such as the Phadiatop test, or Skin Prick Tests, found that subjects are most frequently sensitized to the common house dust mite species *Blomia tropicalis* and *Dermatophagoides pteronyssinus*.[7] Among airspora in the Singapore region, *Curvularia spp*. fungi spore and *Elaeis g*. pollen sensitivity rates were among the highest.[8] Moreover, the seasonal behaviour of *Elaeis g.*, its peak concentration in the air occurring around the January period, implicates it as a potential cause for seasonal allergy exacerbations in Singapore.[9]

Allergic rhinitis prevalence worldwide and in Singapore

Earlier reviews have found prevalence estimates of AR to vary from 9% to 42% worldwide.[10] However, the prevalence of AR has been changing, following an apparent upward trend.[11–13] Recent prevalence estimates of AR now range from 5% to 52%.[14,15] In Singapore, the prevalence of AR occurrent in the past 12 months was estimated at 4.5% in a 1994 cross-sectional cohort of 2868 adults aged 20–74 years, with a notable risk for AR in the younger age group (20–39-year-olds).[16] A separate 1994 study of 6234 students aged 6–7 and 12–15 years estimated prevalence of rhinitis in the past years as 27.6% and 41.5%, respectively.[17] Comparison of the same age groups in another 9363 students 7 years later in 2004 showed that prevalence of rhinitis in the past year had not significantly changed (25.5% in 6–7-year-olds, 42.1% in 12–15-year-olds).[18]

Objectives and rationale

Our previous meta-analysis found that Asian individuals in the approximate 20–45-year-old age range appear more likely to manifest AR.[19]

Similarly, earlier studies of AR in Singapore identified that individuals between their second to fourth decade of life display a higher risk of AR.[16] Thus, our present study examined a population predominantly comprising an at-risk age group (young adults aged 18–25 years-old), with the aim of obtaining a current prevalence estimate of AR and identifying its risk factors. Additionally, in those with AR, we hoped to document the patterns of AR symptoms, their frequency of occurrence (persistency), impact on standard of living (severity), and duration of disease (chronicity). Concurrently, we explore the utility of the Total Nasal Symptom Score (TNSS) as an indicator of AR severity. Moreover, we noted the possibility of inaccurate prevalence estimates of AR made when based solely on ISAAC questionnaire responses.[20] Hence, we endeavored to elucidate the patterns of AR according to updated classifications and criteria per Allergic Rhinitis and its Impact on Allergy (ARIA) 2008 guidelines.[1]

MATERIALS AND METHODS

Participants and data collection

The Singapore/Malaysia Cohort Genetic Epidemiology Study (SMCGES) is an ongoing cross-sectional study conducted at 3 universities in Singapore and Malaysia. Beginning in August 2005, participants were recruited via email and poster advertisements across each university. The exclusion criteria was as follows: participants below the age of 18, or had just taken antihistamines before the Skin Prick Test (SPT). Participants currently taking antihistamines were scheduled to return at a later date to undergo the SPT. Consenting and eligible subjects completed an investigator-administered questionnaire and skin prick test.

Additionally, we assessed overall dietary Glycaemic Index (GI) quality using a novel Quality of Diet based on Glycemic Index Score (QDGIS). Food types were categorized according to their GI value, whereby 'high-GI' foods had a GI value of 55 and above, while 'low-GI' foods had a GI value of less than 55.[21] The QDGIS considered burgers/fast food, cereals, rice, and potatoes as "high-GI" foods; and fruits, vegetables, pulses, nuts, milk, and probiotic drinks as "low-GI" foods.[22] Next, we adapted a previously used rubric to quantify dietary GI.[23] Frequency of consumption of each "high-GI" and "low-GI" food was determined for each subject and values of 7, 2, and 0 were assigned to each category of frequency – most or all days, once or twice per week, and never or only occasionally, respectively. Values were affixed with negative signs for "high-GI" foods to give more negative scores for increased consumption of "high-GI" foods, and with positive signs for "low-GI" foods to give more positive scores increased consumption of "low-GI" foods. The QDGIS was a sum of all scores and grouped into poor (QDGIS >0), moderate ($0 \leq$ QDGIS <10), and good (QDGIS ≥ 10) categories.

Skin prick test (SPT)

Atopy status was determined using a skin prick test (SPT) administered by trained personnel to participants who had not taken antihistamines only for at least 3 days prior. Extracts from 2 common House Dust Mite (HDM) species in Southeast Asia, *Blomia tropicalis* and *Dermatophagoides pteronyssinus*, and a positive and negative control of histamine and saline, respectively, were included in the SPT. Emergence of a wheal of at least 3 mm diameter in response to an allergen was considered as a positive SPT result for the given allergen, according to protocol consistent with previous descriptions.[24] Individuals who exhibited a positive SPT result to either the *Blomia tropicalis* or *Dermatophagoides pteronyssinus* extracts were considered atopic cases, while participants exhibiting a wheal of less than 3 mm in diameter or no reaction to both the *Blomia tropicalis* and the *Dermatophagoides pteronyssinus* extracts were considered as non-atopic.

Questionnaire and disease definition

The International Study of Allergies and Asthma in Childhood (ISAAC) Phase Three Core and Environmental Questionnaires (henceforth, ISAAC questionnaire) have been standardized and validated for the facilitation of research into allergic diseases, including AR.[25] Via an adapted ISAAC questionnaire, we collected participant-reported information pertaining to the respondents' demographics, lifestyle, personal and familiar

medical history, and allergic disease (ie, AR and asthma) symptomology.

Subject responses were analyzed in the sequence of the proceeding description (summarized in Fig. 1). First, *self-reported ever rhinitis* cases were determined as subjects who indicated having had a problem with sneezing, or runny, or blocked nose when in the absence of a cold or flu. Next, subjects indicating having had a problem with sneezing, or runny, or blocked nose when in the absence of a cold or flu in the past 12 months were classified as *self-reported current rhinitis* cases. Participants were further queried on the presence of the following symptoms: itchy-watery eyes, itchy nose, sneezing, runny nose, nose blockage, snoring, and nose bleeding. Per ARIA guidelines, itchy nose, sneezing, runny nose, and nose blockage were considered as ARIA symptoms; participants previously classified as a *self-reported current rhinitis* case and who exhibited at least 2 ARIA symptoms were considered as a current rhinitis per ARIA 2008 guidelines (henceforth *current rhinitis per ARIA*) case. *Self-reported ever AR* cases were also determined as those who affirmed ever having had allergic rhinitis. Heretofore, conflicting responses were removed at each step. Per ISAAC

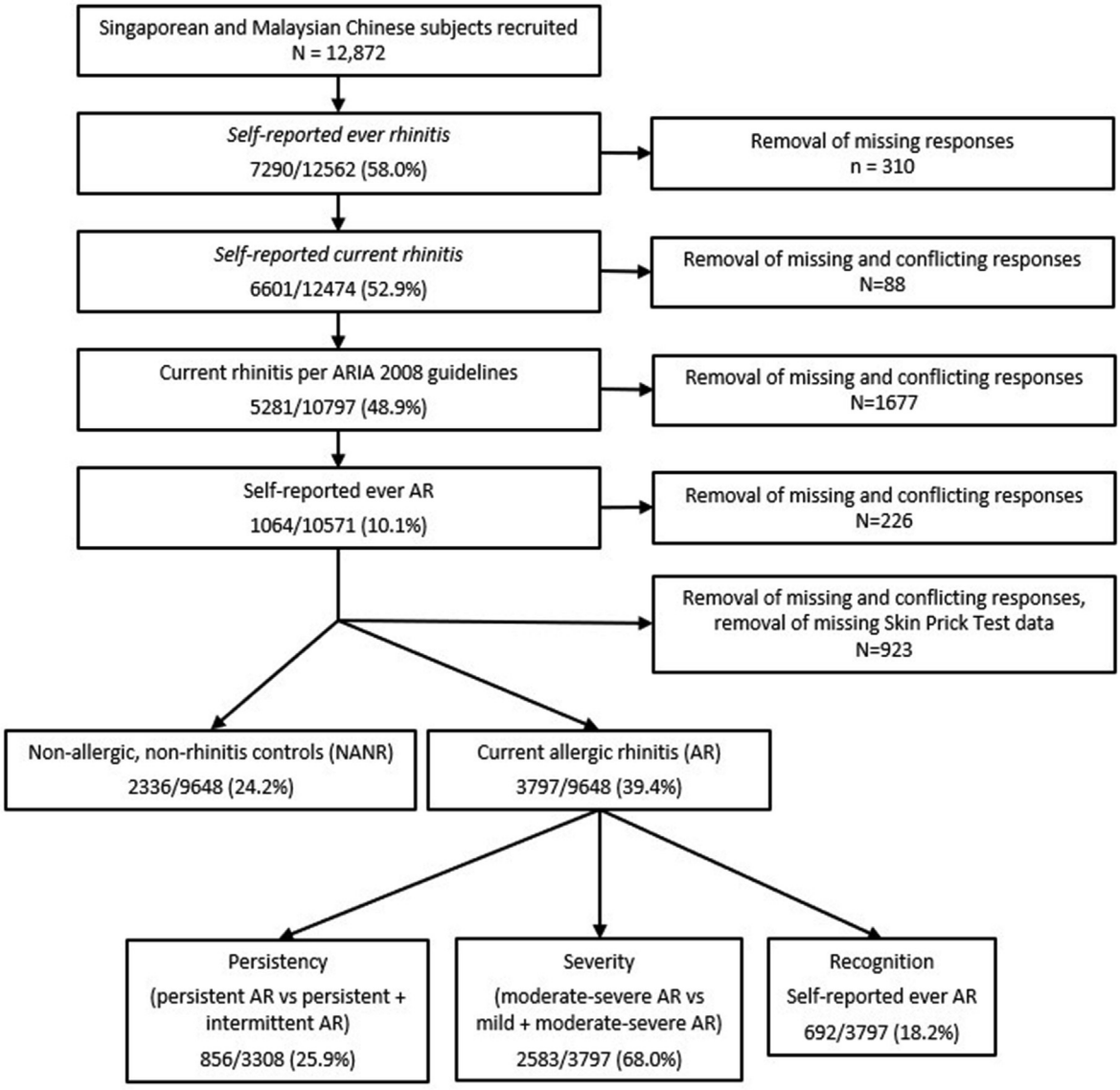

Fig. 1 Flowchart of analysis of study participants' disease status

recommendations, missing or "other" responses were included in the denominator.[26]

From hitherto complete responses, subjects classified as *current rhinitis per ARIA* cases and showing sensitization to either *Blomia tropicalis* and *Dermatophagoides pteronyssinus* during the Skin Prick Test (described in Section 6.1.1) were classified as current allergic rhinitis (henceforth *current AR*) cases. Among *current AR* cases, persistency, severity, duration, and recognition of AR were determined. AR persistency comprises 2 categories: persistent and intermittent AR – the former comprising *current AR* cases who indicated that at least 1 of their ARIA symptoms lasted for both at least 4 days per week and at least 4 consecutive weeks in the past 12 months, while the latter comprised *current AR* cases suffering from ARIA symptoms, all of which lasted for either less than 4 days per week or less than 4 consecutive weeks in the past 12 months. AR severity was categorized as either mild or moderate-severe. Moderate-severe AR cases experienced disturbances at least 1 of sleep, daily activities, leisure or sport, school or work, and troublesome symptoms. Mild AR cases indicated none of the foregoing disturbances. Duration of disease was also determined in *current AR* cases, in categories of less than 1 year, 1–4 years, 5–10 years, and 10 or more years. Recognition of AR was estimated among AR cases, with recognizant subjects indicating ever having had allergic rhinitis. Cases and their respective criteria are summarized in Table 1.

Total Nasal Symptom Score (TNSS) were calculated for *current AR* cases. First, each ARIA symptom reported currently experienced by each subject was graded according to severity from 0 to 3, with 0 indicating minimal evidence of said symptom and 3 corresponding to severe symptom manifestation which was intolerable, resulting in interference with daily life. The TNSS was derived by taking the sum of all ARIA symptom scores and can range from 0 to 12.

Finally, non-allergic non-rhinitis controls (NANR) comprised subjects who exhibited no evidence of sensitization to either *Blomia tropicalis* or *Dermatophagoides pteronyssinus* during the Skin Prick Test and fulfilled none of the criteria for *current rhinitis per ARIA*. Subjects that could not be recruited into either the AR or NANR category were not considered in the present analysis.

Statistical analysis

Statistical analyses were conducted using R version 4.0.3.[27] TNSS was analyzed in relation with various AR patterns (ie, persistency, severity, number of disturbances, and duration of disease). Unpaired T-tests were conducted to ascertain any significant differences in TNSS between different subgroups of *current AR* cases. Preliminary association analyses comparing between AR cases and NANR controls were performed using simple logistic regression models to calculate odds ratios (OR) and their respective 95% confidence intervals (95% CI). Adjustment for confounding variables was done using multiple logistic regression models, from which adjusted odds ratios (aOR) and their corresponding 95% CI were obtained. Statistical significance was determined using the significance level of 0.05.

RESULTS

Demographics of study population

Of 16 336 subjects recruited overall, 12 872 subjects fulfilled the following criteria: Chinese ethnicity and provided response to the AR section of our questionnaire. The mean age of the Chinese cohort was 22.21 (SD = 4.95), with a preponderance of young university student participants aged 18 to 25 (84%) due to the study's university setting. More than half of the participants were female (58%), and the mean BMI of the cohort was 21.13 kg/m^2 (SD = 3.26). The total monthly family income was most frequently in the RM4000 – 5999 range in Malaysia (51%), and the SGD2000 – 3999 range in Singapore (34%). Residence in landed property was more frequently reported in the Malaysian cohort (60%), while residence in public Housing and Development Board (HDB) housing was more common in the Singapore cohort (68%). Participant demographics are described in detail in Table 2.

Prevalence and patterns of atopy and allergic rhinitis

Prevalence of sensitization to *Blomia tropicalis* and *Dermatophagoides pteronyssinus* were 54.8%

Case classification	Criteria	N (case/control)	Prevalence (%)
Self-reported ever rhinitis	Indicated having had a problem with sneezing, or runny, or blocked nose when in the absence of a cold or flu.	7290/12,562	58.0
Self-reported current rhinitis	Indicated having had a problem with sneezing, or runny, or blocked nose when in the absence of a cold or flu in the past 12 months.	6601/12,474	52.9
Current rhinitis per ARIA 2008 guidelines (henceforth *current rhinitis per ARIA*)	Fulfilled criteria for *Self-reported current rhinitis* case classification, and indicated the presence of two or more of the following symptoms: runny nose, nose blockage, nasal itching, and sneezing (henceforth ARIA symptoms).	5281/10,797	48.9
Self-reported ever AR	Indicated ever having had allergic rhinitis	1064/10,571	10.1
Allergic rhinitis (henceforth *current AR*)	Fulfilled criteria for *Current rhinitis per ARIA* case classification, and developed a positive Skin Prick Test result to either of *Blomia tropicalis* or *Dermatophagoides pteronyssinus*	3797/9648 (vs any that did not fulfil *current AR* criteria)	39.4
		3797/6133 (vs non-allergic, non-rhinitis controls)[a]	61.9
Recognized AR	Fulfilled criteria for current AR case classification, and indicated ever having had allergic rhinitis	692/3797	18.2
Intermittent AR	Fulfilled criteria for *current AR* case classification, and all ARIA symptoms indicated lasted for less than 4 days per week and/or less than 4 consecutive weeks in the past 12 months.	856/3308 (Persistent AR vs persistent + intermittent AR)	25.9

(continued)

Case classification	Criteria	N (case/control)	Prevalence (%)
Persistent AR	Fulfilled criteria for *current AR* case classification, and at least one ARIA symptom persisted for both at least 4 days per week and at least 4 consecutive weeks in the past 12 months		
Moderate-severe AR	Fulfilled criteria for *current AR* case classification, and indicated suffering from at least one of the following disturbances: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, troublesome symptoms.	2583/3797 (moderate-severe AR vs mild + moderate-severe AR)	68.0

Table 1. (Continued) A summary of case classifications and their corresponding criteria. [a]*Non-allergic and non-rhinitis (NANR) controls showed no evidence of sensitization to either of* Blomia tropicalis *or* Dermatophagoides pteronyssinus*, and did not fulfill the case criteria for* current rhinitis per ARIA

Variable	Country of collection		Overall (N = 12,872)
	Malaysia (N = 3038)	Singapore (N = 9834)	
Age (continuous)	20.81 ± 3.35	22.65 ± 5.28	22.21 ± 4.95
Not stated	1	50	51
BMI (kg/m^2, continuous)	22.26 ± 4.07	20.76 ± 2.86	21.13 ± 3.26
Not stated	240	1115	1355
Gender			
Female	1844 (62%)	5614 (57%)	7458 (58%)
Male	1115 (38%)	4202 (43%)	5317 (42%)
Not stated	79	18	97
Housing type			
HDB (Public housing)	7 (9.3%)	6318 (68%)	6325 (67%)
Condominium/Private apartment	23 (31%)	1771 (19%)	1794 (19%)
Landed property	45 (60%)	1255 (13%)	1300 (14%)
Not stated	2963	490	3453
Income level			
< $2000	37 (7.4%)	2135 (22%)	2172 (22%)
$2000–3999	189 (38%)	3247 (34%)	3436 (34%)
$4000–5999	254 (51%)	1883 (20%)	2137 (21%)
> $6000	17 (3.4%)	2271 (24%)	2288 (23%)
Not stated	2541	298	2839

Table 2. Demographic characteristics of subjects from the Malaysian and Singaporean cohorts.

(6328/11 546) and 57.9% (6678/11 544), respectively. Overall, 66.5% (7680/11 546) were allergic to either of the two HDMs. *Current rhinitis per ARIA* was found in 48.9% (5281/10 797) of respondents. In individuals with SPT and *current rhinitis per ARIA* status, prevalence of *current AR* was estimated at 39.4% (3797/9648), while 24.2% (2336/9648) were identified as NANR controls. A detailed summary of prevalences are indicated in Table 1.

Among *current AR* cases, 25% (856/3308) were categorized as persistent AR cases, and 68% (2583/3797) had moderate-severe AR, and 18.2% (692/3797) indicated *self-reported ever AR*. Of the ARIA symptoms, sneezing presented most frequently at 91.3% (3468/3797). 44.9% (1616/3600) of *current AR* cases suffered from AR for 10 or more years. Table 3 presents a detailed breakdown of the patterns among *current AR* cases.

Total nasal symptom score analyses

TNSS data was available for 3701 *current AR* cases for whom the mean TNSS (mTNSS) was 4.32 (SD = 2.54). The mTNSS of mild AR and moderate-severe AR cases was 3.25 (SD = 2.00) and 4.82 (SD = 2.61), respectively. Moderate-severe AR cases reported a significantly higher mTNSS than mild AR cases (p-value < 0.001). When stratified by persistency, mTNSS among intermittent AR cases was 4.09 (SD = 2.46), and 5.24 (SD = 2.57) among persistent AR cases. Persistent AR cases reported a significantly higher mTNSS than intermittent AR cases (p-value < 0.001). Combination of the severity and persistency classifications into AR class gave 4 categories: mild-intermittent, mild-persistent, moderate/severe-intermittent, moderate/severe-persistent (abbreviated respectively as MI, MP, MSI, and MSP). The mTNSS for MI, MP, MSI, and MSP groups were, 3.12 (SD = 1.86), 4.26 (SD = 2.29), 4.62 (SD = 2.58), and 5.57 (SD = 2.57), respectively, with significant differences between each group (p-value$\leq$0.01). Stratifying AR cases by number of disturbances resulted in the segmentation of the moderate-severe AR category. Hence, mTNSS of AR cases suffering no disturbances was 3.25 (SD = 2.00) and corresponded to that of the mild AR group. The number of disturbances ranged from one to four amongst moderate-severe AR cases, and mTNSS was 4.19 (SD = 2.32), 5.10 (SD = 2.54), 6.43 (SD = 2.64), and 6.65 (SD = 2.97), respectively. Apart from the non-significant difference in mTNSS of AR cases with three disturbances and four disturbances (p-value = 0.42), the difference between mTNSS of AR cases reporting one, two and three disturbances were statistically significant (p-values $<$ 0.001). Trends in TNSS among AR categories are summarized in Fig. 2.

	N	Prevalence (%)
All symptoms (n = 3797)		
Itchy-watery eyes	1908	50.3
Itchy nose[a]	2940	77.4
Sneezing[a]	3468	91.3
Runny nose[a]	3270	86.1
Nose blockage[a]	3066	80.7
Snoring	819	21.6
Nose bleeding	281	7.4
Duration of disease (n = 3600)		
Less than 1 year	391	10.9
1–4 years	750	20.8
5–10 years	843	23.4
10 or more years	1616	44.9
Disturbances to lifestyle (n = 3797)		
Sleep disturbance	1239	32.6
Impairment of daily activities, leisure, or sport	889	23.4
Impairment of school or work	829	21.8
Troublesome symptoms	1335	35.2

Table 3. Summary of patterns among *current AR* cases. [a]*ARIA symptoms – rhinitis cases manifested at least two of the indicated symptoms*

Risk factors associated with AR

Results from the simple and multiple logistic regression analyses are summarized in Table 4.

Preliminary univariable logistic regression analyses of our study population showed that AR manifestation was significantly associated with all demographic variables - higher BMI (OR: 1.029, 95% CI: 1.012, 1.047; p-value <0.001), male gender (OR: 2.053; 95% CI: 1.839, 2.294; p-value <0.001), and higher income (>$6000 vs < $2000; OR: 2.501; 95% CI: 2.103, 2.978; p-value <0.001) were all risk factors for AR. Conversely, increased age was associated with a reduced risk of AR (OR: 0.979; 95% CI: 0.969, 0.989; p-value <0.001). Living in a condominium or private apartment as compared to a HDB flat decreased the likelihood of AR (OR: 0.660; 95% CI: 0.570, 0.764; p-value <0.001), and there was a dose-effect relationship between income level and AR manifestation wherein the odds of AR were higher in those from higher income households. Having a prior history of drug allergy (OR: 1.898; 95% CI: 1.563, 2.316; p-value <0.001) and any parental history of allergic disease (OR: 2.750; 95% CI: 2.284, 3.316; p-value <0.001) also increased the likelihood of AR manifestation. Among lifestyle factors, frequently engaging in physical activity (most or all days vs

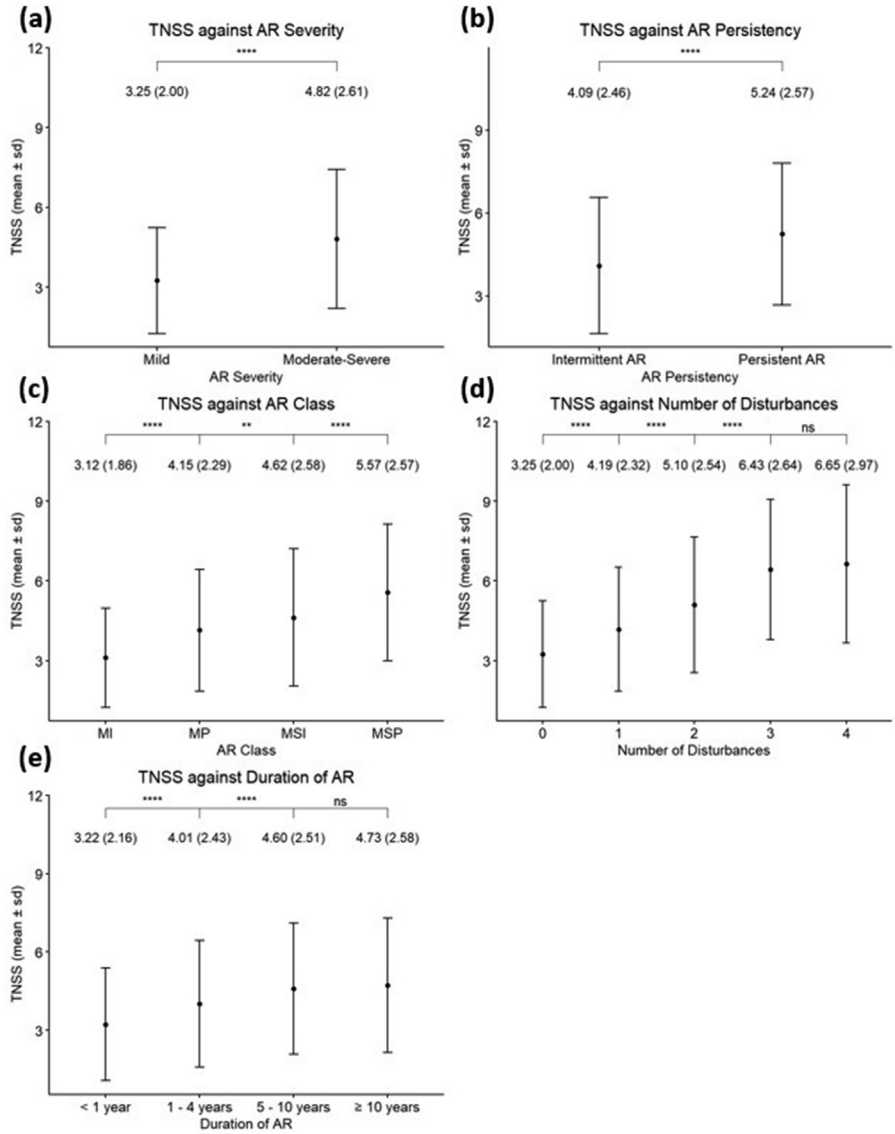

Fig. 2 Trends in total nasal symptom score (TNSS) by AR subcategorizations. The significance of differences between mean TNSS for each category of AR was determined via unpaired T-tests. Significance coding were as follows: "****": p-value < 0.000; "***": p-value≤0.001; "**": p-value≤0.01; "*": p-value≤0.05; "ns": p-value > 0.05. (a) TNSS and AR severity. (b) TNSS and AR persistency. (c) TNSS and AR severity and persistency classes combined (MI, mild-intermittent; MP, mild-persistent; MSI, moderate/severe-persistent; MSP, moderate/severe-persistent) (d) TNSS and number of disturbances to living among AR cases. (e) TNSS and duration of AR

Variable	N	NANR (N = 2336)	AR (N = 3797)	Overall (N = 6133)	Univariable logistic regression			Multiple logistic regression[c]		
					OR[a]	95% CI[b]	p-value	OR[a]	95% CI[b]	p-value
Demographics										
Age (continuous)	6113	22.41 ± 5.78	21.91 ± 4.12	22.10 ± 4.82	0.979	0.969, 0.989	<0.001			
Not stated		11	9	20						
BMI (continuous)	5666	20.90 ± 3.21	21.19 ± 3.25	21.08 ± 3.24	1.029	1.012, 1.047	<0.001	1.006	0.987, 1.025	0.6
Not stated		198	269	467						
Gender	6125									
Female		1677 (71.9%)	2107 (55.5%)	3784 (61.8%)	–	–				
Male		654 (28.1%)	1687 (44.5%)	2341 (38.2%)	2.053	1.839, 2.294	<0.001			
Not stated		5	3	8						
Housing type	4648									
HDB (Public housing)		1091 (61.7%)	1963 (68.1%)	3054 (65.7%)	–	–		–	–	
Condominium/Private apartment		438 (24.8%)	520 (18.0%)	958 (20.6%)	0.660	0.570, 0.764	<0.001	0.632	0.543, 0.736	<0.001
Landed property		238 (13.5%)	398 (13.8%)	636 (13.7%)	0.929	0.779, 1.110	0.4	0.867	0.722, 1.041	0.13
Not stated		569	916	1485						
Income category	4959									
< $2000		557 (28.9%)	534 (17.6%)	1091 (22.0%)	–	–		–	–	
$2000–3999		670 (34.8%)	1030 (33.9%)	1700 (34.3%)	1.604	1.376, 1.870	<0.001	1.643	1.402, 1.926	<0.001
$4000–5999		361 (18.8%)	662 (21.8%)	1023 (20.6%)	1.913	1.607, 2.279	<0.001	1.956	1.634, 2.345	<0.001
> $6000		337 (17.5%)	808 (26.6%)	1145 (23.1%)	2.501	2.103, 2.978	<0.001	2.461	2.058, 2.947	<0.001
Not stated		411	763	1174						
History of allergy										
Any drug allergy	5129									
No		1856 (92.6%)	2711 (86.8%)	4567 (89.0%)	–	–		–	–	
Yes		149 (7.4%)	413 (13.2%)	562 (11.0%)	1.898	1.563, 2.316	<0.001	1.820	1.491, 2.232	<0.001
Not stated		331	673	1004						

Parental history of allergic disease	5587									
No		450 (21.0%)	436 (12.7%)	886 (15.9%)	–	–				
Yes		304 (14.2%)	810 (23.5%)	1114 (19.9%)	2.750	2.284, 3.316	<0.001			
Don't know		1393 (64.9%)	2194 (63.8%)	3587 (64.2%)	1.626	1.402, 1.885	<0.001			
Not stated		189	357	546						
Modifiable factors										
Ever kept animals	4195									
No		822 (50.6%)	1224 (47.6%)	2046 (48.8%)	–	–		–	–	
Yes		801 (49.4%)	1348 (52.4%)	2149 (51.2%)	1.130	0.998, 1.280	0.054	1.167	1.025, 1.328	0.019
Not stated		713	1225	1938						
Frequency of physical activity	6093									
Never or only occasionally		819 (35.3%)	1044 (27.7%)	1863 (30.6%)	–	–		–	–	
Once or twice per week		1261 (54.3%)	2165 (57.4%)	3426 (56.2%)	1.347	1.201, 1.511	<0.001	1.210	1.069, 1.368	0.002
Most or all days		241 (10.4%)	563 (14.9%)	804 (13.2%)	1.833	1.538, 2.189	<0.001	1.394	1.150, 1.694	<0.001
Not stated		15	25	40						
Duration of TV or computer use	6106									
<1 h		395 (17.0%)	524 (13.9%)	919 (15.1%)	–	–		–	–	
1–3 h		867 (37.3%)	1371 (36.2%)	2238 (36.7%)	1.192	1.020, 1.393	0.027	1.177	0.991, 1.397	0.063
>3–5 h		589 (25.4%)	1029 (27.2%)	1618 (26.5%)	1.317	1.116, 1.554	0.001	1.187	0.983, 1.434	0.075
>5 h		472 (20.3%)	859 (22.7%)	1331 (21.8%)	1.372	1.155, 1.630	<0.001	1.224	1.006, 1.489	0.043
Not stated		13	14	27						
Duration of sleep (hours)	334	6.73 ± 1.06	6.55 ± 1.09	6.60 ± 1.09	0.853	0.671, 1.072	0.2	0.813	0.628, 1.045	0.11
Not stated		2249	3550	5799						
Smoking status	6105									
Non-smoker		2282 (98.2%)	3678 (97.3%)	5960 (97.6%)	–	–		–	–	

(continued)

Variable	N	NANR (N = 2336)	AR (N = 3797)	Overall (N = 6133)	Univariable logistic regression			Multiple logistic regression[c]		
					OR[a]	95% CI[b]	p-value	OR[a]	95% CI[b]	p-value
Ex-smoker		28 (1.2%)	63 (1.7%)	91 (1.5%)	1.396	0.901, 2.217	0.14	1.045	0.653, 1.713	0.9
Smoker		14 (0.6%)	40 (1.1%)	54 (0.9%)	1.773	0.986, 3.381	0.066	1.427	0.779, 2.764	0.3
Not stated		12	16	28						
Passive smoking	4835									
No		1647 (87.4%)	2621 (88.8%)	4268 (88.3%)	–	–		–	–	
Yes		238 (12.6%)	329 (11.2%)	567 (11.7%)	0.869	0.728, 1.038	0.12	0.876	0.730, 1.053	0.2
Not stated		451	847	1298						
Frequency of alcohol consumption	6117									
Non-drinker		1205 (51.7%)	1697 (44.8%)	2902 (47.4%)	–	–		–	–	
Occasional		1078 (46.3%)	2002 (52.9%)	3080 (50.4%)	1.319	1.188, 1.464	<0.001	1.234	1.101, 1.382	<0.001
Frequent		47 (2.0%)	88 (2.3%)	135 (2.2%)	1.330	0.931, 1.922	0.12	1.025	0.697, 1.525	>0.9
Not stated		6	10	16						
QDGIS[d] (categorical)	5135									
Poor [-24,0]		428 (21.3%)	857 (27.4%)	1285 (25.0%)	–	–		–	–	
Moderate (0,10]		1057 (52.6%)	1578 (50.5%)	2635 (51.3%)	0.746	0.648, 0.857	<0.001	0.744	0.644, 0.858	<0.001
Good (10,35]		523 (26.0%)	692 (22.1%)	1215 (23.7%)	0.661	0.562, 0.777	<0.001	0.682	0.577, 0.807	<0.001
Not stated		328	670	998						

Table 4. (Continued) Univariable and multiple logistic regression analyses of AR and its risk factors. Multiple logistic regression analysis was adjusted for age, gender, and parental history of allergic diseases. *[a]OR, Odds Ratio. [b]CI, Confidence interval. [c]Adjusted for age, gender, and parental history of allergic diseases. [d]Quality of Diet based on Glycemic Index Score*

never or only occasionally; OR: 1.833; 95% CI: 1.538, 2.189; p-value <0.001), having a longer duration of TV/computer usage (OR: 1.372; 95% CI: 1.155, 1.630; p-value <0.001), and occasionally consuming alcohol (OR: 1.319; 95% CI: 1.188, 1.464; p-value <0.001) were significant predisposing factors for AR. Conversely, ever keeping pets (p-value = 0.054), longer duration of sleep (p-value = 0.2), and both active and passive smoking (p-value = 0.066 and 0.12, respectively) were non-significantly associated with AR. Finally, the association between QDGIS and AR indicated that a diet generally lower in GI lowered the risk of AR manifestation (OR: 0.682; 95% CI: 0.577, 0.807; p-value <0.001).

Multiple logistic regression was performed to adjust for confounding by age, gender, and parental history of allergic diseases. BMI was statistically non-significant (p-value = 0.6) as a risk factor for AR, while housing type (aOR: 0.632; 95% CI: 0.543, 0.736; p-value <0.001) decreased the likelihood of AR manifestation. A dose-effect relationship between higher income level and increased risk of AR evident (>$6000 vs < $2000; aOR: 2.461; 95% CI: 2.058, 2.947; p-value <0.001), while having a prior history of drug allergy was a risk factor for AR (aOR: 1.820; 95% CI: 1.491, 2.232; p-value <0.001). Among lifestyle habits, having ever kept pets was a statiscally significant risk factor (aOR: 1.167; 95% CI: 1.025, 1.328; p-value = 0.019), and frequency of physical activity significantly increased the risk of AR (aOR: 1.394; 95% CI: 1.150, 1.694; p-value <0.001). Likewise, longer duration of TV/computer usage (aOR: 1.224; 95% CI: 1.006, 1.489; p-value = 0.043) and occasional alcohol consumption (aOR: 1.234; 95% CI: 1.101, 1.382; p-value <0.001) increased risk of AR. Having a longer duration of sleep (p-value = 0.11), active and passive smoking (p-value = 0.3 and 0.2, respectively) were non-significantly associated with AR.

DISCUSSION

Prevalence of AR

The prevalence estimates of *self-reported ever rhinitis*, *self-reported current rhinitis*, *current rhinitis per ARIA*, and *current AR* in sequence followed a downward trend. The *self-reported ever rhinitis* classification likely included both self-reported current rhinitis cases and both recovered and "dormant" rhinitis cases, resulting in a higher prevalence of *self-reported ever rhinitis* as compared to that of *self-reported current rhinitis*. However, the downward variation in prevalence of *self-reported current rhinitis*, *current rhinitis per ARIA*, and *current AR* suggests a potential overestimation of AR in studies, as reported previously.[20] Individuals' perception of their health and symptoms are likely exaggerated, resulting in a skewed response in self-report-based surveys (eg, European Community Respiratory Health Survey, ISAAC questionnaire) used in an abundance of studies estimating AR prevalence.[28,29] In the present study, we aimed to obtain a more accurate estimate of current rhinitis (indicated as *current rhinitis per ARIA*) by accounting for each of the symptoms of rhinitis to verify respondents' claim of current rhinitis. Additionally, conducting SPTs discerned allergic rhinitis cases from non-allergic rhinitis cases. We thus posit that the present epidemiological criteria, according to ARIA guidelines and including the objective SPT for atopy, was reasonably stringent.

In Singapore, previous estimates for AR prevalence were 4.5% in adults aged 20–74 in 1994, and rhinitis prevalence around 42% in 12–15-year-olds in 2004.[16,18] Differences in previous prevalence estimates of AR compared to ours (39.4%) could be attributed to varying sample age groups. Indeed, age influences allergic sensitization, with the highest prevalence in 21–40-year-olds in a population of age range 21–86 years, while rhinitis prevalence increases steadily in children aged 4–18, to a peak at 35.8% in 18-year-olds.[30,31] Moreover, Wang et al (2004) estimated the prevalence of rhinitis, which potentially included non-allergic rhinitis cases, resulting in a higher prevalence estimate of AR in 2004.[18]

Total nasal symptom score analyses

The mTNSS of 4.32 in our study population was lower than that reported in the existing literature and summarized in a recent review (pooled mean TNSS = 6.06).[32] We attributed this discrepancy to the differences in study settings, wherein studies assessing TNSS were frequently against a clinical backdrop, resulting in study samples comprising

patients perceiving their AR as sufficiently severe so as to warrant treatment and meriting a higher TNSS.[33] Indeed, one study which occurred in a non-clinical setting similar to ours reported lower mean TNSS in rhinitics.[34]

Comparisons of both moderate/severe versus mild AR, and persistent versus intermittent AR each showed a significant difference in mTNSS between each category. Notably, the increase in mTNSS from mild to moderate/severe AR, and intermittent to persistent AR was of at least one point. Likewise, there were significant differences in mTNSS between the combined ARIA classes MI, MP, MSI, and MSP. While there was an approximate one-point increase from MI to MP and MSI to MSP, the increase from MP to MSI was roughly half a point. Overall, the mTNSS comparisons indicated a significant difference in severity of AR between ARIA classifications. Moreover, the TNSS is calculated according to a separate rubric from those of ARIA guidelines, permitting the independent quantification of the difference in AR severity between the ARIA severity and persistency classifications. Thus, we have provided some evidence supporting the ARIA classification criteria and quantified the difference in ARIA categories using the TNSS.

Additionally, there was a significant stepwise increase in mTNSS between AR cases who have suffered from AR for less than 1 year, 1 to 4 years, and 5 to 10 years. In contrast, the difference in mTNSS between AR lasting for 5 to 10 years versus at least 10 years was non-significant. An earlier study has found that there was a significant increase in severity of AR symptoms after 5 years and 10 years.[35] Concordantly, the trend in mTNSS against duration of AR in our study sample suggests that rhinitis worsens over time until an approximate five-year mark. However, this progression in AR severity is not observed between 5 and 10 years, possibly due to a lowered perception of symptom severity in those having suffered from AR for a relatively long period. Our findings could also reflect a true trend wherein AR severity remains relatively constant from the fifth year onwards, but this would require further verification through independent investigation or future analyses utilizing a larger sample size.

Lastly, we provide evidence supporting the separation of the moderate/severe AR category established in ARIA into moderate and severe AR. Studies have found that the ARIA categorization of AR severity results in a preponderance of moderate/severe AR cases.[36] Classifying AR severity using number of quality-of-life disturbances, by mild (no disturbances), moderate (1–3 disturbances), and severe (4 disturbances) has been previously suggested.[37] However, results from our study indicated while there was a significant difference in mTNSS from 0 to 3 disturbances, the difference in mTNSS between in those with 3 disturbances versus 4 disturbances was non-significant. Furthermore, repeating our analysis for mTNSS in relation to number of disturbances in a subset of individuals who have had a doctor's diagnosis of AR yielded the same trends (see Supplementary Material 1 and 2). Thus, according to present evidence, we propose grouping those with 1 or 2 disturbances as moderate AR cases, and those with 3–4 disturbances as severe AR cases.

Risk factors associated with allergic rhinitis

A prior systematic review found that age, gender, income, and residence were significant risk factors for AR manifestation.[19] With age, the highest prevalence of AR generally occurred in the second and fourth decades of life.[16,19,38] Concordantly, we found that increasing age was associated with lower risk of AR, likely attributable to the preponderance of young adults aged 18 to 25, the minimum age being 18 years, and lower prevalence of AR in the older age groups in our study population. Residence type and income levels were plausibly related, with higher socioeconomic residence types and higher income levels (pooled OR: 2.75; 95% CI: 2.38, 3.18) being associated with increased AR risk across separate studies.[19] Presently, we have found that higher income levels correlated with increased AR risk in a dose-effect manner. Additionally, we found that comparing condominium/private apartment residence to HDB residence increases the risk of AR manifestation. In general, condominium and private housing are a costlier alternative to HDB residences; thus its residents generally comprise those with more disposable income and likely higher income status.

Both having a personal history of drug allergy and having a familiar history of allergic diseases were significant risk factors for AR. It has been established in prior literature that genetics are an important predisposing factor for atopic diseases such as AR.[39,40] Indeed, having a parental history of allergic diseases was consistently an important risk factor when adjusted for age, gender, or both (see Supplementary Material 3). Likewise, we have identified personal history of any drug allergy as another risk factor for AR. Notably, this association between drug sensitivity and atopy or AR has not been formerly identified in earlier reports.[41]

Pet ownership and thus pet exposure significantly increased the risk of AR only when adjusted for age and gender. The significance of association pet ownership and AR manifestation varied between studies, and while evidence for the association between general pet exposure and AR risk exists, the specific animal species and allergen has yet to be clearly defined.[19] Specifically, the direction association of pet fur with allergic respiratory disease was unclear when stratified by pet type (eg, cats and dogs), with cat exposure being an apparent protective factor, and dog ownership presenting a risk factor. Additionally, exposure to any furry pet was a significant risk factor for asthma, but a protective factor for allergic rhinitis.[42] Besides fur, pet dander has been implicated in as an important aeroallergen with high prevalence of sensitization but its link to allergic disease yet to be elucidated.[28,43] Overall, we posit that the "instability' in findings is likely due to modifiability of exposure to pet biological material. For instance, increased frequency or extensiveness in housecleaning activities, or avoidance of the implicated pet would mitigate the effect of pet exposure on allergic reactions and allergic rhinitis.

We found that a higher frequency of physical activity was significantly associated with increased risk of AR. In contrast, previous studies have found that increased physical activity decreases the risk of current AR symptoms, hayfever, and rhinoconjunctivitis.[44-46] Another study diagnosing AR using clinical symptoms in conjunction with an objective test of atopy found that vigorous physical activity increased the likelihood of severe and intermittent AR, and worsened rhinorrhea symptoms.[47] However, moderate-intensity exercise was found to decrease pro-inflammatory cytokine levels and improve AR symptoms.[48] Overall, while the association between physical activity and AR severity in AR cases remains to be further elucidated, the protective effect of physical activity against AR presentation appears to be consistent between studies. We hypothesize that our discrepant findings might be attributed to setting and intensity of physical activity. Outdoor activities such as running and cycling are among the most popular sports in Singapore, resulting in a possible increase in allergen exposure.[49,50] Additionally, there was no discrimination between levels of sports intensity, thus participants whose physical activity were insufficiently intensive to reach a beneficial level likely contributed to our findings.

We found that greater than 5 h of TV or computer use, when adjusted for age and gender, was significantly associated with increased AR risk. Extended duration of screen usage was likely an indicator of an unhealthy lifestyle, entailing sedentary habits and unhealthy food consumption.[51] Moreover, the computer environment serves as an accumulation ground for allergens due to the low frequency of cleanings, resulting in higher risk of allergic sensitization.[52]

Both smoking status and passive smoking to be non-significantly associated with AR. In contrast, previous studies' results indicated smoke exposure as a significant risk factor for AR manifestation.[19] We noted a possible lack of statistical power, whereby our sample population contained relatively few current smokers and passive smokers. Moreover, smoke exposure was a modifiable factor, with avoidance of the smoke source possible via changes to lifestyle and habits. Additionally, tobacco control campaigns targeted at youths, such as those conducted by the Singapore Health Promotion Board, likely contributed to the low number of smokers in our study sample.[53]

Finally, regarding diet, occasional drinking was a significantly risk factor for AR. However, this association was not observed in frequent drinkers. While there is evidence of association between alcohol consumption and AR, the causal

relationship of alcohol on AR is disputed.[54,55] Separately, previous studies of diet and AR have focused on food types separately and in combination as a Mediterranean diet.[56–58] Further studies have also analyzed the effect of overall nutritional intake on AR – notably, the risk of AR significantly increased with each 10% increment in fat intake and 10% decrease in carbohydrate intake.[59] Here, we have estimated the overall dietary GI using food options from the ISAAC questionnaire using the QDGIS, and identified a dose-effect relationship wherein the lower the overall glycemic burden of diet, the lower the risk of AR.

LIMITATIONS AND CONCLUSION

Although all ethnicities were included in the data collection, the disproportion between races in our sample, particularly of Malays and Indians constituting significant portions of both the overall Singaporean and Malaysian populations, posed the issue of ascertainment bias. Indeed, there was an overrepresentation of Chinese in our sample population (83.6%). In comparison, the Singapore population census of 2020 indicated that the resident proportion of Chinese in the Singaporean population was 74.3%, while Chinese made up 69.9% of the Singapore residents aged 20–24 years. Moreover, the potentially small sample sizes of Malay and Indian ethnicities ($n < 2000$) predispose separate analysis of these groups to a lack of statistical power. Aside, upon obtaining a sufficient sample size, we plan to stratify our sample population by race for a more accurate analysis in future. Nonetheless, the present analysis focused on the ethnic Chinese subset of our sample population.

In conclusion, we have established an updated prevalence of AR in a population of young adults from Malaysia and Singapore. Additionally, significant differences were found between the mTNSS of AR persistency and severity categories. Based on the mTNSS of AR cases categorized by number of disturbances to quality of life, we propose that AR severity can be categorized into mild (0 disturbances), moderate (1–2 disturbances), and severe (3–4 disturbances). Separately, age, gender and parental history of allergic diseases were important risk factors for AR. We have also found evidence of pet ownership as a predisposing factor for AR manifestation, while smoking was non-significantly associated with AR. Finally, having a lower overall GI of diet appears to be protective against AR. Moving forward, gene expression analyses can be carried out to further verify and unravel the processes underlying AR and its risk factors.

Abbreviations:

95% CI: 95% confidence interval; aOR: adjusted odds ratio; AR: allergic rhinitis; BM: body mass index; mTNSS: mean total nasal symptom score; NANR: non-allergic non-rhinitis; OR, odds ratio; QDGIS: quality of diet based on glycemic index score; RM: Malaysian ringgit; SD: standard deviation; SGD: Singapore dollar; SPT: skin prick test; TNSS: total nasal symptom score.

Acknowledgements

We extend our sincerest gratitude to all participants for their contributions to this study.

Funding

F.T.C. (Singapore) received grants from the National University of Singapore (N-154-000-038-001), Singapore Ministry of Education Academic Research Fund (R-154-000-191-112; R-154-000-404-112; R-154-000-553-112; R-154-000-565-112; R-154-000-630-112; R-154-000-A08-592; R-154-000-A27-597; R-154-000-A91-592; R-154-000-A95-592; R154-000-B99-114), Biomedical Research Council (BMRC) (Singapore) (BMRC/01/1/21/18/077; BMRC/04/1/21/19/315; BMRC/APG2013/108), Singapore Immunology Network (SIgN-06-006; SIgN-08-020), National Medical Research Council (NMRC) (Singapore) (NMRC/1150/2008), and the Agency for Science Technology and Research (A*STAR) (Singapore) (H17/01/a0/008; and APG2013/108). The funding agencies had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

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

Author contributions

F.T.C. conceived and supervised the current research study. Q.Y.A.W. conducted the literature review, analyzed, and interpreted the data, and wrote the manuscript. Q.Y.A.W., J.J.L., J.Y.N., P.M., W.Y.T., Y.Y.E.L., Y.T.N., Y.Y.S, S.A.M., Y.R.W., K.F.T., S.M.R.S., K.R., and Y.H.S. assisted in recruiting study participants and data collation. All authors read and approved the final manuscript.

Ethics approval and consent

Ethical approval for this study was granted by the NUS Institutional Review Board (IRB reference code: NUS-07-023, NUS-09-256, NUS-10-445, NUS-13-075, NUS-14-150, and NUS-18-036), the Scientific and Ethical Review

Committee of UTAR (reference code: U/SERC/03/2016), and the Sunway University Research Ethics Committee (reference code: SUREC 2019/029). This study was performed in compliance with the Declaration of Helsinki, Good Clinical Practice, and local regulatory guidelines. Before participation, each subject was informed of this study's details via a Participant Information Sheet and provided written informed consent to participation through the signature of a Consent Form.

Authors' consent for publication

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

Declaration of competing interest

F.T.C. reports grants from Singapore Ministry of Education Academic Research Fund, Singapore Immunology Network, National Medical Research Council (Singapore), Biomedical Research Council (Singapore), and the Agency for Science Technology and Research (Singapore), during the conduct of the study; and has received consultancy fees from Sime Darby Technology Centre, First Resources Ltd, Genting Plantation, and Olam International, outside the submitted work. The other authors declare no other competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100704.

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REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the world health organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8–160. https://doi.org/10.1111/j.1398-9995.2007.01620.x.
2. Greiner AN, Meltzer EO. Overview of the treatment of allergic rhinitis and nonallergic rhinopathy. *Proc Am Thorac Soc*. 2011;8:121–131. https://doi.org/10.1513/pats.201004-033RN.
3. Dispenza MC. Classification of hypersensitivity reactions. *Allergy Asthma Proc*. 2019;40:470–473. https://doi.org/10.2500/aap.2019.40.4274.
4. Lei DK, Grammer LC. An overview of allergens. *Allergy Asthma Proc*. 2019;40:362–365. https://doi.org/10.2500/aap.2019.40.4247.
5. Chew FT, Lim SH, Goh DYT, Lee BW. Sensitization to local dust-mite fauna in Singapore. *Allergy*. 1999;54:1150–1159. https://doi.org/10.1034/j.1398-9995.1999.00050.x.
6. Chew FT, Zhang L, Ho TM, Lee BW. House dust mite fauna of tropical Singapore. *Clin Exp Allergy*. 1999;29:201–206. https://doi.org/10.1046/j.1365-2222.1999.00493.x.
7. Yeoh SM, Kuo IC, Wang DY, Liam CK, Sam CK, De Bruyne JA, et al. Sensitization profiles of Malaysian and Singaporean subjects to allergens from dermatophagoides pteronyssinus and blomia tropicalis. *Int Arch Allergy Immunol*. 2003;132:215–220. https://doi.org/10.1159/000074302.
8. Chew FT, Lim SH, Shang HS, Dahlia MD, Goh DY, Lee BW, et al. Evaluation of the allergenicity of tropical pollen and airborne spores in Singapore. *Allergy*. 2000;55:340–347. https://doi.org/10.1034/j.1398-9995.2000.00308.x.
9. Ong TC, Lim SH, Chen X, Mohd Dali SD, Tan HTW, Lee BW, et al. Fern spore and pollen airspora profile of Singapore. *Aerobiologia*. 2012;28:135–151. https://doi.org/10.1007/s10453-011-9217-z.
10. Ellis AK, Soliman M, Steacy L, Boulay M, Boulet LP, Keith PK, et al. The Allergic Rhinitis - clinical Investigator Collaborative (AR-CIC): nasal allergen challenge protocol optimization for studying AR pathophysiology and evaluating novel therapies. *Allergy Asthma Clin Immunol*. 2015;11:16. https://doi.org/10.1186/s13223-015-0082-0.
11. de Marco R, Cappa V, Accordini S, Rava M, Antonicelli L, Bortolami O, et al. Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010. *Eur Respir J*. 2012;39:883–892. https://doi.org/10.1183/09031936.00061611.
12. Zhang Y, Zhang L. Increasing prevalence of allergic rhinitis in China. *Allergy Asthma Immunol Res*. 2019;11:156–169.
13. Leth-Møller KB, Skaaby T, Linneberg A. Allergic rhinitis and allergic sensitisation are still increasing among Danish adults. *Allergy*. 2020;75:660–668. https://doi.org/10.1111/all.14046.
14. Alqahtani JM. Atopy and allergic diseases among Saudi young adults: a cross-sectional study. *J Int Med Res*. 2020;48,300060519899760. https://doi.org/10.1177/0300060519899760.
15. Oliveira TB, Persigo ALK, Ferrazza CC, Ferreira ENN, Veiga ABG. Prevalence of asthma, allergic rhinitis and pollinosis in a city of Brazil: a monitoring study. *Allergol Immunopathol*. 2020;48:537–544. https://doi.org/10.1016/j.aller.2020.03.010.
16. Ng TP, Tan WC. Epidemiology of allergic rhinitis and its associated risk factors in Singapore. *Int J Epidemiol*. 1994;23:553–558. https://doi.org/10.1093/ije/23.3.553.
17. Goh D, Chew F, Quek S, Lee B. Prevalence and severity of asthma, rhinitis, and eczema in Singapore schoolchildren. *Arch Dis Child*. 1996;74:131–135.
18. Wang XS, Tan TN, Shek LP, Chng SY, Hia CP, Ong NB, et al. The prevalence of asthma and allergies in Singapore; data from two ISAAC surveys seven years apart. *Arch Dis Child*. 2004;89:423–426. https://doi.org/10.1136/adc.2003.031112.
19. Chong SN, Chew FT. Epidemiology of allergic rhinitis and associated risk factors in Asia. *World Allergy Organ J*. 2018;11:17. https://doi.org/10.1186/s40413-018-0198-z.
20. Kim DH, Lim DH, Samra M, Kim EH, Kim JH. How accurate are the ISAAC questions for diagnosis of allergic rhinitis in Korean children? *Int J Environ Res Publ Health*. 2018;15. https://doi.org/10.3390/ijerph15071527.

21. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values. *Diabetes Care*. 2008;31:2281–2283. https://doi.org/10.2337/dc08-1239, 2008.

22. Henry CJ, Quek RYC, Kaur B, Shyam S, Singh HKG. A glycaemic index compendium of non-western foods. *Nutr Diabetes*. 2021;11:2. https://doi.org/10.1038/s41387-020-00145-w.

23. Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A, Polychronopoulou A, et al. Diet and colorectal cancer: a case-control study in Greece. *Int J Cancer*. 1983;32:1–5. https://doi.org/10.1002/ijc.2910320102.

24. Andiappan AK, Wang DY, Anantharaman R, Parate PN, Suri BK, Low HQ, et al. Genome-wide association study for atopy and allergic rhinitis in a Singapore Chinese population. *PLoS One*. 2011;6, e19719. https://doi.org/10.1371/journal.pone.0019719.

25. ISAAC Steering Committee. *ISAAC – the International Study of Asthma and Allergies in Childhood*; 2021. http://isaac.auckland.ac.nz.

26. ISAAC Steering Committee. *ISAAC Phase Three Newsletter*. 2001.

27. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2010.

28. Katelaris CH, Lee BW, Potter PC, Maspero JF, Cingi C, Lopatin A, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. *Clin Exp Allergy*. 2012;42:186–207.

29. Wise SK, Lin SY, Toskala E, Orlandi RR, Akdis CA, Alt JA, et al. International consensus statement on allergy and rhinology: allergic rhinitis. *Int Forum Allergy Rhinol*. 2018;8:108–352. https://doi.org/10.1002/alr.22073.

30. Kurukulaaratchy RJ, Karmaus W, Raza A, Matthews S, Roberts G, Arshad SH, et al. The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life. *Clin Exp Allergy*. 2011;41:851–859. https://doi.org/10.1111/j.1365-2222.2011.03765.x.

31. Warm K, Hedman L, Lindberg A, Lötvall J, Lundbäck B, Rönmark E, et al. Allergic sensitization is age-dependently associated with rhinitis, but less so with asthma. *J Allergy Clin Immunol*. 2015;136:1559–1565. https://doi.org/10.1016/j.jaci.2015.06.015. e1552.

32. Li AR, Zhang K, Reddy PD, Nguyen SA, Miglani A, Fried J, et al. Systematic review of measures of disease severity in rhinitis. *Int Forum Allergy Rhinol*. 2021;11:1367–1377. https://doi.org/10.1002/alr.22794.

33. Van Hoecke H, Vastesaeger N, Dewulf L, Sys L, van Cauwenberge P. Classification and management of allergic rhinitis patients in general practice during pollen season. *Allergy*. 2006;61:705–711. https://doi.org/10.1111/j.1398-9995.2006.01057.x.

34. Downie SR, Andersson M, Rimmer J, Leuppi JD, Xuan W, Akerlund A, et al. Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. *Allergy*. 2004;59:406–414. https://doi.org/10.1111/j.1398-9995.2003.00420.x.

35. Rondon C, Campo P, Eguiluz-Gracia I, Plaza C, Bogas G, Galindo P, et al. Local allergic rhinitis is an independent rhinitis phenotype: the results of a 10-year follow-up study. *Allergy*. 2018;73:470–478. https://doi.org/10.1111/all.13272.

36. Van Hoecke H, Vastesaeger N, Dewulf L, De Bacquer D, van Cauwenberge P. Is the allergic rhinitis and its impact on asthma classification useful in daily primary care practice? *J Allergy Clin Immunol*. 2006;118:758–759. https://doi.org/10.1016/j.jaci.2006.05.015.

37. Valero A, Ferrer M, Sastre J, Navarro AM, Monclús L, Martí-Guadaño E, et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. *J Allergy Clin Immunol*. 2007;120:359–365. https://doi.org/10.1016/j.jaci.2007.04.006.

38. Cazzoletti L, Ferrari M, Olivieri M, Verlato G, Antonicelli L, Bono R, et al. The gender, age and risk factor distribution differs in self-reported allergic and non-allergic rhinitis: a cross-sectional population-based study. *Allergy Asthma Clin Immunol*. 2015;11:36. https://doi.org/10.1186/s13223-015-0101-1.

39. Wang DY. Genetic predisposition for atopy and allergic rhinitis in the Singapore Chinese population. *apa*. 2011;1:152–156. https://doi.org/10.5415/apallergy.2011.1.3.152.

40. Wang DY. Risk factors of allergic rhinitis: genetic or environmental? *Therapeut Clin Risk Manag*. 2005;1:115–123. https://doi.org/10.2147/tcrm.1.2.115.62907.

41. Haddi E, Charpin D, Tafforeau M, Kulling G, Lanteaume A, Kleisbauer JP, et al. Atopy and systemic reactions to drugs. *Allergy*. 1990;45:236–239. https://doi.org/10.1111/j.1398-9995.1990.tb00489.x.

42. Takkouche B, González-Barcala FJ, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. *Allergy*. 2008;63:857–864.

43. Passali D, Cingi C, Staffa P, Passali F, Muluk NB, Bellussi ML, et al. The international study of the allergic rhinitis survey: outcomes from 4 geographical regions. *apa*. 2018;8. https://doi.org/10.5415/apallergy.2018.8.e7, 0-0.

44. Vlaski E, Stavric K, Seckova L, Kimovska M, Isjanovska R. Influence of physical activity and television-watching time on asthma and allergic rhinitis among young adolescents: preventive or aggravating? *Allergol Immunopathol*. 2008;36:247–253. https://doi.org/10.1016/s0301-0546(08)75218-2.

45. Garcia-Marcos L, Canflanca IM, Garrido JB, Varela AL, Garcia-Hernandez G, Guillen Grima F, et al. Relationship of asthma and rhinoconjunctivitis with obesity, exercise and Mediterranean diet in Spanish schoolchildren. *Thorax*. 2007;62:503–508. https://doi.org/10.1136/thx.2006.060020.

46. Kohlhammer Y, Zutavern A, Rzehak P, Woelke G, Heinrich J. Influence of physical inactivity on the prevalence of hay fever. *Allergy*. 2006;61:1310–1315. https://doi.org/10.1111/j.1398-9995.2006.01131.x.

47. Park J, Park JH, Park J, Choi J, Kim TH. Association between allergic rhinitis and regular physical activity in adults: a nationwide cross-sectional study. *Int J Environ Res Publ Health*. 2020;17. https://doi.org/10.3390/ijerph17165662.

48. Tongtako W, Klaewsongkram J, Jaronsukwimal N, Buranapraditkun S, Mickleborough TD, Suksom D, et al. The effect of acute exhaustive and moderate intensity exercises on nasal cytokine secretion and clinical symptoms in allergic

rhinitis patients. *Asian Pac J Allergy Immunol*. 2012;30:185–192.

49. Government of Singapore. *Top Sport & Physical Activity by SG Residents - Overall*; 2020. https://data.gov.sg/dataset/top-sport-physical-activity-by-sg-residents-overall>.
50. Bonini S, Bonini M, Bousquet J, Brusasco V, Canonica GW, Carlsen KH, et al. Rhinitis and asthma in athletes: an ARIA document in collaboration with GA2LEN. *Allergy*. 2006;61:681–692. https://doi.org/10.1111/j.1398-9995.2006.01080.x.
51. García-Almaraz R, Reyes-Noriega N, Del-Río-Navarro BE, Berber A, Navarrete-Rodríguez EM, Ellwood P, et al. Prevalence and risk factors associated with allergic rhinitis in Mexican school children: global Asthma Network Phase I. *World Allergy Organ J*. 2021;14, 100492. https://doi.org/10.1016/j.waojou.2020.100492.
52. Li CW, Chen DH, Zhong JT, Lin ZB, Peng H, Lu HG, et al. Epidemiological characterization and risk factors of allergic rhinitis in the general population in guangzhou city in China. *PLoS One*. 2014;9, e114950. https://doi.org/10.1371/journal.pone.0114950.
53. Health Promotion Board. *Health Promotion Board Unveils Two-Pronged Strategy to Step up Tobacco Control Efforts on World No Tobacco Day*; 2014. https://www.hpb.gov.sg/article/health-promotion-board-unveils-two-pronged-strategy-to-step-up-tobacco-control-efforts-on-world-no-tobacco-day>.
54. Bendtsen P, Grønbaek M, Kjaer SK, Munk C, Linneberg A, Tolstrup JS, et al. Alcohol consumption and the risk of self-reported perennial and seasonal allergic rhinitis in young adult women in a population-based cohort study. *Clin Exp Allergy*. 2008;38:1179–1185. https://doi.org/10.1111/j.1365-2222.2008.02945.x.
55. Skaaby T, Kilpeläinen TO, Taylor AE, Mahendran Y, Wong A, Ahluwalia TS, et al. Association of alcohol consumption with allergic disease and asthma: a multi-centre Mendelian randomization analysis. *Addiction*. 2019;114:216–225. https://doi.org/10.1111/add.14438.
56. Ellwood P, Asher MI, Björkstén B, Burr M, Pearce N, Robertson CF, et al. Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. ISAAC Phase One Study Group. *Eur Respir J*. 2001;17:436–443. https://doi.org/10.1183/09031936.01.17304360.
57. Ellwood P, Asher MI, Garcia-Marcos L, Williams H, Keil U, Robertson C, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the International Study of Asthma and Allergies in Childhood (ISAAC) phase three. *Thorax*. 2013;68:351–360. https://doi.org/10.1136/thoraxjnl-2012-202285.
58. Castro-Rodriguez JA, Garcia-Marcos L. What are the effects of a mediterranean diet on allergies and asthma in children? *Front Pediatr*. 2017;5. https://doi.org/10.3389/fped.2017.00072.
59. Kim SY, Sim S, Park B, Kim J-H, Choi HG. High-fat and low-carbohydrate diets are associated with allergic rhinitis but not asthma or atopic dermatitis in children. *PLoS One*. 2016;11, e0150202. https://doi.org/10.1371/journal.pone.0150202.