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The burden of allergic rhinitis is undermanaged in a large proportion of Chinese young adults from Singapore

Qi Yi Ambrose Wong BSC (Hons), Jun Jie Lim BSc (Hons), Jun Yan Ng BSc (Hons), Praneeth Malipeddi MSc, Yi Ying Eliza Lim BSc (Hons), Yang Yie Sio Ph.D. and Fook Tim Chew Ph.D.*

ABSTRACT

Background: Allergic rhinitis (AR) is a nasal disorder characterized by the simultaneous manifestation of at least 2 out of 4 possible symptoms: rhinorrhea, nasal itching, nasal pruritus, and sneezing. Presently, among Chinese young adults from Singapore, we characterised AR phenotypes, established Total Nasal Symptom Score (TNSS) baselines, and examined the management of AR.

Methods: Participants completed an investigator-administered International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and underwent a skin prick test (SPT). Individuals exhibiting sensitization during the SPT while having at least 2 rhinitis symptoms were identified as AR cases, then categorized into Allergic Rhinitis in Asthma (ARIA) classifications.

Results: There were 9323 subjects analyzed. AR prevalence was estimated at 35.4%. Rhinorrhea was perceived as the most severe (mean Nasal Symptom Score (mNSS) $\pm$ SD: 1.42 $\pm$ 0.74), while nasal pruritus was the least severe (mNSS $\pm$ SD: 1.24 $\pm$ 0.68). Among moderate-severe AR (68.1%), most were affected by either troublesome symptoms (27.7%) or sleep disturbances (18.4%). By ARIA classes, 26.6% were mild intermittent, 5.4% were mild persistent, 50.3% were moderate-severe intermittent, and 17.6% were moderate-severe persistent. The mean TNSS (mTNSS) of AR cases was 4.43 (SD $=$ 2.49) and between AR classifications, the mTNSS was significantly different. Notably, a large proportion of AR cases remained undiagnosed (85.2%), untreated (72.5%), or both (65.4%); 19.8% self-medicated for AR.

Conclusions: There was a significant difference in TNSS of the AR phenotypes, and among phenotypes with a higher mTNSS, a large proportion remained untreated, undiagnosed, or both. The evidence indicates an existing burden of AR among Chinese young adults in Singapore which is notably undermanaged.

Keywords: Allergic rhinitis, ARIA, Disease management, ISAAC, TNSS

Department of Biological Sciences, Faculty of Science, National University of Singapore, 117543, Singapore
*Corresponding author. Department of Biological Sciences, Faculty of Science, National University of Singapore, Allergy and Molecular Immunology Laboratory, Lee Hiok Kwee Functional Genomics Laboratories, Block S2, Level 5, 14 Science Drive 4, Lower Kent Ridge Road, 117543, Singapore. E-mail: dbscft@nus.edu.sg
Full list of author information is available at the end of the article

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INTRODUCTION

Background of Allergic Rhinitis

Allergic rhinitis (AR) describes the disorder of the nose wherein IgE-mediated inflammation of the nasal membrane results in symptoms characteristic of rhinitis.[1] Per Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, rhinitis manifests as the simultaneous presence of at least 2 out of 4 possible symptoms: rhinorrhea, nasal itching, nasal pruritus, and sneezing.[1] Worldwide, AR has been estimated to affect approximately 500 million people.[2] Nevertheless, AR appears to present itself heterogeneously across the globe: variations in definitions, diagnosis methods, and sample populations have resulted in a collection of prevalence estimates for AR which range from less than 5%–52%.[3–5] While AR is not associated with severe morbidity and mortality, the burden of this disease is not trivial.[6] AR is a detriment to health-related quality of life, disrupting sleep, social functioning, mental state, and various aspects of daily living.[1,2,4,7] The impacts of AR on the individual further translate into direct healthcare costs and indirect presenteeism-absenteeism costs.[4,6] Although the cost of treating AR is lower than asthma, the high prevalence of AR renders the total cost of treatment on the population scale a significant one.[4,6] Additionally, AR symptoms and medications, especially regarding the sedative effect of antihistamines, further result in lowered productivity, resulting in economic productivity losses among employees.[4,8]

Objectives and rationale

Previously, in the Singapore/Malaysia Cross-sectional Genetics Epidemiology Study (SMCGES) we established the patterns of AR manifestation among Chinese young adults with respect to categorization according to persistency, severity, disturbances to life, and duration of disease.[9] Moreover, the differences in AR categorization translated into statistically significant differences in Total Nasal Symptom Score (TNSS), an indicator of AR severity.[9,10] Presently, we focus on the Chinese young adult Singaporean subgroup of our study with 3 aims: (I) identifying the patterns of AR in the Singaporean cohort only, (II) establishing current baselines of the severity of AR, and (III) examining the burden of AR and its management among AR cases.

MATERIALS AND METHODS

Participants and data collection

As part of the Singapore/Malaysia Cohort Genetic Epidemiology Study (SMCGES), an ongoing large-scale cross-sectional study that began in 2005, participants were recruited from the National University of Singapore, Singapore via email and poster advertisements. The exclusion criterion for individuals intending to participate in this study was being below the age of 18 years and having taken antihistamines within the past 3 days. Consenting and eligible subjects completed an investigator-administered questionnaire and skin prick test (SPT).

The skin prick test (SPT) was administered by trained personnel to participants who had not taken antihistamines for at least 3 days prior; those who had consumed antihistamines within 3 days preceding data collection were rescheduled. The SPT tested for subject sensitization to *Blomia tropicalis* and *Dermatophagoides pteronyssinus*, 2 common House Dust Mites (HDM) in Southeast Asia. The emergence of a wheal of at least 3 mm diameter at the site of allergen application was considered a positive SPT result indicating sensitization to the applied allergen, thus designating the test subject as an atopic case. A positive histamine control and negative saline control were included in the SPT, and the SPT procedure was consistent with previous descriptions.[11]

Our questionnaire was adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three Core and Environmental Questionnaires, which have been standardized and validated for the research of allergic diseases, including AR.[12] Per the established ISAAC protocol, data pertaining to symptoms of rhinitis and epidemiological background were collected from each participant as previously described (Supplementary Table 1).[9] Additionally, we considered the usage of 5 medication types used to treat AR: antihistamines, nasal sprays, nasal irrigation therapies, decongestants, and mucolytics. Respondents indicating the usage of any of the aforementioned medications were considered as

ever medication users, of whom those who were AR cases were further classified as medicating AR individuals.

Disease definition and classification criteria for allergic rhinitis

Data on rhinitis symptoms were obtained according to methods described previously (Supplementary Table 1).[9] *Current rhinitis* cases were classified according to ARIA guidelines, of whom those who also showed sensitization to either *Blomia tropicalis* or *Dermatophagoides pteronyssinus* during the SPT were further classified as *allergic rhinitis* cases, henceforth referred to as AR cases.[2] Under ISAAC recommendations, missing or "other" responses were included in the denominator as AR controls.[13] Those who separately affirmed ever having had allergic rhinitis were classified as *diagnosed allergic rhinitis* cases.

AR persistency (ie, intermittent or persistent AR), and AR severity (ie, mild or moderate-severe AR) were also classified per ARIA guidelines.[2] The classification criteria for AR persistency were applied to the individual rhinitis symptoms to obtain symptom persistency status (ie, intermittent or persistent AR symptoms). AR persistency and severity classifications were further combined to obtain the four ARIA classes: mild intermittent (MI), mild persistent (MP), moderate-severe intermittent (MSI), and moderate-severe persistent (MSP). The Total Nasal Symptom Score (TNSS), a separate metric indicating AR severity described in existing publications, was also calculated from symptom scores of each AR symptom for each AR case.[10] Lastly, the duration of disease for AR was determined in categories of less than 1 year, 1–4 years, 5–10 years, and 10 or more years.

Overall, the classification criteria for atopy, rhinitis, AR, and AR classifications (ie, persistency, severity) were consistent with ARIA guidelines and previous descriptions.[1,2,9]

Statistical analysis

Statistical analyses were conducted using R version 4.0.3.[14] For demographic factors, the Wilcoxon rank sum test (Mann Whitney *U* test) was conducted to compare the means of continuous variables for each AR status (eg, mean age of AR cases versus mean age of AR controls), while Pearson's Chi-squared test was conducted for categorical variables (eg, gender). Severities of rhinitis symptoms were assessed via pairwise comparisons of mean symptom NSS using Welch Two Sample t-tests. Mean TNSS (mTNSS) was calculated for each phenotype within the AR classes (ie, persistency, severity, number of disturbances, and duration of disease) and reported with its accompanying standard deviation (SD). Additionally, mTNSS of phenotypes within each AR classification were compared using both Welch Two Sample t-tests and using a Minimum Clinically Important Difference (MCID) threshold calculated using Cohen's method, the latter of which entailed multiplying the SD of the mTNSS for the comparison phenotype by 0.2.[15] A difference in mTNSS exceeding that MCID threshold indicated a clinically important difference in mTNSS. Results with a corresponding p-value of less than 0.05 were considered statistically significant.

RESULTS

Demographics of study sample and prevalence of AR

Rhinitis and SPT data from 9323 subjects of Chinese ethnicity recruited between 2007 and 2021 were analyzed. The mean age of the Singapore cohort was 22.6 years (SD = 5.2 years) with 94.5% falling within the 18–35 year age range, and the prevalence of AR was estimated at 35.4% (3304/9323). Among AR controls and AR cases, the mean age was 22.7 years (5.6 years) and 22.3 years (SD = 4.4 years), respectively. Females made up 57.9% (5386/9323) study sample, constituting 60.0% (3605/6019) of AR controls and 53.9% (1781/3304) of AR cases. 68.2% (6354/9323) of participants were born in Singapore, with 62.9% (3785/9323) of AR controls and 77.8% (2569/9323) of AR cases being Singapore-born individuals. Of those not born in Singapore, the mean number of years lived in Singapore was 6.0 years (SD = 6.9 years); non-local AR controls and non-local AR cases had spent a mean duration of 5.7 years (SD = 6.6 years) and 7.1 years (SD = 7.5 years) in Singapore, respectively. Participants predominantly resided in Singapore government Housing Development Board (HDB) flats (67.0%, 5947/9323) and fell within the total monthly family

income bracket of more than SGD2000 and less than SGD4000 (33.8%, 3.057/9323). The study sample demographics are summarized in Table 1.

Patterns and severity of rhinitis symptoms

Proportions of rhinitis symptom manifestation among AR cases, arranged in order of decreasing frequency was 91.7% (3024/3298) sneezing, 89.3% (2940/3291) rhinorrhea, 81.3% (2668/3280) nasal blockage, and 76.5% (2515/3286) nasal pruritus (Supplementary Fig. 1). Across rhinitis symptoms, the temporal trend of symptom occurrence was similar – most symptom cases (≥79.1%) reported at most 3 days per week of symptom occurrence, and a majority of symptom cases (≥71.9%) reported at most 3 weeks of consecutive symptom occurrence (Supplementary Table 2). By individual symptom persistency, persistent nasal blockage was the most frequently reported (15.6%, 369/2362), while persistent nasal pruritus was the least frequent (13.4%, 299/2238) (Supplementary Fig. 1).

Variable	Overall N = 9323	Allergic rhinitis		p-value[b]
		No N = 6019	Yes N = 3304	
Age at collection[a]	22.6 ± 5.2	22.7 ± 5.6	22.3 ± 4.4	0.529
NA	36	27	9	
Gender				<0.001
Female	5386 (57.9%)	3605 (60.0%)	1781 (53.9%)	
Male	3921 (42.1%)	2400 (40.0%)	1521 (46.1%)	
NA	16	14	2	
Born in Singapore				<0.001
No	2969 (31.8%)	2234 (37.1%)	735 (22.2%)	
Yes	6354 (68.2%)	3785 (62.9%)	2569 (77.8%)	
Years in Singapore among non-locals	6.0 ± 6.9	5.7 ± 6.6	7.1 ± 7.5	0.003
NA	6586	3960	2626	
Housing type				0.015
Housing Development Board (HDB) flat	5947 (67.0%)	3746 (66.0%)	2201 (68.8%)	
Condominium/Private apartment	1738 (19.6%)	1160 (20.4%)	578 (18.1%)	
Landed property	1190 (13.4%)	768 (13.5%)	422 (13.2%)	
NA	448	345	103	
Income category				<0.001
<SGD2000	1983 (21.9%)	1412 (24.2%)	571 (17.7%)	
≥SGD2000 and <SGD4000	3057 (33.8%)	1978 (34.0%)	1079 (33.4%)	
≥SGD4000 and ≤SGD6000	1775 (19.6%)	1118 (19.2%)	657 (20.3%)	
>SGD6000	2240 (24.7%)	1316 (22.6%)	924 (28.6%)	
NA	268	195	73	

Table 1. Summary table for demographics of the Singapore cohort *[a]Mean ± SD. [b]Wilcoxon rank sum test was conducted for age and years spent in Singapore among non-locals; Pearson's Chi-squared test was performed for gender, being born in Singapore, housing type, and income category*

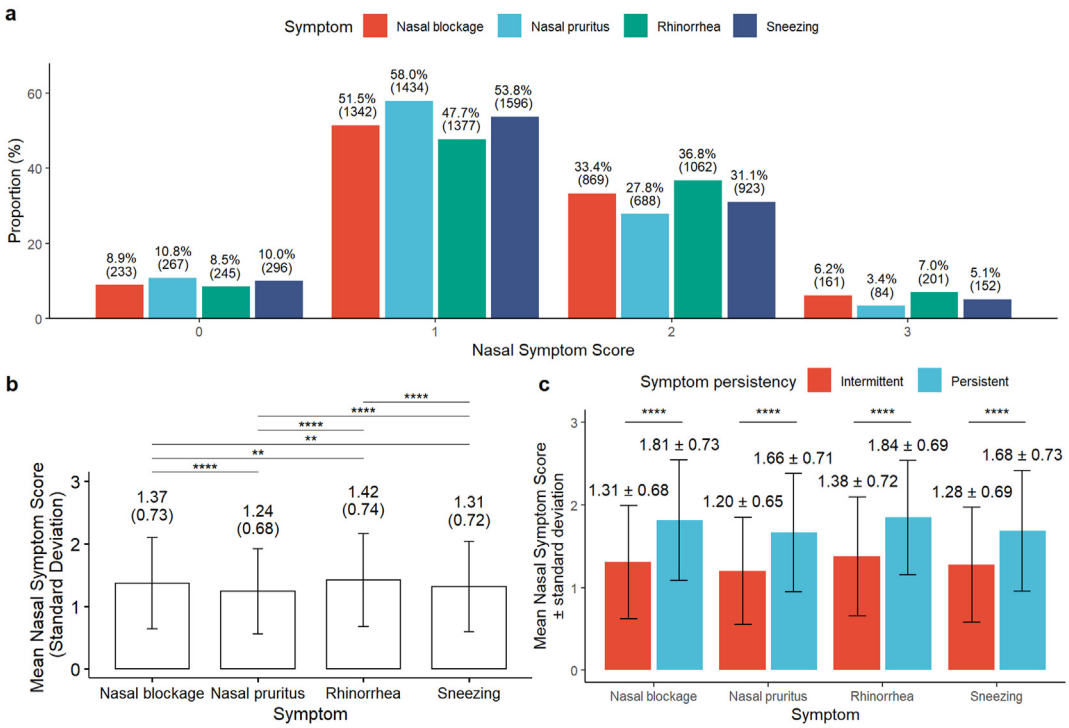

Fig. 1 Patterns of Nasal Symptom Score (NSS) for each rhinitis symptom: nasal blockage, nasal pruritus, rhinorrhea, and sneezing. Where applicable, statistical significance is represented by asterisks – ns: $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. (a) Distribution of responses to NSS for each rhinitis symptom. Proportions of each NSS value are denominated against the total number of NSS responses for each symptom. (b) Mean NSS and standard deviation of each rhinitis symptom, and their statistical comparison to other rhinitis symptoms. (c) Mean NSS and standard deviation of intermittent and persistent variants of each rhinitis symptom, and their statistical comparison

The distribution of NSS responses to each rhinitis symptom was roughly similar, with the majority of responses being NSS = 1 and a resultant median NSS of 1 for all rhinitis symptoms (Fig. 1a). Nonetheless, mean NSS (mNSS) was different between each symptom, with pairwise t-tests showing that each mean symptom NSS was significantly different from all other mean symptom NSS ($p \leq 0.01$ for all t-tests, Fig. 1b). In order of decreasing severity, the mNSS of each symptom was 1.42 (SD = 0.74) for rhinorrhea, 1.37 (SD = 0.73) for nasal blockage, 1.31 (SD = 0.72) for sneezing, and 1.24 (SD = 0.68) for nasal pruritus. Stratified for symptom persistency, mNSS of persistent rhinitis symptoms were consistently higher than that of intermittent symptoms, to a statistically significant degree ($p \leq 0.0001$ for all t-tests, Fig. 1c).

AR phenotypes and analyses of their corresponding mTNSS

The proportion of intermittent AR cases was 76.9% (2216/2880), while 23.1% (664/2880) suffered persistent AR (Fig. 2a). 68.1% (2250/3304) AR cases had moderate-severe AR, among which the modal number of disturbances to life due to AR was 1 (58.1%, 1307/2250) (Fig. 2b and c). Having either troublesome symptoms (27.7%, 624/2250) or only sleep disturbances (18.4%, 413/2250) accounted for most of the AR disturbance responses (Fig. 2d). Overlaying the persistency and severity classifications gave the proportions of ARIA classes: MI - 26.6% (766/2880); MP - 5.4% (156/2880); MSI - 50.3% (1450/2880); MSP - 17.6% (508/2880) (Supplementary Table 3). By duration suffered from AR, 9.3% (295/3179) indicated less than 1 year, 20.1% (640/3179) 1–4 years, 24.0% (764/3179) 5–10 years, and 46.6% (1480/3179) at least 10 years (Fig. 2e). A large proportion of AR cases (22.8%) had suffered MSI AR for at least 10 years, while another 4 groups constituted at least one-tenth of AR cases: ordered by decreasing frequency, MSI AR lasting 5–10 years (12.9%), MSI AR lasting 1–4 years (10.7%), MSP AR lasting at least 10 years (10.6%), and MI AR lasting at least 10 years (10.0%) (Fig. 2f).

Of all AR cases, the mean TNSS (mTNSS) was 4.43 (SD = 2.49) and median TNSS was 4 (interquartile range: 3–6) (Fig. 3a). The mTNSS of persistent AR was 5.51 (SD = 2.40), significantly higher than the mTNSS of intermittent AR (mTNSS ± SD: 4.31 ± 2.37; $p \leq 0.0001$; Fig. 3b). Moderate-severe AR cases reported a mTNSS of 4.93 (SD = 2.55), significantly higher than that of mild AR (mTNSS ± SD: 3.35 ± 1.96; $p \leq 0.0001$; Fig. 3c). Deconstruction of the severity criteria into number of disturbances showed between each increase from no disturbances (mTNSS ± SD: 3.35 ± 1.95) to experiencing three disturbances (mTNSS ± SD: 6.33 ± 2.63), there was a statistically significant mTNSS increase ($p \leq 0.0001$; Fig. 3d). In contrast, the increase in mTNSS from 3 disturbances to 4 disturbances (mTNSS ± SD: 6.86 ± 2.78) was non-significant.

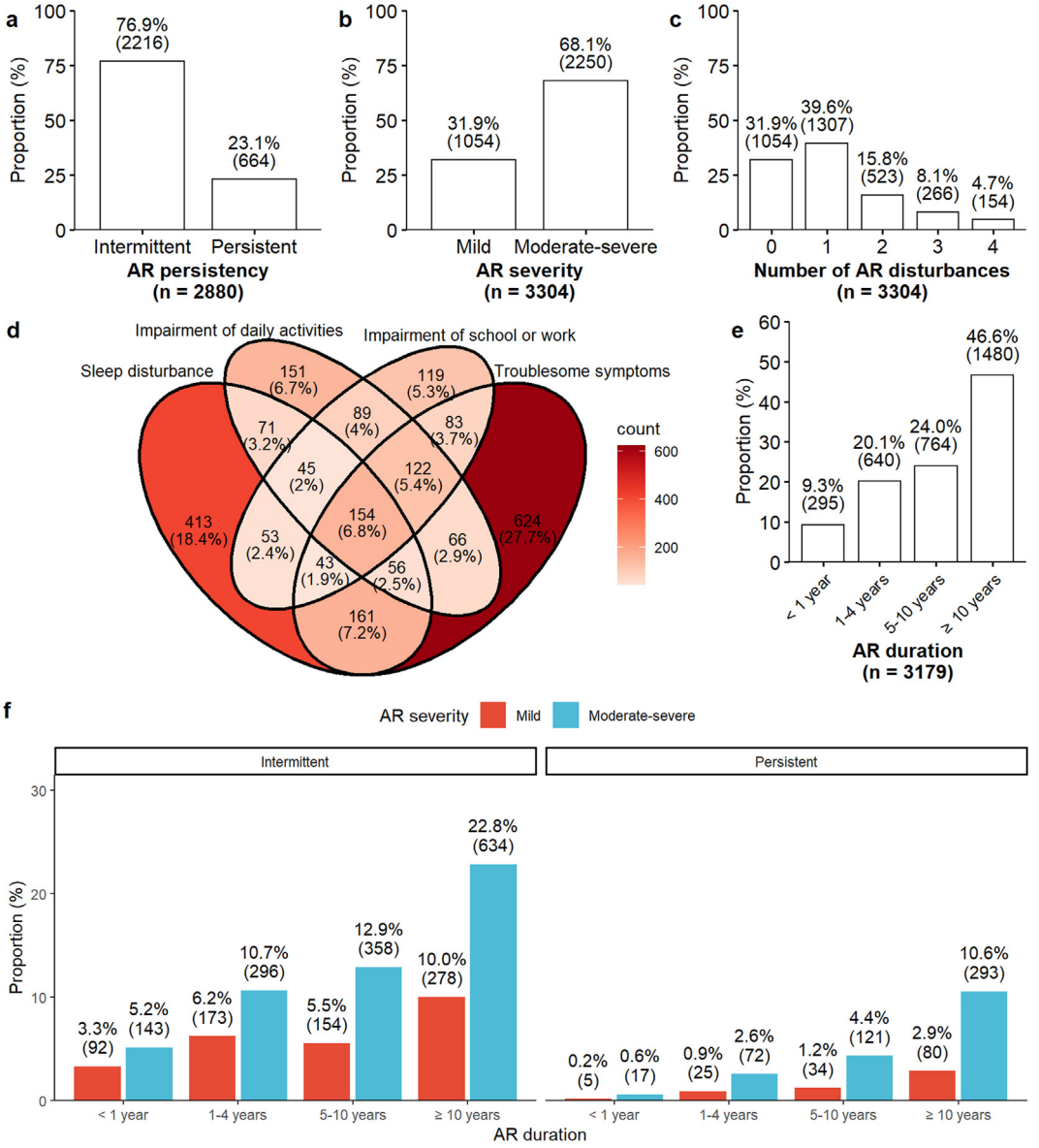

Fig. 2 Patterns of AR phenotypes among the AR classifications. (a) Proportions of AR cases by ARIA persistency. (b) Proportions of AR cases by ARIA severity. (c) Proportions of AR cases by disturbances to life due to AR. (d) Venn diagram representing the distribution of responses among AR cases suffering from disturbances to life due to AR. (e) Proportions of AR cases by duration of AR. (f) Proportions of AR cases by ARIA persistency, severity, and duration of disease

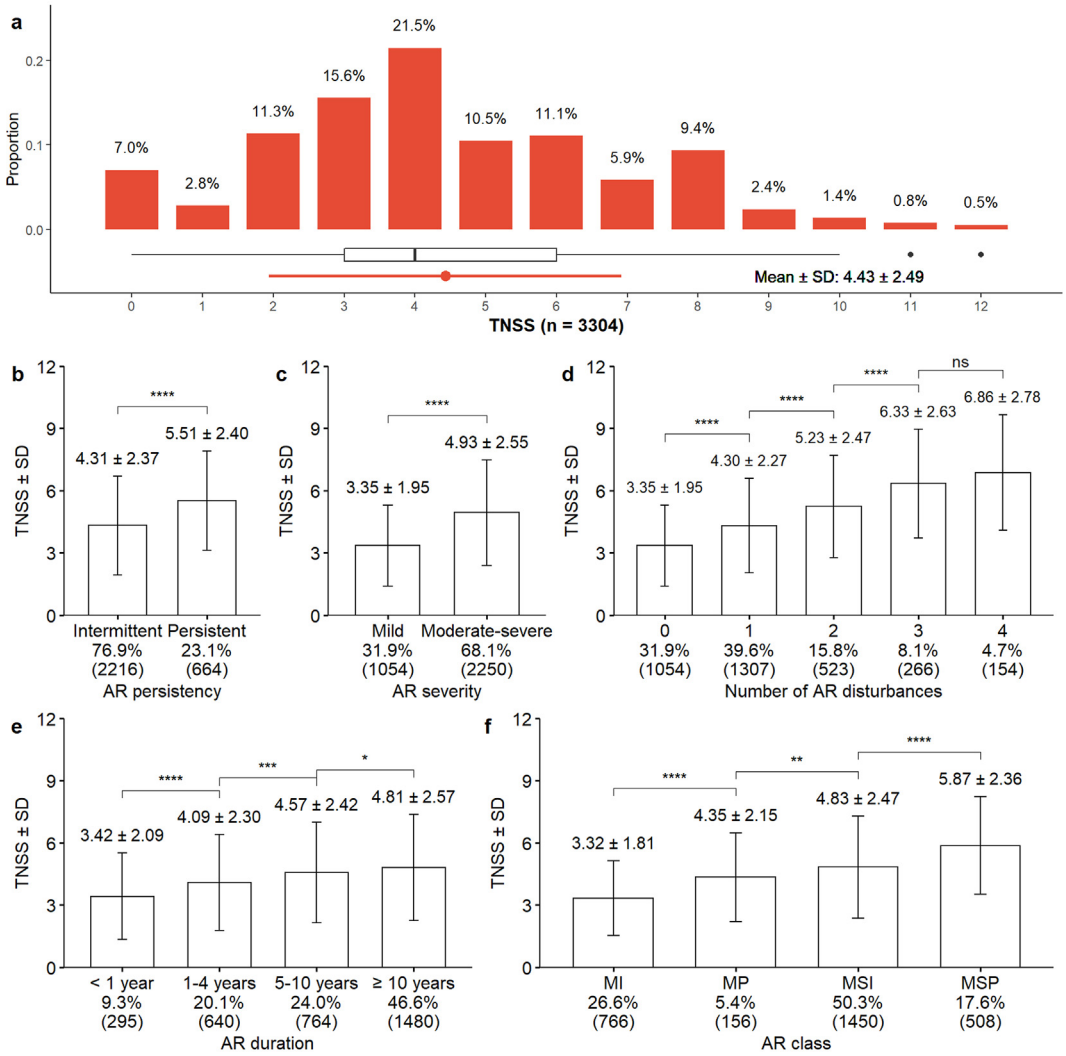

Fig. 3 Summary of Total Nasal Symptom Score (TNSS) responses among AR cases. Where applicable, statistical significance is represented by asterisks – ns: $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. (a) Distribution of TNSS responses among AR cases, along with the corresponding summary statistics. (b) Comparison of mean TNSS among ARIA persistency phenotypes. (c) Comparison of mean TNSS among ARIA severity phenotypes. (d) Comparison of mean TNSS among total number of disturbances reported. (e) Comparison of mean TNSS among duration of AR. (f) Comparison of mean TNSS among AR classes (i.e., combination of ARIA persistency and severity classifications)

AR lasting for a longer duration was accompanied by a significantly higher mTNSS ($p \leq 0.05$; Fig. 3e). Lastly, comparisons of mTNSS between each AR class phenotype revealed a significant stepwise increase in mTNSS in the following order: MI MP, MSI, and MSP (Fig. 3f). Using MCID thresholds, there was no apparent difference between AR lasting for ≥10 years versus 5–10 years, while the differences in mTNSS for 4 versus 3 disturbances, AR lasting for 5–10 years versus 1–4 years, and MSI versus MP AR fell close to the MCID threshold (Supplementary Table 4). The remaining comparisons of mTNSS showed a clinically relevant difference where the mTNSS differences exceeded the MCID threshold.

Diagnosis and medication of AR

Most AR cases were undiagnosed, with 14.8% (485/3278) indicating a prior AR diagnosis. Between 2007 and 2021, a persistent trend of undermanagement of AR was observed, with no significant difference across the years. Stratification of each classification per AR phenotype by AR

diagnosis showed that diagnosed AR was consistently the minority (Fig. 4). By AR persistency, 12.5% of intermittent AR cases and 23.1% of persistent AR cases had a diagnosis of AR (Fig. 4a). Among AR severity classifications, 8.5% of mild AR cases and 17.7% of moderate-severe AR cases were diagnosed with AR (Fig. 4b). A further breakdown of moderate-severe cases into number of disturbances suffered showed that the proportion of diagnosed AR cases increased as number of disturbances increased (1 disturbance – 12.9%, 2 disturbances – 19.7%, 3 disturbances – 28.0%, 4 disturbances – 33.1%; Fig. 4c). A similar trend was observed for AR diagnoses by AR duration, where a longer duration of AR affliction was accompanied by an increased proportion of AR diagnosis (<1 year–4.1%, 1–4 years – 9.8%, 5–10 years – 15.9%, ≥10 years–19.0%; Fig. 4d).

Considering the 5 medication types commonly used to treat AR separately, majority of AR patients were non-medicating (Supplementary Table 5). Among the medicating AR cases using either antihistamines, nasal sprays, or decongestants, the mean TNSS was significantly higher than non-medicating patients (Supplementary Fig. 2). Similarly, the majority of AR cases were non-medicating; 27.5% (903/3278) of AR cases indicated ever consuming any medication used to treat AR. Among AR phenotypes, the proportions of medication users never exceeded 50% although these proportions were consistently higher among AR phenotypes with a greater impact on quality of life – ie, 38.3% among persistent AR, 30.8% among moderate-severe AR, and 32.8% of AR cases lasting for at least 10 years. The proportion of medication users was the highest among AR cases suffering 4 disturbances at 48.1% (Fig. 5a–d).

Stratifying medication usage by AR diagnosis showed that the proportion of medication users was significantly higher among diagnosed AR cases than undiagnosed cases (7.8% versus 7.0%, $p < 0.001$, Supplementary Table 6), while a large proportion of those whose AR remained undiagnosed did not consume medications for AR (65.4%). Overall, 14.8% of AR cases were diagnosed, and 27.5% had taken medications to treat their AR. Mean TNSS among AR cases grouped by both medication usage and diagnosis showed that those who used medications and had an AR diagnosis exhibited a mTNSS of 6.06 (SD = 2.58), significantly higher than AR cases who did not consume medications

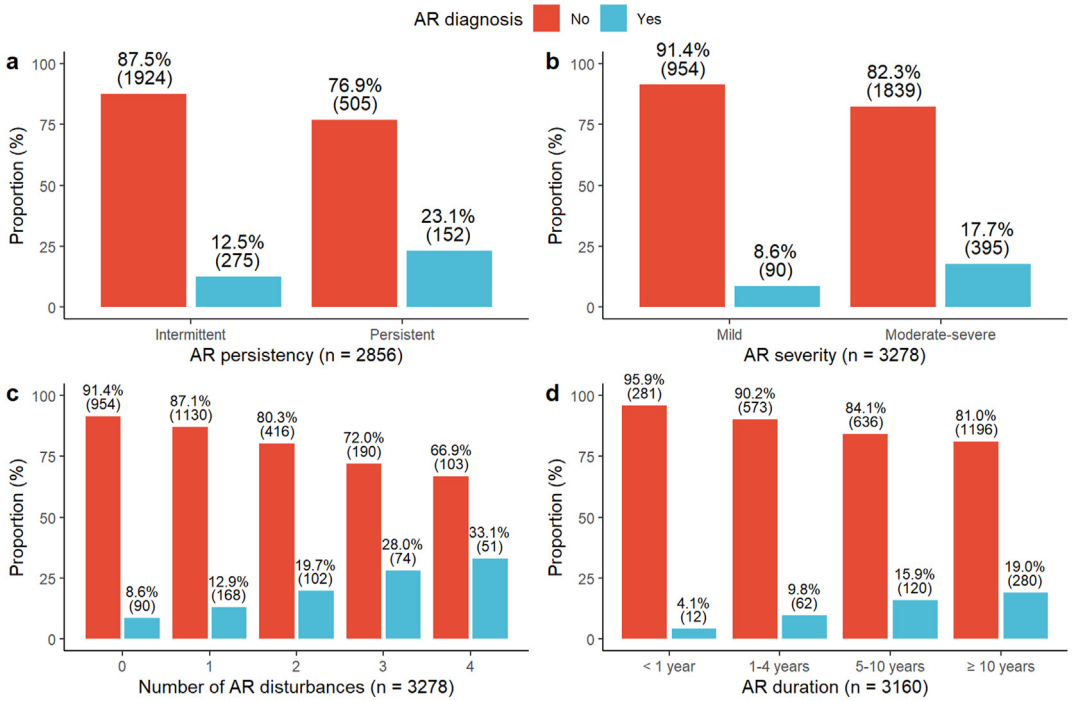

Fig. 4 Proportions of AR diagnosis among each AR classification. (a) Proportions of AR diagnosis among ARIA persistency phenotypes. (b) Proportions of AR diagnosis among ARIA severity phenotypes. (c) Proportions of AR diagnosis by total number of AR disturbances. (d) Proportions of AR diagnosis by AR duration

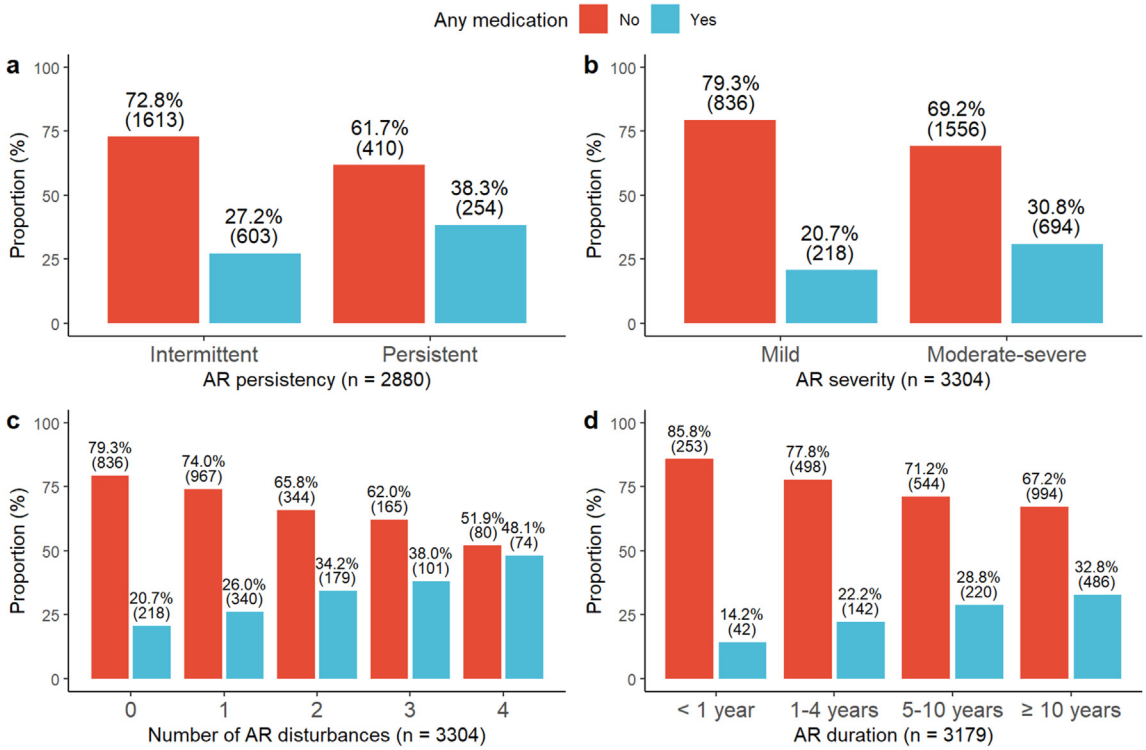

Fig. 5 Proportions of AR medication usage among each AR classification. (a) Proportions of AR medication usage among ARIA persistency phenotypes. (b) Proportions of AR medication usage among ARIA severity phenotypes. (c) Proportions of AR medication usage by total number of AR disturbances. (d) Proportions of AR medication usage by AR duration

but had an AR diagnosis (mTNSS ± SD: 4.79 ± 2.79; $p \leq 0.0001$; Fig. 6a), or consumed medications but did not have an AR diagnosis (mTNSS ± SD: 4.91 ± 2.31; $p \leq 0.0001$). Among non-medicated undiagnosed AR cases, mTNSS was significantly lower than all other groups at 4.04 (SD = 2.38; $p \leq 0.001$ for all tests).

Stratification of AR classifications by both medication usage and diagnosis showed that within each phenotype, the majority never used medications and remained undiagnosed (Fig. 6b–e). Additionally, individuals taking medication but having never been diagnosed consistently constituted the second largest group within each AR phenotype. Proportions of non-medicating diagnosed AR and medicating diagnosed AR fluctuated across phenotypes, with larger proportions of medicating diagnosed AR cases found respectively in the persistent (13.4%), moderate-severe (9.3%), 3 to 4-disturbances (16.4%, 21.4%), and over 10-year duration (10.7%) AR phenotypes.

DISCUSSION

Patterns and severity of AR symptoms

Presently, for each rhinitis symptom among AR cases, we have established the prevalence and persistency. The most frequent symptom among AR cases was sneezing – consistent with some preceding reports from Nigeria (patients predominantly aged below 39 years) and Turkey (university students).[16,17] The mNSS provided a gauge of individual symptom severity; mNSS of rhinorrhea was the highest (1.42) among rhinitis symptoms, roughly corresponding to mild-moderate symptom severity. Concordantly, findings from European showed that runny nose manifested preponderantly with moderate to severe intensity, and was more severe compared to other rhinitis symptoms.[18] In counterpoint to our findings, nasal blockage was the most frequent AR symptom in study populations from Canada and United States, effecting a significant impact on quality of life.[19,20] While nasal blockage was neither the most frequent nor most severe

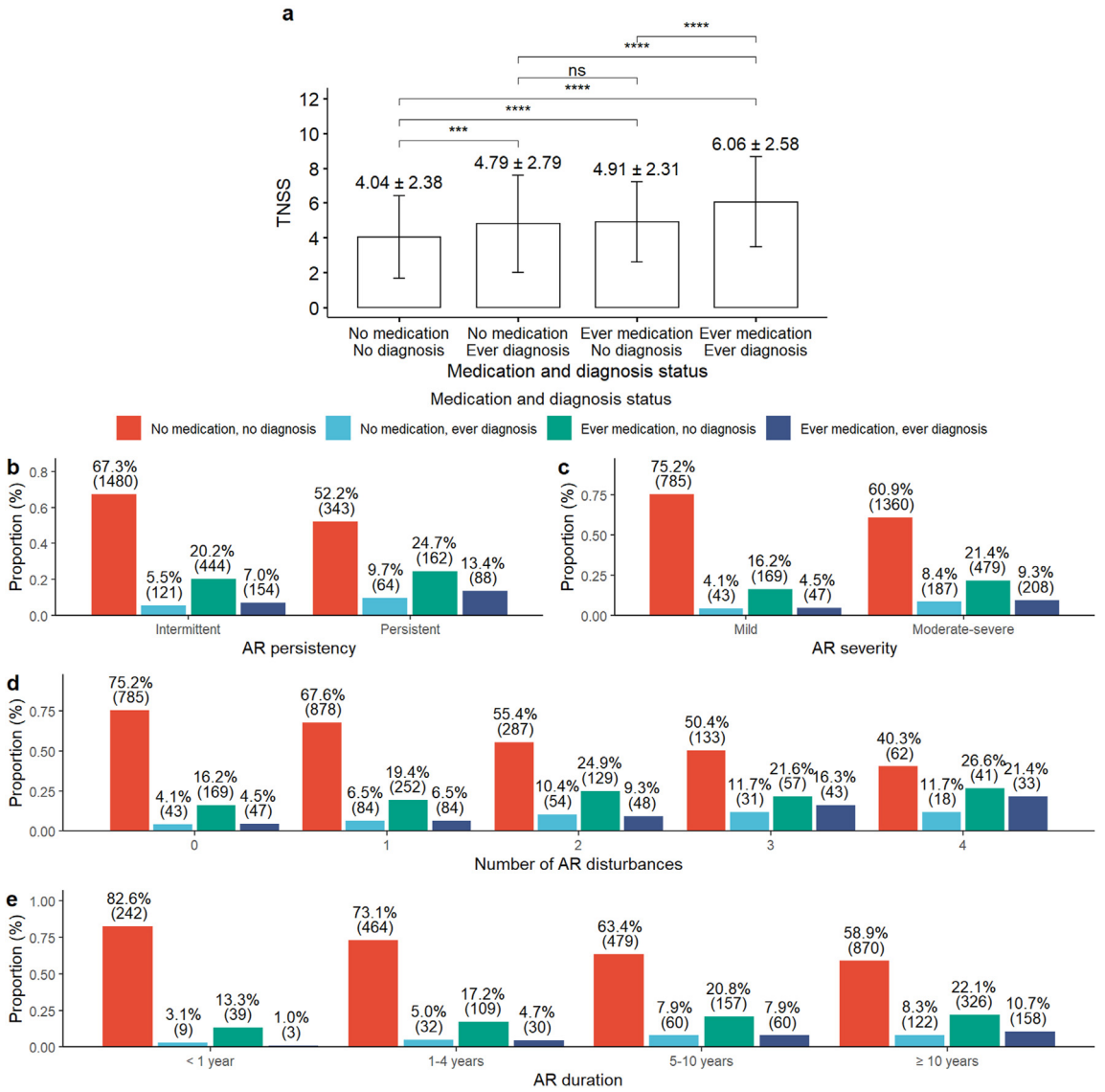

Fig. 6 Summary of either AR medication usage or AR diagnosis, or both, among AR phenotypes. Proportions are denominated against each phenotype. (a) Mean TNSS and standard deviation for each combination of AR medication usage and diagnosis status. Statistical significance is represented by asterisks – ns: $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$. (b) AR medication and diagnosis status among ARIA persistency phenotypes. (c) AR medication and diagnosis status among ARIA severity phenotypes. (d) AR medication and diagnosis status by AR disturbances. (e) AR medication and diagnosis status by AR duration

symptom among AR cases from our study population, the proportion of those affected by persistent nasal congestion was the highest out of all symptoms. Furthermore, analyses of mNSS between intermittent and persistent symptoms showed that persistent nasal congestion was more severe than intermittent nasal congestion. Overall, the symptom characteristics of AR appear to manifest distinctly between different study populations, with sneezing likely more prevalent in younger-aged adults.

AR phenotypes and analyses of their corresponding mTNSS

The present findings for AR classifications and TNSS patterns among AR cases in the Singaporean subset of the SMCGES were consistent with that of the entire SMCGES cohort.[9] More than three-quarters of AR were intermittent cases, at least two-thirds were moderate-severe cases, and almost half had had AR for at least 10 years. As with publications following ARIA guidelines, we have also considered AR persistency in

conjunction with AR severity and characterized the distribution of AR classes (ie, MI, MSI, MP, and MSP AR) in our cohort.[1,21-23] Of the AR classes, MSI AR was the predominant AR phenotype, of which most had suffered from it for at least 10 years.

The TNSS is a patient-reported outcome measure that gauges the severity of each ARIA rhinitis symptom (ie, nasal blockage, nasal pruritus, runny nose, and sneezing), to assess the overall severity of AR.[10,24] Across studies, AR medications have been evaluated using the TNSS.[24] In 2013, the US Agency for Healthcare Research and Quality (AHRQ) suggested a MCID for any scale to be 30% of the maximum score (3.6 points for the TNSS).[25] However, proceeding studies failed to demonstrate differences in treatment effectiveness based on the 30% threshold, leading to a shift in favor of anchor- and distribution-based models to determine the MCID.[25-28] Here, t-tests indicated the statistical significance of the difference in mTNSS but lacked information on the real-life implications; mTNSS differences were thus assessed using the MCID to interpret the clinical relevance of mTNSS differences.

Presently, analyses of mTNSS for each AR phenotype showed that for the AR persistency, severity, disturbances, duration, and class, there was a quantifiable difference in the severity of AR. Comparisons of mTNSS via both t-tests and against the MCID calculated according to Cohen suggested that the differences in mTNSS between phenotypes were both statistically significant and likely clinically relevant.[15,28] However, the clinical importance of the increase in severity of AR appeared to diminish as the duration of AR increased, despite the statistical significance in mTNSS difference. Thus, we have provided evidence supporting the ARIA guidelines for AR classification, along with additional evidence that there is a clinically relevant increase in AR severity according to TNSS with each increase in disturbance caused by AR. Although the severity of AR appeared to increase with duration suffered from AR, this increase was not of clinical relevance.

Diagnosis and medication of AR

Overall, less than one-fifth of AR cases had been diagnosed with AR, and less than 30% were medicated for AR. Stratification of each AR classification by AR diagnosis showed that despite the statistically significant and clinically important increase, the majority of AR cases exhibiting the more severe AR phenotypes did not have a diagnosis of AR. Similarly, while the proportions of medication usage were higher among AR phenotypes than that of ever having an AR diagnosis, most were never medicated for AR even among more severe AR phenotypes. Overlaying the proportions of AR medication and diagnosis showed that out of those attempting to manage their AR via diagnosis or medication, more individuals engaged in self-medication without an AR diagnosis. Our findings pointed to an undermanagement of AR in young adults, especially among those suffering from AR of increased severity. Not only do the proportions of self-medicating undiagnosed AR cases point to an unaddressed burden of AR, there also exists a high likelihood of uninformed therapeutic choices being made in the treatment of AR symptoms, possibly resulting in an under-treatment of bothersome AR symptoms.[29]

Indeed, undermanagement of AR is not unique to our study sample. Identified burdens of AR have been identified in various study populations despite relatively high prevalence estimates of AR.[29,30] Likewise, among those without a doctor's diagnosis of AR, a large proportion self-treated their symptoms with over-the-counter medications.[29] As with these study populations, undiagnosed, untreated, or under-treated AR in our study population has the potential to negatively impact individuals' quality of life, resulting in direct and indirect costs.[6,31]

Potentially, the low awareness of allergic rhinitis exacerbates the trend of AR under-management. A European survey found that only 19% were self-aware of AR, of which 70% received a physician's diagnosis.[32] Furthermore, due to the non-life-threatening nature of AR, many tolerate its symptoms and do not seek help.[31] In fact, the possibility that AR was "incidentally" diagnosed during a doctor's visit for a separate affliction was considered - current asthma prevalence was

6.4%, but only 22% of subjects with a physician's diagnosis of AR reported having current asthma.[32]

With regards to AR in Singapore, we posit that besides low awareness among the general public and under-diagnosis due to the relatively benign nature of AR, there are additional dimensions of management deficit contributing to its under-recognition. Firstly, research studies establishing an updated prevalence and epidemiology of AR in the general Singaporean population are few and far between, with the latest population-based study having been published in 2004.[33,34] Although separate Singaporean studies were conducted previously, these focus on specific population subsets which cannot be readily generalized to the overall Singaporean population.[9,35,36] Furthermore, surveys of primary care management for AR are lacking for the Singapore healthcare scene; there is yet to be a local consensus on the use of ARIA guidelines in the diagnosis and treatment of AR – intensity of AR treatment should be commensurate with the severity of AR.[34] Analyses of patient databases from primary healthcare providers and hospitals could provide insight to these areas. Finally, since there is a proportion of self-medicating AR patients in the current study population, policymakers might consider the education of pharmacists in the classification and management of AR to better address patients who forego visiting the doctor.

LIMITATIONS AND CONCLUSION

Our study was accompanied by limitations characteristic of cross-sectional studies; time-trend patterns and data on causal factors were unavailable due to the study design.[37] While we were able to identify differences in the severity of AR phenotypes and gaps in the management of AR, further data would be needed to confirm our reasoning regarding the causes. Furthermore, our current analysis focused on the Chinese subset of the Singapore cohort recruited in our large-scale study. Minority races (eg, Indians and Malays) were excluded due to the over-representation of ethnic Chinese in our cohort, potentially skewing our findings should race stratification be foregone. As such, our results may not be readily generalized to the Singaporean population due to its heterogenous racial demographic.[38] Notwithstanding, our findings confirmed that undermanagement of AR is occurring in young adult Chinese from Singapore, as with several separate populations elsewhere.[29–31] Furthermore, as our sample size for the minority races grows and gains statistical power, we plan to conduct analyses of these groups and compare them to the Chinese sample via matching methods.[39] Other possible future analyses include multivariate analyses of comorbidities such as asthma and chronic rhinosinusitis, and epidemiological factors known to influence AR, such as family history and smoking, to evaluate their effects on the severity of AR.

Overall, this report has presented data on the patterns of AR phenotypes among young Chinese adults from Singapore. The prevalence for AR was estimated at 35.4%. AR cases were categorized by persistency, severity, number of disturbances due to AR, duration suffered from AR, and AR classes (combining persistency and severity). There was a predominance of intermittent, moderate-severe cases, resulting in a preponderance of moderate-severe intermittent AR, and most had suffered from AR for at least 10 years. The modal number disturbances to life due to AR was one, with the main disturbance being either troublesome symptoms, or sleep disturbances. AR severity was separately assessed using the TNSS, and there was a significant increase in mTNSS from intermittent to persistent AR, mild to moderate-severe AR, an increased number of disturbances due to AR, and a longer duration suffered from AR. There was also a significant stepwise increase in mTNSS from mild intermittent, to mild persistent, to moderate-severe intermittent, to moderate-severe persistent AR. Notably, only 14.8% of AR cases were diagnosed and 27.5% took medications for AR. Especially among AR phenotypes with higher TNSS, majority of AR cases were undiagnosed, untreated, or undertreated. This suggested an undermanagement of AR among our study population, contributing to a significant yet heretofore undetected burden of AR.

Abbreviations

AR, Allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; ISAAC, International Study of Asthma and Allergies in Childhood; MI, mild intermittent; MP, mild persistent; MSI, moderate-severe intermittent; MSP, moderate-severe persistent; mTNSS, Mean Total Nasal Symptom Score; mNSS, Mean Nasal Symptom Score; NSS,

Nasal Symptom Score; SD, Standard deviation; SMCGES, Singapore/Malaysia Cross-sectional Genetics Epidemiology Study; SPT, Skin prick test; TNSS, Total Nasal Symptom Score; AHRQ, Agency for Healthcare Research and Quality (US); MCID, Minimum Clinically Important Difference.

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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.).

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., Y.Y.E.L., and Y.Y.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). 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
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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.2024.100954.

Author details
Department of Biological Sciences, Faculty of Science, National University of Singapore, 117543, Singapore.

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