

Respiratory disease in the Asia-Pacific region: Cough as a key symptom

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ABSTRACT

Background: Respiratory diseases represent a significant impact on health care. A cross-sectional, multicountry (India, Korea, Malaysia, Singapore, Taiwan, and Thailand) observational study was conducted to investigate the proportion of adult patients who received care for a primary diagnosis of asthma, allergic rhinitis (AR), chronic obstructive pulmonary disease (COPD), or rhinosinusitis.

Objective: To determine the proportion of patients who received care for asthma, AR, COPD, and rhinosinusitis, and the frequency and main symptoms reported.

Methods: Patients ages ≥ 18 years, who presented to a physician with symptoms that met the diagnostic criteria for a primary diagnosis of asthma, AR, COPD, or rhinosinusitis were enrolled. Patients and physicians completed a survey that contained questions related to demographics and respiratory symptoms.

Results: A total of 13,902 patients with a respiratory disorder were screened, of whom 7030 were eligible and 5250 enrolled. The highest percentage of patients who received care had a primary diagnosis of AR (14.0% [95% confidence interval {CI}, 13.4–14.6%]), followed by asthma (13.5% [95% CI, 12.9–14.1%]), rhinosinusitis (5.4% [95% CI, 4.6–5.3%]), and COPD (4.9% [95% CI, 5.0–5.7%]). Patients with a primary diagnosis of COPD (73%), followed by asthma (61%), rhinosinusitis (59%), and AR (47%) most frequently reported cough as a symptom. Cough was the main reason for seeking medical care among patients with a primary diagnosis of COPD (43%), asthma (33%), rhinosinusitis (13%), and AR (11%).

Conclusion: Asthma, AR, COPD, and rhinosinusitis represent a significant proportion of respiratory disorders in patients who presented to health care professionals in the Asia-Pacific region, many with concomitant disease. Cough was a prominent symptom and the major reason for patients with respiratory diseases to seek medical care.

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Asthma, allergic rhinitis (AR), chronic obstructive pulmonary disease (COPD), and rhinosinusitis are chronic diseases of the airways and other structures

of the lungs. Chronic respiratory diseases are the cause of ~7% of all deaths worldwide and account for 4% of the global burden of disease.¹ These preventable chronic diseases have a significant impact on the individual, community, and economy.¹ In recent years, the Asia-Pacific region has undergone a period of rapid growth, urbanization, and economic change. Results of a number of studies indicate a rise in the prevalence of asthma, allergic disorders, and COPD in the region, and, although the underlying reasons remain unclear, there is evidence that environmental, population, genetic, and socioeconomic factors may play a pivotal role.^{1–5} Symptoms associated with chronic respiratory diseases, such as cough, sneezing, and difficulty breathing, may adversely impair patients' work activities, sleep quality, and physical and mental well-being.^{2,6} Often, patients are diagnosed with multiple, concomitant respiratory disorders, such as AR and asthma, which results in increased morbidity and health care resource use.^{2,7–11}

Understanding the frequency of and the socioeconomic burden on health care resources that arise from these respiratory diseases is essential to identify effective treat-

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ment practices that lead to improved patient outcomes. To date, little research has been conducted in the Asia-Pacific region that explored the occurrence and the potential burden on care as it relates to these four diseases in adults who present to health care professionals under one standard protocol. As such, a cross-sectional observational study, Asia-Pacific Burden of Respiratory Diseases, was conducted across six countries in the Asia-Pacific region: India, Korea, Malaysia, Singapore, Taiwan (China), and Thailand. The main objectives were to determine the following: (1) the proportion of patients who received care for asthma, AR, COPD, and rhinosinusitis as a proportion of all patients who presented with a respiratory disease to primary care or specialist (*e.g.*, allergy, otolaryngology, respiratory medicine) clinics; (2) the enrolled patients who received care for asthma, AR, COPD, or rhinosinusitis who had combinations of the four diseases; and (3) the frequency and main symptoms reported by enrolled patients who received care for asthma, AR, COPD, or rhinosinusitis.

METHODS

Study Design

To increase the generalizability of the findings, the study design included multiple study sites across six countries in the Asia-Pacific region. Study sites included both primary care and specialist medical practices. Subjects were recruited from a total of 22 sites between October 31, 2012, and October 13, 2013, during a routine medical visit to a health care provider, including primary and specialist care physicians, outpatient and/or polyclinics, or medical centers, depending on the health care setting in each of the countries. Possible reasons for a patient's medical visit related to his or her new or existing primary diagnosis of respiratory disease, including physical, diagnostic, therapeutic, and/or nontherapeutic reasons. All study related data were collected during a single visit. The study was approved by the institutional review boards or ethics committees in each jurisdiction.

Patient Eligibility

At each study site, consecutive adult patients who presented during a routine consultation were assessed and screened for eligibility by a physician to participate in the study. Eligibility criteria included patients ages ≥ 18 years and received care for a new or existing primary diagnosis of asthma, AR, COPD, or rhinosinusitis. Subjects were excluded if they had participated in any interventional clinical study within the 12 weeks before entering the current study. Eligible patients were invited to participate in the study, and informed consent was obtained from each patient. A patient could only participate in the study once; no follow-up visits were recorded.

Sample Size

The sample size calculation was based on precision regarding the proportion of all adults who received care for a respiratory disease that was related to a primary diagnosis of asthma. Based on the epidemiology literature,^{2,7,9,12,13} asthma was expected to be the least common of the four diseases of interest in the study. No data were available that reported the proportion of presentations to medical centers in the Asia-Pacific region that was related to asthma. Consequently, data from a register of general practitioners (GP) in Australia was used to estimate the proportion of presentations in Asia Pacific that was related to asthma. This register indicated that asthma was managed at 2.1% of patient visits to GPs.¹⁴ When applying preset assumptions, including patient presentations, prevalence, and the number of consenting patients, it was expected that 4% of all adult patients who received care for a respiratory disease would have a new or existing diagnosis of asthma. Based on this calculation, a total sample size of ~5000 enrolled patients (which provides precision of $\pm 0.3\%$ around the assumed 4% [95% confidence interval {CI}, 3.7–4.3%]) was selected as being appropriate given the lack of epidemiologic data in the Asia-Pacific region.

Survey Instruments and Data Collection

During the study visit, physicians completed Screening and Consent Logs and a Physician Survey. The Consent Log captured basic demographics, respiratory diagnosis of each eligible patient, and patient consent. The diagnosis of respiratory disease was defined by International Classification of Diseases, Tenth Edition classifications.¹⁵ This excluded some infectious and parasitic diseases that may affect the respiratory system (*e.g.*, tuberculosis) and also excluded neoplasms of the respiratory system. The study relied on a diagnosis made by the attending physician by using criteria based on international guidelines.^{16–19} For patients who had a new diagnosis of any of the four diseases, the physician was asked to indicate the clinical criteria used to make the diagnosis from a list of criteria for each disease adapted from international clinical practice guidelines for asthma, AR, COPD, and rhinosinusitis. The study was not intended to influence patients' clinical management and physicians' usual diagnostic practices; however, some patients may have been diagnosed by using a more rigorous and standardized approach than may have occurred before commencement of the study. No attempt was made to independently verify or confirm the patient's diagnosis.

No suitable validated instruments existed for the four diseases of interest and, as such, the Physician and Patient Surveys were developed specifically to meet the objectives of the study. For each enrolled patient,

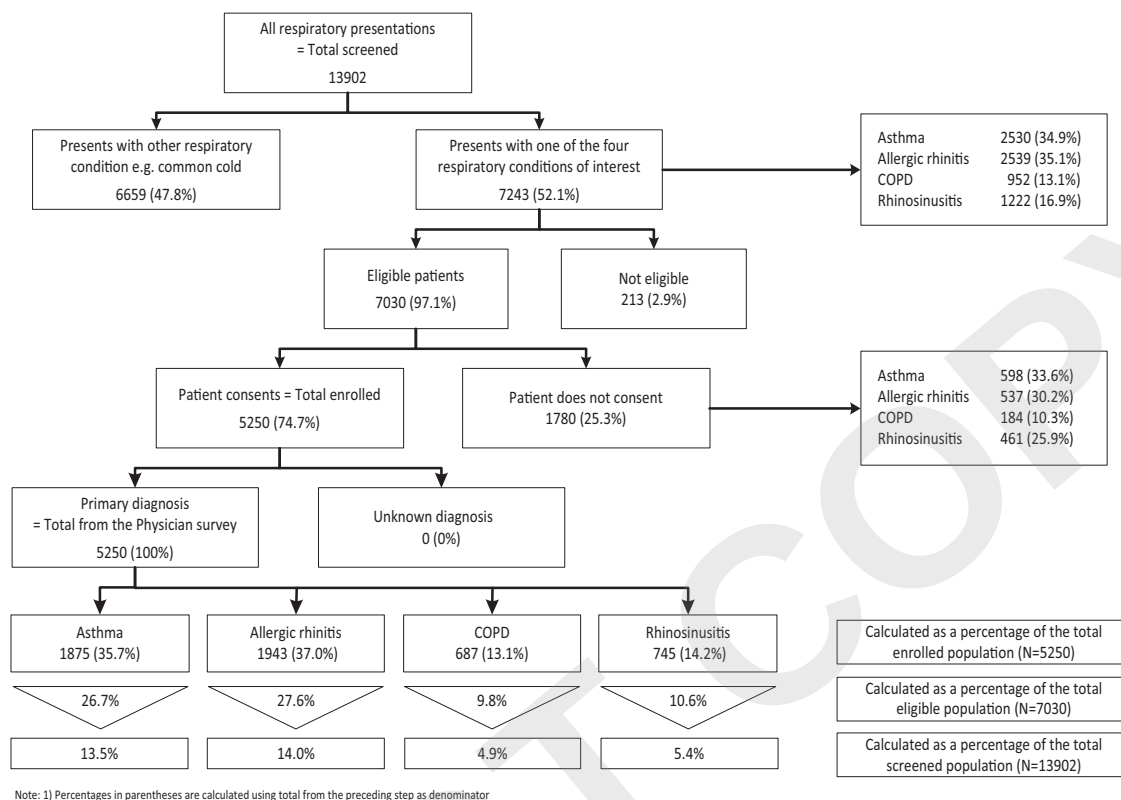


Figure 1. Patient flow in the study.

the physician completed the Physician Survey, which comprised questions that related to the primary diagnosis of asthma, AR, COPD, or rhinosinusitis; the reason for the patient's visit; new and existing diagnoses for the four diseases; family history of the four diseases; referrals to other medical services; medication use; and intended medication use after the study visit.

The Patient Survey was self-administered and made available in a range of languages relevant to the participating countries. The Patient Survey included questions regarding general demographics, history of exposure to risk factors, respiratory symptoms, and health care resource use. Additional validated surveys that assessed work productivity and health-related quality of life were also completed by patients (the results of which have been reported elsewhere²⁰). These included Work Productivity and Activity Impairment—Specific Health Problem, Short Form Health Survey 12 items version 2, and disease-specific health-related quality of life measures (*i.e.*, Mini Asthma Quality of Life Questionnaire, Mini Rhinoconjunctivitis Quality of Life Questionnaire, Sino-Nasal Outcomes Test 20, COPD Assessment Test). All study-related data were collected in a single study visit.

Statistical Analysis

Statistical analyses were performed by using SAS for Windows, version 9.3 (SAS Institute Inc., Cary, N.C.).

Patient demographics and clinical characteristics were described by using mean (standard deviation) for continuous variables and number (percentage) for categorical variables. The percentage and 95% CI of patients with each disease were calculated by using the exact (Clopper-Pearson) method.

RESULTS

A total of 13,902 patients were diagnosed with a respiratory disease and were subsequently screened (Fig. 1). Of these, 7,243 (52%) presented with asthma, AR, COPD, or rhinosinusitis, of whom 7,030 (97%) were eligible to enroll in the study. Of the eligible patients, 5,250 (74.7%) consented and were enrolled in the study. The percentage of enrolled eligible patients was similar for asthma (78.3%), AR (75.8%), and COPD (78.9%) compared with rhinosinusitis (61.8%). The percentage of eligible patients who were enrolled was highest for India (96.7%), Singapore (91.9%), Thailand (87.6%), and Malaysia (83.6%) compared with lower consent rates for Taiwan (62.3%) and Korea (56.2%). Of the enrolled patients, 5,247 (99.9%) completed all surveys.

The mean (standard deviation) age of enrolled patients was 48.8 ± 17.55 years, and 53% were women (Table 1), which reflected the eligible, nonconsenting patients mean age of 54.2 ± 17.31 years and 57% female population. Sex was similarly represented across the diseases, with the exception of COPD: 85% were men.

Table 1 Demographics of eligible and enrolled patients by primary disease*

Characteristic	Allergic Rhinitis	Asthma	COPD	Rhinosinusitis	Total Population
Eligible (<i>n</i> = 7030) vs enrolled (<i>n</i> = 5250) patients by primary disease, no. (%)					
Eligible, consented and enrolled	1875 (35.7)	1943 (37.1)	687 (13.1)	745 (14.2)	5250 (74.7)
Eligible, did not consent and did not enroll	598 (33.6)	537 (30.2)	184 (10.3)	461 (25.9)	1780 (25.3)
Enrolled patients (<i>n</i> = 5250)					
Sex, no. (%)#					
<i>N</i>	1943	1875	687	745	5250
Women, no. (%)	1106 (57)	1159 (62)	103 (15)	404 (54)	2772 (53)
Men, no. (%)	837 (43)	716 (38)	584 (85)	341 (46)	2478 (47)
Age, years					
<i>N</i>	1943	1875	687	745	5250
Mean (SD) age, y	41.6 ± 16.32	51.7 ± 16.28	65.7 ± 12.28	44.7 ± 15.32	48.8 ± 17.55
Age range, y	18–93	18–94	23–91	18–87	18–94
Ethnicity#					
<i>N</i>	1942	1871	686	744	5243
Chinese, no. (%)§	487 (25)	392 (21)	251 (37)	319 (43)	1449 (28)
Indian, no. (%)	338 (17)	570 (30)	245 (36)	67 (9)	1220 (23)
Korean, no. (%)	555 (29)	313 (17)	56 (8)	69 (9)	993 (19)
Malaysian, no. (%)	15 (1)	88 (5)	9 (1)	2 (0)	114 (2)
Thai, no. (%)	422 (22)	231 (12)	75 (11)	236 (32)	964 (18)
Other, no. (%)	125 (6)	277 (15)	50 (7)	51 (7)	62 (1)
Malay, no. (%)	103 (5)	249 (13)	48 (7)	41 (6)	441 (8)
Employment status#					
<i>N</i>	1941	1870	687	745	5243
Full-time, no. (%)	1020 (53)	736 (39)	146 (21)	444 (60)	2346 (45)
Part-time, no. (%)	120 (6)	120 (6)	35 (5)	38 (5)	313 (6)
Retired, no. (%)	206 (11)	433 (23)	364 (53)	115 (15)	1118 (21)
Student, no. (%)	280 (14)	68 (4)	2 (0)	60 (8)	410 (8)
Unemployed, no. (%)	144 (7)	390 (21)	122 (18)	46 (6)	1028 (20)
Other, no. (%)	171 (9)	123 (7)	18 (3)	42 (6)	354 (7)
Smoking history					
Ever smoked# ¶					
<i>N</i>	1933	1871	687	742	5233
Yes, no. (%)	434 (22)	412 (22)	517 (75)	210 (28)	1573 (30)
No, no. (%)	1499 (78)	1459 (78)	170 (25)	532 (72)	3660 (70)
Current smoking status#					
<i>N</i>	423	409	511	209	1552
Current smoker, no. (%)	178 (42)	139 (34)	119 (23)	71 (34)	507 (33)
Former smoker, no. (%)	245 (58)	270 (66)	392 (77)	138 (66)	1045 (67)
Exposure to risk factors (smoke, dust, pollution, chemicals, animals) (<i>n</i> = 5250)					
At work					
<i>N</i>	1659	1691	597	684	4631
None, no. (%)	690 (42)	922 (55)	332 (56)	258 (38)	2202 (48)
Exposed to at least one risk factor, no. (%)	969 (58)	769 (45)	265 (44)	426 (62)	2429 (52)
At home					
<i>N</i>	1871	1843	677	718	5109
None, no. (%)	594 (32)	567 (31)	273 (40)	262 (36)	1696 (33)
Exposed to at least one risk factor, no. (%)	1277 (68)	1276 (69)	404 (60)	456 (64)	3413 (67)

COPD = chronic obstructive pulmonary disease; SD = standard deviation.

*Not all patients responded to all questions.

#Calculation of percentage excludes missing values.

§Includes Malaysian Chinese.

¶Excludes 21 ever-smokers whose current smoking status was unknown.

||Calculated from participants who answered "Yes" to "ever smoked."

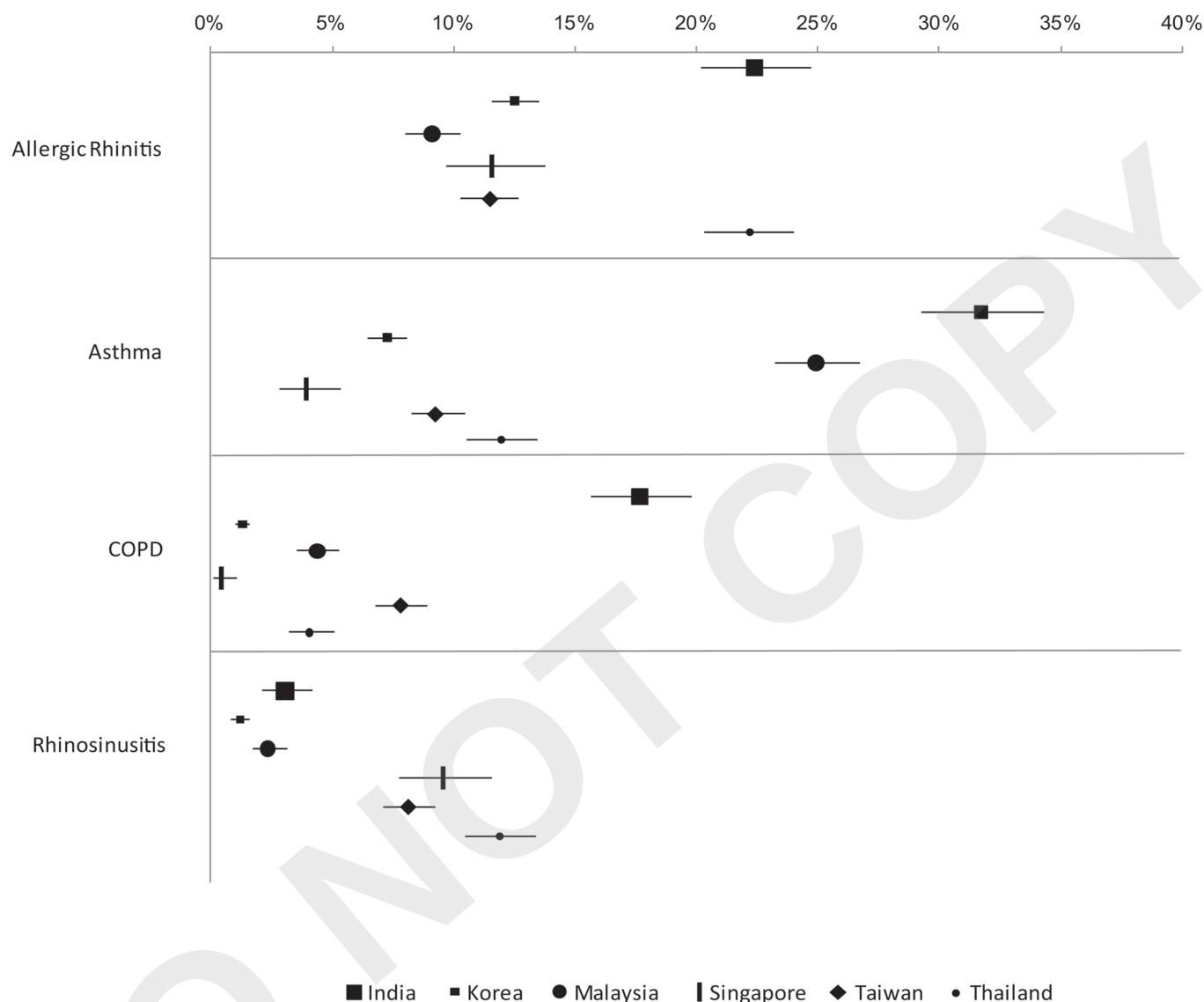


Figure 2. Adults with primary diagnosis of a respiratory disease by country.

To minimize selection bias for the four respiratory diseases, comparisons were made between eligible consenting and nonconsenting participants. These were comparable; however, a greater percentage of participants with rhinosinusitis were nonconsenting, and this may have resulted in a slight underrepresentation of the disease.

Fifty-one percent of enrolled patients were employed in full- or part-time work, with the remaining retired, unemployed, or students. Fewer than a third of patients reported ever smoking across all primary diseases, with the exception of COPD: 75% had smoked. Approximately 33% of the study population to report ever smoking were current smokers. Of the enrolled population, 52% and 67%, at work and at home, respectively, reported exposure to one or more disease risk factors: smoke, dust, pollution, chemicals, and animals.

The proportion of enrolled patients who had existing diagnosis or were newly diagnosed for each primary diagnosis was examined. Newly diagnosed patients accounted for 21% ($n = 1087$) of the enrolled population, with rhinosinusitis (44%) and AR (27%) accounting for the highest proportion of new diagnoses. Only a minority of patients with asthma and COPD were newly diagnosed.

In terms of receiving care for each respiratory disorder, the highest percentage of patients who received care (as a proportion of patients screened see Fig. 1) for a respiratory disorder had a primary diagnosis of AR (14.0% [95% CI, 13.4–14.6%]), followed by asthma (13.5% [95% CI, 12.9–14.1%]), rhinosinusitis (5.4% [95% CI, 4.6–5.3%]), and COPD (4.9% [95% CI, 5.0–5.7%]). The primary diagnosis varied among the individual study countries (Fig. 2). The highest percentage of pa-

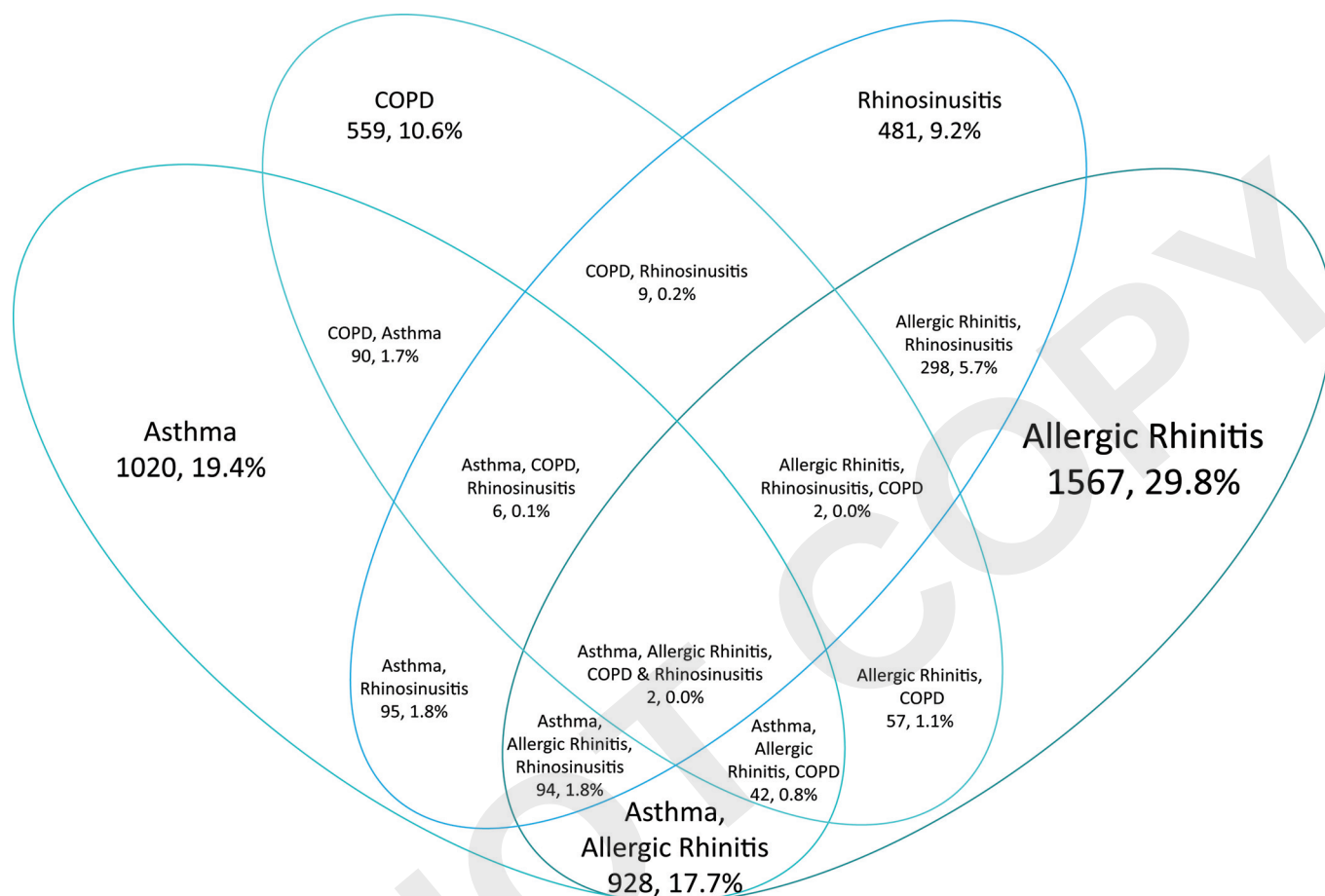


Figure 3. Percentage of patients ($N = 5250$) with a combination of diseases.

tients who received care for AR, asthma, and COPD was in India, and the highest for rhinosinusitis was among patients in Thailand and Singapore.

Patients identified as having concomitant respiratory diseases are shown in Fig. 3. In total, 1624 patients (30.9%) presented with a combination of the four diseases of interest. The most common combination was AR and asthma, with or without other conditions (1066 patients, 20.3% of the total enrolled). Of the patients who presented with asthma as the primary diagnosis ($N = 1875$), 761 patients (40.6%) were in combination with AR, with or without other conditions. Of patients who had a diagnosis of AR (primary or secondary, $N = 2990$), 35.7% had both AR and asthma. A high proportion of patients with rhinosinusitis as the primary diagnosis ($N = 745$) were also diagnosed with patients in combination with AR (29.7%).

Patients were required to list all respiratory-related symptoms at the current visit and to indicate which symptom was the main reason for the visit (Fig. 4). Overall cough or coughing up phlegm was the most frequently reported symptom (57%) for the enrolled population, followed by sneezing (48%) and blocked nose or congestion (44%). Cough or coughing up phlegm was also most frequently reported as the main reason for the current visit (23%),

followed by watery nose (14%), and blocked nose (13%). It was both the most frequently reported symptom and the main reason for the current visit in patients with a primary diagnosis of COPD (73% and 43%, respectively) and asthma (61% and 33%, respectively). For patients with a primary diagnosis of rhinosinusitis, blocked nose or congestion were the most frequently reported symptom (68%) and main reason for the current visit (23%), with cough or coughing up phlegm as the second most frequently reported symptom (59%) and third most frequently reported main reason (13%). For patients with a primary diagnosis of AR, sneezing (69%) and watery, runny nose (64%) were the most frequently reported symptoms; however, watery nose (24%) and blocked nose (20%) were the main reasons for the current visit. Cough or coughing up phlegm, although less common than in the other diseases, was still notable in patients with AR; the fifth most frequently reported symptom (45%) and the third most frequently reported main reason (11%). The duration of cough varied in the study population (Table 2), with almost half reporting cough duration of <3 weeks. This was highest in patients with asthma, followed by those with rhinosinusitis, AR, and COPD.

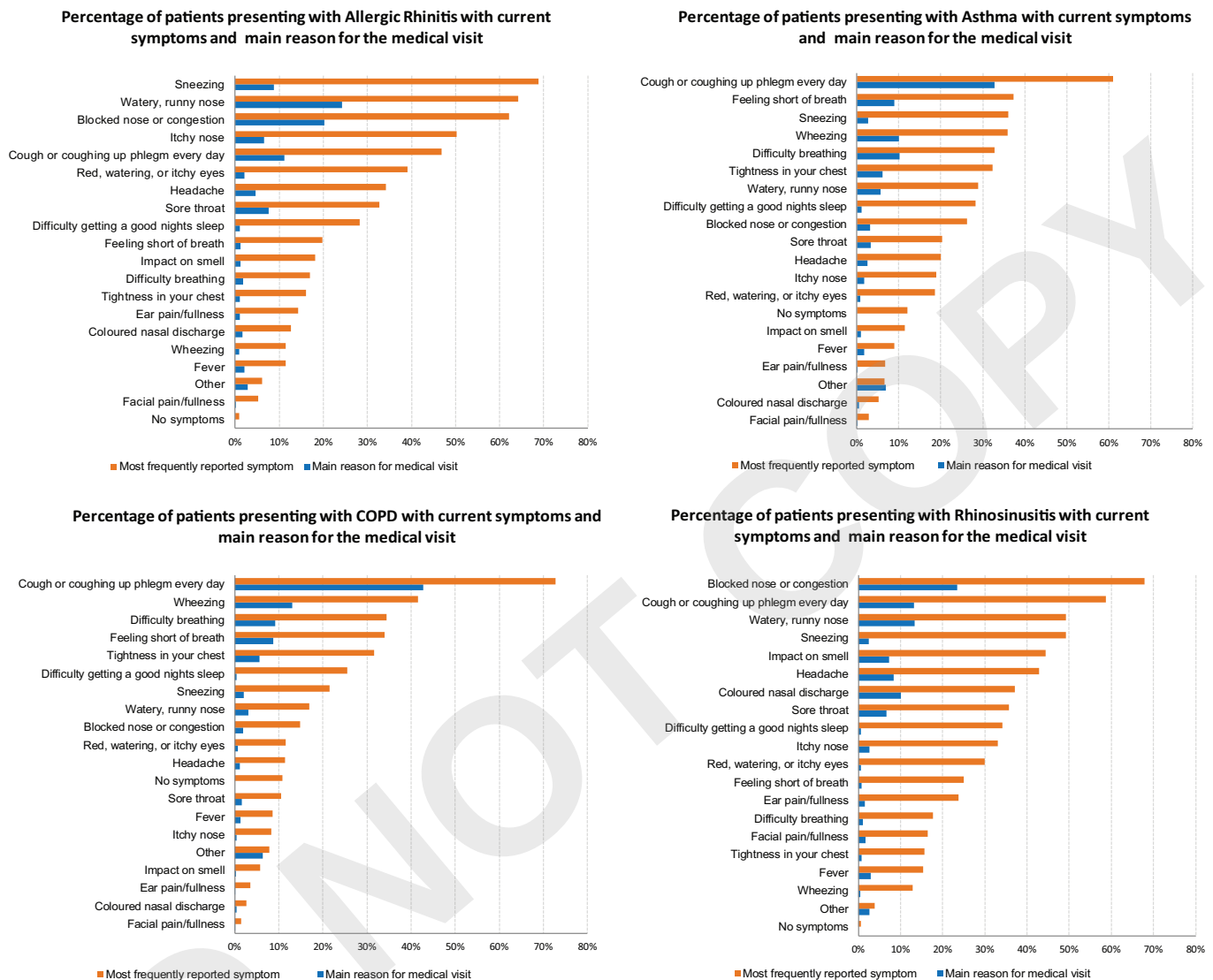


Figure 4. Percentage of patients who reported current symptoms at the medical visit ($n = 5245$) and the main reason for their visit by primary diagnosis ($n = 4887$).

Table 2 Patient-reported duration of cough symptoms, if present, by primary diagnosis*

Duration	Allergic Rhinitis, no. (%) ($n = 170$)	Asthma, no. (%) ($n = 476$)	COPD, no. (%) ($n = 226$)	Rhinosinusitis, no. (%) ($n = 83$)	Total Population, no. (%) ($n = 955$)
<3 wk	72 (42)	276 (58)	77 (34)	42 (51)	467 (49)
~8 wk	49 (29)	96 (20)	66 (29)	19 (23)	230 (24)
>8 wk	49 (29)	104 (22)	83 (37)	22 (27)	258 (27)

COPD = chronic obstructive pulmonary disease.

*Calculation of percentage excludes missing values; total number of current symptoms selected by each patient.

DISCUSSION

This study showed that asthma, AR, COPD, or rhinosinusitis may contribute to a significant percentage of all respiratory disorders in patients who present to health care professionals in Asia. The highest percentage of screened visits was associated

with a primary diagnosis of AR (14.0%) and asthma (13.5%) compared with rhinosinusitis (5.4%) and COPD (4.9%). The majority of visits to health care professionals was for previously diagnosed disease, with only 21% of patients newly diagnosed. This highlights both the significant utilization of health

care professionals' time for disease management and the proportion of patients that may be undiagnosed and untreated, particularly patients with AR and rhinosinusitis.

Intercountry variability of the frequency of disease was evident (Fig. 3). The number of patients who received care for AR, asthma, and COPD was highest in India in comparison with rhinosinusitis in Thailand and Singapore. This diversity may be attributable to a number of factors, such as the varying incidence and prevalence of these diseases among countries,^{2-5,21} differences in health care systems and treatment practices (GP, specialist, polyclinic), and access to and availability of health services in each country. Of interest was the disparate mix of specialists (ear, nose, and throat; respiratory; and allergy) and GP clinics in each study country. For example, in Singapore, there were two GP clinics and no allergy clinics, whereas GP clinics were not always common in other countries. These differences in practice clinics and health care systems may explain some of the significant intercountry variability in the proportion of the four diseases of interest. Furthermore, factors such as smoking rates and environmental influences could have contributed to the variability, although 48% of patients at work and 33% at home reported no exposure to certain environmental risk factors. One explanation might be that patients visit a health care professional more frequently with milder symptoms when health services are readily accessible, when compared with countries where access may be restricted by location, availability, and cost. Disease diagnosis by health care professionals may have impacted the reported frequency of the disease because the method of diagnosis was not standardized and was based on physician judgment to reflect current treatment practices in the real-world setting. However, previous research found that asthma and COPD are often under- or misdiagnosed in primary care.²²⁻²⁵

A combination of diseases was reported in approximately one-third of enrolled patients, with AR and asthma the most common combination. Of patients with a diagnosis of AR, 35.7% also had concomitant AR and asthma. This result was similar to a previous study in six European countries that reported asthma prevalence of 31.5% in patients with AR treated by primary care and specialist physicians.¹⁰ Furthermore, a study of AR in nine countries in the Asia-Pacific region found that 20% of adults with AR had concomitant asthma.² Notably, this study comprised countries (*e.g.*, Vietnam, Hong Kong, China) that reported a lower percentage of diagnosed asthma and did not include India, which, in the present study, reported both the highest percentage of patients with AR and asthma, which highlighted

not only the considerable intercountry variability in respiratory disorders but the need for further investigation into concomitant respiratory disease in countries where reports of respiratory disease, particularly asthma and/or AR, is frequent, to ensure prompt diagnosis and that appropriate treatment strategies are implemented.

Interestingly, cough or coughing up phlegm was the most frequently reported symptom and main reason for the medical visit by patients enrolled in the study. Cough has long been recognized as one of the key clinical symptoms of asthma and COPD.²⁶⁻²⁸ This was confirmed by the present study for patients with a primary diagnosis of asthma or COPD. A high percentage of patients with rhinosinusitis also reported cough or coughing up phlegm as a symptom (59%), a figure similarly reported in a U.S. study that found that cough is a presenting symptom in 65% of patients with chronic rhinosinusitis.^{29,30} Results from the present study found 47% of patients with a primary diagnosis of AR reported cough or coughing up phlegm as a symptom. This was significantly higher than studies in Europe and the Asia-Pacific region, which reported ~20% of patients with AR having cough.^{10,31} These studies, however, included patients surveyed regardless of whether or not they were visiting a physician at the time of the study. The results from the present study may indicate that patients with AR are more likely to visit a physician when cough is present. It was positive to note that almost half of the patients reported cough duration of <3 weeks before seeking medical attention. The impact of cough or coughing up phlegm on patients with AR was emphasized; despite being the fifth most reported symptom, it was the third most reported main reason for the medical visit. Contributing to the presence of cough in patients with AR and rhinosinusitis is the significant percentage of patients with concomitant asthma or COPD. These results underscore the need for patients presenting with cough to be comprehensively investigated for combinations of multiple respiratory disorders to ensure early detection and treatment.

As with all studies, limitations are inevitable and should be taken into account when interpreting the results. Although not all eligible patients consented to participate in the study, our sample captured a representative sample of patients between the consenting and nonconsenting participants. Despite the study recruiting at multiple sites across six countries in the Asia-Pacific region, adult patients presented to primary care physicians and specialist medical practices in urban settings of convenience; it was not the intention of the study to obtain prevalence estimates that are generalizable to the entire population, country, or region. As such, study participants may not be entirely representative of the broader population with respira-

tory diseases. Furthermore, only adult patients were recruited from urban centers, and results may not be generalizable either to patients <18 years of age or to rural populations.

Despite the use of clinical guidelines, the method of diagnosing respiratory disease was not standardized and based on physician judgment, which may have led to inconsistencies in the diagnosis and frequency rate of the various diseases. Validity of the Physician and Patient Surveys was not assessed as part of this study; however, other validated surveys were used to assess work productivity and health-related quality-of-life measures. In addition, factors such as age, smoking rates, environment, and seasonality may also have influenced the reported frequency of symptoms and may have resulted in variations in reporting between diseases and countries. As noted earlier, the study did not establish prevalence but provided a description of the extent of the four diseases of interest in patients who presented to primary and specialist health care professionals with respiratory symptoms within a restricted period of time.

This study showed that the four diseases of AR, asthma, COPD, and rhinosinusitis may represent a significant percentage of all respiratory diseases in patients who presented to health care professionals in the Asia-Pacific region. Almost one-fifth of presenting patients were newly diagnosed, and a significant proportion of patients may present with concomitant respiratory disease. Although patients presented with multiple symptoms, cough was the most prominent symptom and major reason for seeking medical care for patients with COPD and asthma, and, to a lesser extent, rhinosinusitis and AR. The study highlighted the need to comprehensively investigate patients who present with cough for any underlying serious respiratory disorders or concomitant disease, to deliver prompt and appropriate disease treatment and management strategies, and reduce the impact and burden of these diseases on patients and the community.

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