Impacts of Comorbidities on Annual Incidence and Frequency of Asthma Exacerbation Hospitalisation: Data from CARN Study

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Abstract

Purpose: While asthma comorbidities are associated with higher health care utilisation, lower quality of life and poorer asthma control, the impact of asthma comorbidities on hospitalisation for asthma exacerbation (H-AX) remains less recognised. We aim to analyse the impact of asthma comorbidities on H-AX.

Methods: Based on a national survey on asthma control and disease perception (CARN 2015 study), we analysed the impact of comorbidities on annual incidence and frequency of H-AX in China. Information on demographic characteristics, asthma comorbidities and annual incidence and frequency of H-AX were presented in this study.

Results: Among 3875 ambulatory asthma patients, 75.9% (2941/3875) had comorbidities, and 26.4% (1017/3858) experienced H-AX during past year. After adjusting for confounding factors such as demographic data, smoking status and asthma control, COPD [OR=2.189, 95%CI (1.673, 2.863)] and coronary heart disease [OR=1.387, 95%CI (1.032, 1.864)] were associated with higher annual incidence, while allergic rhinitis [OR=0.692, 95%CI (0.588, 0.815)] was associated with lower annual incidence, of H-AX. In terms of frequency, allergic rhinitis [OR=1.630, 95%CI (1.214, 2.187)], COPD [OR=1.472, 95%CI (1.021, 2.122)] and anxiety [OR=2.609, 95%CI (1.051, 6.477)] showed statistically significant correlation with frequent H-AX.

Conclusions: Comorbidities such as COPD, coronary heart disease and allergic rhinitis, may have an important role in the risk and/or frequency of annual hospitalisations due to asthma exacerbation. The goal of asthma control should rely on a multi-disciplinary treatment protocol but not merely on efforts of respiratory physicians.

Introduction

Bronchial asthma is a heterogeneous disease characterised by chronic airway inflammation and associated with hefty social and economic burdens [1]. Asthma exacerbations, especially those necessitating hospital admissions, contribute to the majority of the healthcare expenses in asthma patients [2]. The risk factors of asthma exacerbation generally include viral infection of the upper respiratory tract [3], exposure to allergens (such as grass pollens [4], soy bean dusts [5], fungal spores, and food allergens [6]), outdoor air pollution [7, 8], climatic seasonality [9] and poor adherence with inhaled corticosteroids (ICS) therapy [10].

Besides these, having uncontrolled asthma is inherently related to frequent exacerbations [11]. The importance of asthma assessment and management therefore cannot be over-emphasised. For this purpose, Global Initiative for Asthma (GINA) recommendations underline the need to identify and handle the comorbidities as a key part of clinical practices for asthma patients [1]. Several studies have shown that comorbidities are associated with higher health care utilisation, lower quality of life and poorer

asthma control [12–15]. Nevertheless, the role of comorbidities on asthma exacerbations remains less recognised, particularly, in a huge population of Chinese patients.

Using data from a national survey on asthma control and disease perception, we aimed to analysis the impact of comorbidities on hospitalisation for asthma exacerbation (H-AX) in China.

Materials And Methods

2.1 Study design and participants

The present study was based on a national survey on asthma control and disease perception conducted by China Asthma Research Network (CARN 2015 study) [16]. Briefly, the CARN 2015 study was a multi-centre, cross-sectional, questionnaire-based survey, carried out in 30 provinces of China from October 2015 to May 2016, recruiting 3875 asthma patients from 30 centres who met all of the following: (1) age ≥ 14 years old; (2) having resided in the study city for at least 2 years; (3) diagnosed with asthma at least 3 months prior to the study according to GINA criteria. In that study steered with approval by the Ethics Committee of China Japan Friendship Hospital, data on demography, asthma control, medical and self-management, exacerbations, and disease perception were collected during face-to-face interviews with written informed consent from the patients.

Recently, to shed light on the impacts of comorbidities on annual incidence and frequency of H-AX, we extracted the following data from all participants in the CARN 2015 study: 1) Demographic characteristics including age, gender, height, weight, and body mass index (BMI); 2) Self-reported comorbidities, including atopic diseases (allergic rhinitis, nasosinusitis, rhinopolypus, and food allergy), respiratory diseases [chronic obstructive pulmonary disease (COPD), bronchiectasis, and obstructive sleep apnea hypopnea syndrome (OSAHS)], cardiovascular diseases (hypertension, coronary heart disease), metabolic disorders (obesity and diabetes), digestive conditions [gastroesophageal reflux disease (GERD)], cerebrovascular disease, psychiatric disorders (depression and anxiety), and other comorbidities such as gestation and osteoporosis; 3) Annual incidence and frequency of H-AX during the year prior to CARN 2015. The data extraction, database input and double-checking were completed by a designated investigator (WQW) under the supervision of our team leader (JTL). Use of CARN data in the present study was again approved by the Ethics Committee of China Japan Friendship Hospital (No.2015-98) with the request to protect patient identity and privacy.

According to GINA 2021, asthma exacerbations were defined as episodes characterised by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decline in lung function, which represent a change from the patient's usual status sufficiently to require a change in treatment [1]. H-AX was defined as any hospitalisation due to asthma exacerbations. According to H-AX in the previous year, the patients who had experienced H-AX were assigned to the H-AX group, and those who had not, into the non-H-AX group. The H-AX group was further stratified into three sub-groups, where the frequency of previous-year H-AX was one, two or at least three, respectively.

2.2 Statistical Analysis

Continuous variables (age, height, weight, and BMI) were presented as mean ± SD and categorical variables (gender, incidence of comorbidities) were presented as frequency. Between-group comparisons were completed using unpaired t test for continuous variables and Chi-square test for categorical variables. Binary logistic regression, followed by multivariate logistic regression, was performed to assess the effect of comorbidities on the incidence of H-AX after adjusting for confounders (demographic status, smoking status, and asthma control). All tests were two-tailed, and P values less than 0.05 were considered statistically significant. All data were processed with SPSS statistical software (version 21.0; IBM SPSS, Armonk, NY, USA).

Results

3.1 Demographics

Data retrieved from the CARN 2015 study with 3875 ambulatory asthma patients, including 2347 females (60.6%), were available for the present study. The mean age was 50.7 ± 16.7 years. Of these patients, 75.9% (2941/3875) had comorbidities. Specifically, 43.4% (1682/3875) had allergic rhinitis, 16.4% (634/3875) had hypertension, 8.7% (338/3875) had nasosinusitis, 7.3% (283/3875) had COPD, and 3.0% (118/3875) had bronchiectasis. Asthma control was achieved in 28.5% (1099/3875) of the patients. The demographic characteristics is shown in Table 1.

Table 1
Demographic Characteristics

Items		Result [Mean ± SD or %(n/N)]
Gender	Male	39.4% (1528/3875)
	Female	60.6% (2347/3875)
Age (years)		50.7 ± 16.7
Height (cm)		163.8 ± 7.9
Weight (kg)		63.8 ± 12.4
BMI (kg/m^2)		23.7 ± 3.9
Comorbidities		
	Allergic rhinitis	43.4% (1682/3875)
	Nasosinusitis	8.7% (338/3875)
	Rhinopolypus	2.9% (114/3875)
	Food allergy	6.0% (232/3875)
	COPD	7.3% (283/3875)
	Bronchiectasis	3.0% (118/3875)
	OSAHS	2.9% (114/3875)
	Hypertension	16.4% (634/3875)
	CHD	6.6% (256/3875)
	Obesity	1.5% (58/3875)
	Diabetes	4.9% (188/3875)
	GERD	3.7% (143/3875)
	CVD	6.6% (256/3875)
	Depression	0.6% (22/3875)
	Anxiety	1.6% (63/3875)
	Gestation	0.5% (20/3875)

Data are presented as mean ± standard deviations (SD) or percentage (%, n/N).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; CHD, Coronary heart disease; GERD, gastroesophageal reflux disease; CVD, Cerebrovascular disease.

Items		Result [Mean ± SD or %(n/N)]
	Osteoporosis	1.6% (63/3875)
	Others	10.6% (409/3875)
Data are presented as mean ± standard deviations (SD) or percentage (%, n/N).		
BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; CHD, Coronary heart disease; GERD, gastroesophageal reflux disease; CVD, Cerebrovascular disease.		

To elucidate on the impacts of comorbidities on the incidence and frequency of H-AX, 17 patients with missing report on the previous-year hospitalisation due to asthma, and likewise, seven more who reported so but did not specify the number of H-AX were excluded from the subsequent analyses (Fig. 1).

3.2 Impact of comorbidities on annual incidence of H-AX

Of the study population, 26.4% (1017/3858) of the study population were hospitalised due to asthma exacerbation during the previous year. Compared to those without H-AX, the asthma patients in the H-AX group were more likely to have advanced age (61.5 ± 14.9 vs. 52.6 ± 15.7 years, $P < 0.001$) and lower height (163.1 ± 7.7 vs. 164.1 ± 8.0 cm, $P < 0.001$). With regards to comorbidities, except for the lower proportion of allergic rhinitis (32.0% vs. 47.4%, $\chi^2 = 73.794$, $P < 0.001$), patients with previous-year H-AX were more likely to have concomitant COPD (15.4% vs. 5.5%, $\chi^2 = 135.262$, $P < 0.001$), bronchiectasis (4.6% vs. 2.5%, $\chi^2 = 11.962$, $P = 0.003$), hypertension (23.3% vs. 13.9%, $\chi^2 = 48.744$, $P < 0.001$), coronary heart disease (11.4% vs. 4.9%, $\chi^2 = 52.790$, $P < 0.001$), and diabetes (8.2% vs. 3.6%, $\chi^2 = 35.145$, $P < 0.001$). The proportions of other comorbidities did not differ statistically between the two groups (Table 2).

Table 2
Subjects with and without the previous-year H-AX

Items		H-AX group	Non-HAX group	χ^2 value	P value
Gender	Male	41.6% (423/1017)	38.6% (1098/2841)	2.719	0.099
	Female	58.4% (594/1017)	61.4% (1743/2841)		
Age (years)		57.5 ± 14.9	48.6 ± 15.7		< 0.001*
Height (cm)		163.1 ± 7.7	164.1 ± 8.0		< 0.001*
Weight (kg)		63.3 ± 12.2	64.1 ± 12.5		0.086
BMI (kg/m^2)		23.7 ± 3.8	23.7 ± 3.0		0.990
Comorbidities					
	Allergic rhinitis	32.0% (325/1017)	47.4% (1348/2841)	73.179	< 0.001*
	Nasosinusitis	8.2% (83/1017)	9.0% (255/2841)	0.621	0.430
	Rhinopolypus	2.8% (28/1017)	3.0% (86/2841)	0.196	0.658
	Food allergy	6.2% (63/1017)	5.9% (167/2841)	0.134	0.715
	COPD	15.4% (157/1017)	5.5% (157/2841)	133.375	< 0.001*
	Bronchiectasis	4.6% (47/1017)	2.5% (71/2841)	11.377	0.001*
	OSAHS	3.0% (31/1017)	2.9% (83/2841)	0.042	0.838
	Hypertension	23.3% (237/1017)	13.9% (394/2841)	48.736	< 0.001*
	CHD	11.4% (116/1017)	4.9% (138/2841)	52.220	< 0.001*
	Obesity	1.7% (17/1017)	1.4% (41/2841)	0.264	0.607
	Diabetes	8.2% (83/1017)	3.6% (103/2841)	33.577	< 0.001*

Data are presented as mean ± standard deviation (SD) or percentage (%, n/N).

*Data with statistical significance

H-AX, Hospitalisation due to asthma exacerbation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; CHD, Coronary heart disease; GERD, gastroesophageal reflux disease, CVD, Cerebrovascular disease.

Items		H-AX group	Non-HAX group	χ^2 value	P value
	GERD	3.2% (33/1017)	3.9% (110/2841)	0.825	0.364
	CVD	1.3% (13/1017)	1.5% (44/2841)	0.376	0.540
	Depression	0.5% (5/1017)	0.6% (17/2841)	0.150	0.698
	Anxiety	1.9% (19/1017)	1.5% (44/2841)	0.476	0.490
	Gestation	0.1% (1/1017)	0.7% (19/2841)	4.726	0.030
	Osteoporosis	2.1% (21/1017)	1.5% (42/2841)	1.604	0.205
	Others	11.7% (119/1017)	10.1% (288/2841)	1.941	0.164
Data are presented as mean ± standard deviation (SD) or percentage (%, n/N).					
*Data with statistical significance					
H-AX, Hospitalisation due to asthma exacerbation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; CHD, Coronary heart disease; GERD, gastroesophageal reflux disease, CVD, Cerebrovascular disease.					

After adjusting for confounding factors such as demographic data, smoking status and asthma control, COPD [OR = 2.189, 95%CI (1.673, 2.863)] and coronary heart disease [OR = 1.387, 95%CI (1.032, 1.864)) were associated with higher annual incidence, while allergic rhinitis [OR = 0.692, 95%CI (0.588, 0.815)] was associated with lower annual incidence, of H-AX (Table 3).

Table 3
Adjusted odds ratio of comorbidities for incidence of H-AX

Comorbidities	OR	95% CI	P value
Allergic rhinitis	0.692	(0.588, 0.815)	< 0.001 *
Nasosinusitis	1.116	(0.839, 1.485)	0.449
Rhinopolypus	1.065	(0.664, 1.708)	0.794
Food allergy	1.282	(0.928, 1.773)	0.132
COPD	2.189	(1.673, 2.863)	< 0.001 *
Bronchiectasis	1.379	(0.921, 2.066)	0.119
OSAHS	0.953	(0.607, 1.497)	0.834
Hypertension	1.107	(0.894, 1.369)	0.351
CHD	1.387	(1.032, 1.864)	0.030*
Obesity	1.079	(0.581, 2.004)	0.809
Diabetes	1.284	(0.922, 1.787)	0.140
GERD	0.776	(0.509, 1.183)	0.239
CVD	0.399	(0.203, 0.783)	0.008*
Depression	0.887	(0.300, 2.623)	0.828
Anxiety	1.076	(0.599, 1.935)	0.805
Gestation	0.273	(0.035, 2.113)	0.214
Osteoporosis	1.039	(0.584, 1.850)	0.896
Data are presented as mean ± standard deviation (SD) or percentage (n/N).			
*Data with statistical significance			
OR, Odds ratio; CI, Confidence interval; H-AX, Hospitalisation due to asthma exacerbation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; CHD, Coronary heart disease; GERD, gastroesophageal reflux disease; CVD, Cerebrovascular disease.			

Table 4
Adjusted odds ratio of comorbidities for frequent H-AX

Comorbidities	OR	95% CI	P value
Allergic rhinitis	1.630	(1.214, 2.187)	0.001*
Nasosinusitis	1.566	(0.964, 2.544)	0.070
Rhinopolypus	1.108	(0.498, 2.466)	0.801
Food allergy	0.807	(0.454, 1.435)	0.465
COPD	1.472	(1.021, 2.122)	0.038*
Bronchiectasis	1.173	(0.637, 2.158)	0.609
OSAHS	0.901	(0.406, 2.000)	0.799
Hypertension	0.994	(0.702, 1.407)	0.972
CHD	1.026	(0.660, 1.595)	0.910
Obesity	0.822	(0.278, 2.435)	0.724
Diabetes	1.557	(0.961, 2.522)	0.072
GERD	1.538	(0.762, 3.106)	0.230
CVD	2.173	(0.721, 6.552)	0.168
Depression	0.304	(0.029, 3.225)	0.323
Anxiety	2.609	(1.051, 6.477)	0.039*
Osteoporosis	1.200	(0.477, 3.019)	0.699
Data are presented as mean ± standard deviation (SD) or percentage (n/N).			
*Data with statistical significance			
OR, Odds ratio; CI, Confidence interval H-AX, Hospitalisation due to asthma exacerbation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHD, Coronary heart disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; GERD, gastroesophageal reflux disease; CVD, Cerebrovascular disease.			

3.3 Impact of comorbidities on frequency of the previous-year H-AX

Frequency of H-AX during the previous year was reported by 1010 asthma patients. Among them, 67.5% (682/1010) experienced one H-AX, 20.2% (204/1010) experienced two, and 12.3% (124/1010)

experienced three or more during the year prior to CARN 2015 study. The asthma patients with frequent H-AX (two, three or more H-AX) tended to be more affected by comorbidities, in particular, by allergic rhinitis (P = 0.014), COPD (P = 0.001), diabetes (P = 0.045), GERD (P = 0.028), and cerebrovascular diseases (P = 0.006). Data were shown in Fig. 2.

After adjusting for confounding factors such as demographic data, smoking status and asthma control level, allergic rhinitis [OR = 1.630, 95%CI (1.214, 2.187)], COPD [OR = 1.472, 95%CI (1.021, 2.122)] and anxiety [OR = 2.609, 95%CI (1.051, 6.477)] were significant correlated with frequent asthma exacerbation hospitalisation (two, three or more H-AX).

Discussion

In this study, we investigated the correlation between comorbidities and hospitalisation for asthma exacerbation (H-AX) based on CARN 2015, a multi-centre cross-sectional survey participated by 3875 asthma patients in China. As shown, 75.9% of our study population suffered a wide range of comorbidities involving the lungs, heart, vessels, immunity and metabolism. Over a quarter (26.4%) experienced at least one hospitalisation for asthma exacerbation during the previous year, of whom, 12.3% experienced three or more hospitalisations. We showed that comorbidities in asthma patients played an important role in H-AX events. Specifically, comorbidities such as structural lung disease (COPD, bronchiectasis), cardiovascular disease (hypertension, coronary heart disease) and metabolic disorders (diabetes) were associated with the likelihood of any H-AX, whereas H-AX ≥ 2 or ≥ 3, was linked to comorbidities like allergic rhinitis, COPD, diabetes, GERD, and cerebrovascular disease.

Of allergic comorbidities, nasosinusitis and rhinopolypus are common in asthma patients, and were found in 75–80% of severe asthma cases [17, 18]. Nasosinusitis and confirmed food allergy are independent risk factors of asthma exacerbation [6, 19]. Several previous study indicated poorer asthma outcome with comorbidity of allergic rhinitis [20–22]. In this study, we failed to determine a correlation between nasosinusitis, rhinopolypus, food allergy, and asthma exacerbation or frequent H-AX. Surprisingly, asthma patients who experienced H-AX presented lower prevalence of allergic rhinitis; we speculated that this puzzling observation may be associated the higher rate of co-treatment in patients with mild allergic rhinitis, although we did not perform a subgroup analysis for demonstration. However, in terms of H-AX frequency, allergic rhinitis was associated with two or more hospitalisation related to asthma in the previous year.

Cardiovascular disease can influence asthma outcomes, and vice versa. Schanen et al. [23] reported that asthma patients were more likely to have cardiovascular disease. In a previous survey among adults aged ≥ 65 years, asthma patients with coronary artery disorders showed fairly higher adjusted odd ratios for one or more asthma-related hospitalisations [24]. In the present study, cardiovascular comorbidities

were linked to H-AX. We indicated that coronary heart disease was associated with significantly higher likelihood, but not frequeny, of H-AX.

Metabolic disorders are also common in asthma. Obesity has been reported to relates with increased asthma severity and exacerbations [25]. In this setting, data about diabetes remain limited. Song et al. found that women who had ever reported asthma or COPD were at a higher risk for diabetes [26, 27]. Diabetes and insulin resistance are associated with decline in lung function [28–30]. In our study, having diabetes was associated with significantly higher likelihood and frequency of H-AX in univariate analyses, but the statistical differences were not reached in subsequent multivariate logistic analyses. In either univariate or multivariate analysis, cormorbidity with obesity did not correlate with H-AX in likelihood or frequency. Therefore, the role of metabolic disorders in H-AX warrants future studies.

The interplay between asthma and respiratory comorbidities, structural lung diseases in particular, should be noteworthy to mention. Compared to asthma or COPD alone, asthma-COPD overlap leads to heavier burden of symptoms [31], incurs more frequent exacerbations [31–33] and accounts for greater use of healthcare resources [32, 34]. Mao et al. [35] noted that concomitant asthma was associated independently with an increase in risk of bronchiectasis exacerbation. In contrast, few studies assessed the impact of bronchiectasis on asthma exacerbation. Kang et al. showed higher annual incidence of asthma exacerbation and frequency of emergency room visits in patients with asthma and bronchiectasis than in those with asthma alone [36]. In the present study, we demonstrated that comorbidity with structural lung diseases, such as COPD, was associated with both higher annual incidence and frequency of H-AX. We believe that our findings add to the evidence supporting the adverse impacts of structural lung disease on asthma outcome.

Concomitant GERD is estimated to affect 34–89% of asthma patients [37]., and has been linked to the severity of asthma [38, 39]. However, our results indicated neither a higher prevalence of GERD in the asthma patients, nor a statistical correlation of GERD with the likelihood of H-AX. We speculated the self-reporting of comorbidities in CARN 2015 study might undercut the GERD prevalence. Notwithstanding this, in our study, GERD was associated with more frequent H-AX in the univariate analysis albeit with no statistical significance in the multivariate logistic regression.

Finally, we need to elaborate on several special considerations pertaining to the strength and weakness of our study. Firstly, to the best of our knowledge and data availability, CARN 2015 study is so far the largest nationwide survey on H-AX and comorbidities among Chinese asthmatics over the recent years. Using relevant information from full dataset of CARN, our findings regarding the relationship between certain comorbidities and the likelihood and/or frequency of H-AX in asthma patients could therefore be a close reflection of the real world in China. Secondly, comorbidities associated to the risk and/or frequency of H-AX in this study chiefly involved structural lung diseases and chronic, systemic disorders. Given that this was merely an observational rather than a mechanistic study, our findings should be interpreted with prudence and do not mean to propose a causative relationship. Nevertheless, comorbid abnormality in pulmonary architecture, systemic inflammation and immune function, could impose unfavorable impacts

on the natural history and treatment outcomes of asthma which is an immune, inflammatory disorder per se. In this context, the goal of asthma control can be achieved not only depending on efforts of respiratory physicians, but also involving a multi-disciplinary treatment protocol. Either other systemic conditions as comorbidity in asthma, or asthma as comorbidity in other systemic conditions, need to be ideally taken together in decision-making for treatments. Thirdly, according to GOLD [40], annual exacerbations ≥ 2 or hospitalisation due to COPD exacerbation ≥ 1 was defined as frequent COPD exacerbation. However, similar criteria have not been widely recognised for “frequent” asthma exacerbations or “frequent” H-AX. As an attempt for description in this study, we tentatively stratified the asthma patients according to one, two, three or more H-AX in the previous year and also by taking into consideration the comorbidities. The times of H-AX statistically differed with such stratification. Our statistics showed that using annual sessions ≥ 2 or ≥ 3 in a patient was comparably acceptable to define exacerbations as “frequent” in asthma, as like in COPD. In this regard, our work may add to determination of the definition of frequent asthma exacerbation, rendering more discussions needed in the future.

The study has several limitations. Self-reported comorbidities may underestimate the real prevalence and be influenced by interviewees compliance. More confounding factors, such as medications and treatment adherence, should have been included in analyses. Future investigations with follow-up study or comorbidity intervention study would help to validate our findings and clarify more on the relationship between comorbidities and hospitalisation due to exacerbation in asthma patients.

Conclusion

Comorbidities such as COPD, coronary heart disease and allergic rhinitis, may have an important role in the risk and frequency of annual hospitalisations due to asthma exacerbation. The goal of asthma control should rely on a multi-disciplinary treatment protocol but not merely on efforts of respiratory physicians.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of China Japan Friendship Hospital (No.2015-98) with the request to protect patient identity and privacy. Written informed consent for participation, publishment, and availability of data was obtained from participants or their legal guardian in the case of children under 18 years old in CARN study. All methods were carried out in accordance with the Declaration of Helsinki. All the protocols, consent to publish, availability of data and materials were approved by the Ethics Committee of China Japan Friendship Hospital.

Consent to publish

NA.

Availability of data and materials

The datasets are available from the corresponding author on reasonable request.

Competing interests

There were no competing interests to declare in this study.

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Authors Contribution

Wenqiao Wang finished the main manuscript text, Jiangtao Lin designed and supervised the study, Wenqiao Wang, Xin Zhou, Changzheng Wang, Mao Huang, Shaoxi Cai, Ping Chen, Qichang Lin, Jianying Zhou, Yuhai Gu, Yadong Yuan, Dejun Sun, Xiaohong Yang, Lan Yang, Jianmin Huo, Zhuochang Chen, Ping Jiang, Jie Zhang, Xianwei Ye, Huiguo Liu, Huaping Tang, Rongyu Liu, Chuntao Liu, Wei Zhang, Chengping Hu, Yiqiang Chen, Xiaoju Liu, Luming Dai, Wei Zhou, Yijiang Huang and Jianying Xu collected data of each centre. All authors reviewed the manuscript.

References

1. GINA Executive and Science Committee. Global Strategy for asthma management and prevention 2021. http://ginasthma.org/2021-gina-report-global-strategy-for-asthma-management-and-prevention/.
2. Lin J, Xing B, Tang H, Yang L, Yuan Y, Gu Y, et al. Hospitalization Due to Asthma Exacerbation: A China Asthma Research Network (CARN) Retrospective Study in 29 Provinces Across Mainland China. Allergy Asthma Immunol Res. 2020;12(3):485-495.
3. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. J Allergy Clin Immunol 2010; 125: 1178-87.
4. Erbas B, Jazayeri M, Lambert KA, Katelaris CH, Dharmage SC. Outdoor pollen is a trigger of child and adolescent asthma emergency department presentations: A systematic review and meta-analysis. Allergy 2018; 73: 1632-41.
5. Anto JM, Sunyer J, Reed CE, Sabria J, Martinez F, Morell F, et al. Preventing asthma epidemics due to soybeans by dust-control measures. N Engl J Med 1993; 329:1760-3.
6. Burks AW, Tang M, Sicherer S, Muraro A, Sampson HA. ICON: food allergy. J Allergy Clin Immunol 2012; 129: 906-20.
7. Mazenq J, Dubus JC, Gaudart J, Charpin D, Viudes G, Noel G. City housing atmospheric pollutant impact on emergency visit for asthma: A classification and regression tree approach. Respir Med 2017; 132: 1-8.
8. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. PLoS One 2017;12: e0174050.
9. Pike KC, Akhbari M, Kneale D, Harris KM. Interventions for autumn exacerbations of asthma in children. Cochrane Database Syst Rev 2018;3: Cd012393.
10. Williams LK, Peterson EL, Wells K, Ahmedani B, Kumar R, Burchard EG. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. J Allergy Clin Immunol 2011; 128:1185-91. e2.
11. Haselkorn T, Fish JE, Zeiger RS, Szefler SJ, Miller DP, Chipps BE. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk

for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. J Allergy Clin Immunol 2009; 124:895-902.e1-4.

12. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005; 128:2099e107.
13. Wijnhoven HA, Kriegsman DM, Hesselink AE, Haan MD, Schellevis FG. The influence of co-morbidity on health-related quality of life in asthma and COPD patients. Respir Med 2003; 97:468e75.
14. Lehrer PM, Karavidas MK, Lu SE, Feldman J, Kranitz L, Abraham S, et al. Psychological treatment of comorbid asthma and panic disorder: a pilot study. J Anxiety Disord 2008; 22:671e83.
15. Deshmukh VM, Toelle BG, Usherwood T, O'Grady B, Jenkins C. The association of comorbid anxiety and depression with asthma-related quality of life and symptom perception in adults. Respirology, 2008, 13(5): 695-702.
16. Lin J, Wang W, Zhou X, Wang C, Huang M, Cai S, et al. The level of asthma control in China from a national asthma control survey. Chin J Tubere Respir Dis, 2017, 40(7):494-498.
17. Ten BA, Grootendorst DC, Schmidt JT, Bruine TD, Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. J Allergy Clin Immunol, 2002, 109(4):621-626.
18. Bachert C, Zhang N. Chronic rhinosinusitis and asthma: novel understanding of the role of IgE 'above atopy'. J Intern Med, 2012, 272(2):133-143.
19. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. Clinical & Experimental Allergy, 2010, 35(3):282-287.
20. Thomas M, Kocevar VS, Zhang Q, Yin DD, Price D. Asthma-related health care resource use among asthmatic children with and without concomitant allergic rhinitis. Pediatrics, 2005, 115(1): 129-134.
21. Bousquet J, Gaugris S, Kocevar VS, Zhang Q, Yin DD, Polos PG, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial. Clin Exp Allergy, 2005, 35(6), 723-727.
22. López-Chacón M, Mullol J, Pujols L. Clinical and biological markers of difficult-to-treat severe chronic rhinosinusitis. Curr Allergy Asthma Rep, 2015, 15(5):19.
23. Schanen J G , Iribarren C , Shahar E , Punjabi NM, Folsom AR. Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study[J]. Thorax, 2005.
24. Hsu J, Chen J, Mirabelli MC. Asthma morbidity, comorbidities, and modifiable factors among older adults. J Allergy Clin Immunol Pract 2018;6:236-43.e7.
25. Fitzpatrick S, Joks R, Silverberg JI. Obesity is associated with increased asthma severity and exacerbations, and increased serum immunoglobulin E in inner-city adults. Clin Exp Allergy, 2012, 42(5): 747-59.
26. Song Y, Klevak A, Manson J, Buring J, Liu S. Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the Women's Health Study[J]. Diabetes Research & Clinical Practice, 2010, 90(3):365-371.

27. Perez M K , Piedimonte G . Metabolic asthma: is there a link between obesity, diabetes, and asthma? [J]. Immunology & Allergy Clinics of North America, 2014, 34(4):777-784.
28. Engstrom G, Hedblad B, Nilsson P, Wollmer P, Berglund G, Janzon L. Lung function, insulin resistance and incidence of cardiovascular disease: a longitudinal cohort study. J Intern Med. 2003;253:574–581.
29. Lawlor DA, Ebrahim S, Smith GD. Associations of measures of lung function with insulin resistance and Type 2 diabetes: findings from the British Women's Heart and Health Study. Diabetologia. 2004;47:195–203.
30. McKeever TM, Weston PJ, Hubbard R, Fogarty A. Lung function and glucose metabolism: an analysis of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2005;161:546–556.
31. Barrecheguren M, Pinto L, Mostafavi-Pour-Manshadi SM, Tan W, Bourbeau J, et al. Identification and definition of asthma-COPD overlap: The CanCOLD study. Respirology 2020;25:836-49.
32. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD overlap syndrome (ACOS): a systematic review and meta analysis. PLoS One 2015;10:e0136065.
33. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 2009;64:728-35.
34. Andersen H, Lampela P, Nevanlinna A, Saynajakangas O, Keistinen T. High hospital burden in overlap syndrome of asthma and COPD. Clin Respir J 2013;7:342-6.
35. Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. European Respiratory Journal, 2016:1680.
36. Kang HR, Choi GS, Park SJ, Song YK, Kim JM, Ha J, et al. The Effects of Bronchiectasis on Asthma Exacerbation[J]. Tuberculosis & Respiratory Diseases, 2014, 77(6).
37. Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. Chest. 1997;111:1389-1402.
38. Rameschandra S, Acharya V, Kunal, Vishwanath T, Acharya P. Prevalence and spectrum of gastro esophageal reflux disease in bronchial asthma. J Clin Diagn Res, 2015, 9(10):OC11-OC14.
39. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol, 2007, 119(2):405-413.
40. Global Initiative for Chronic Obstructive Lung Disease. https://goldcopd.org/2021-gold-reports/.

Figures

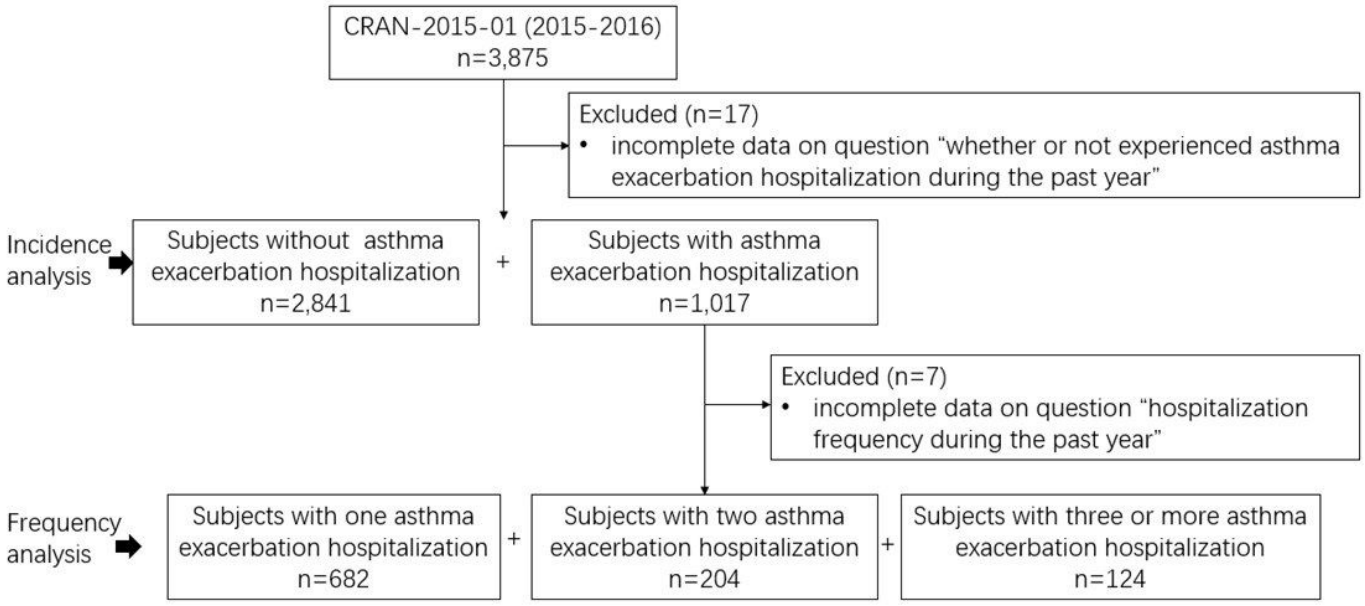

Figure 1

Flow chart of the present study

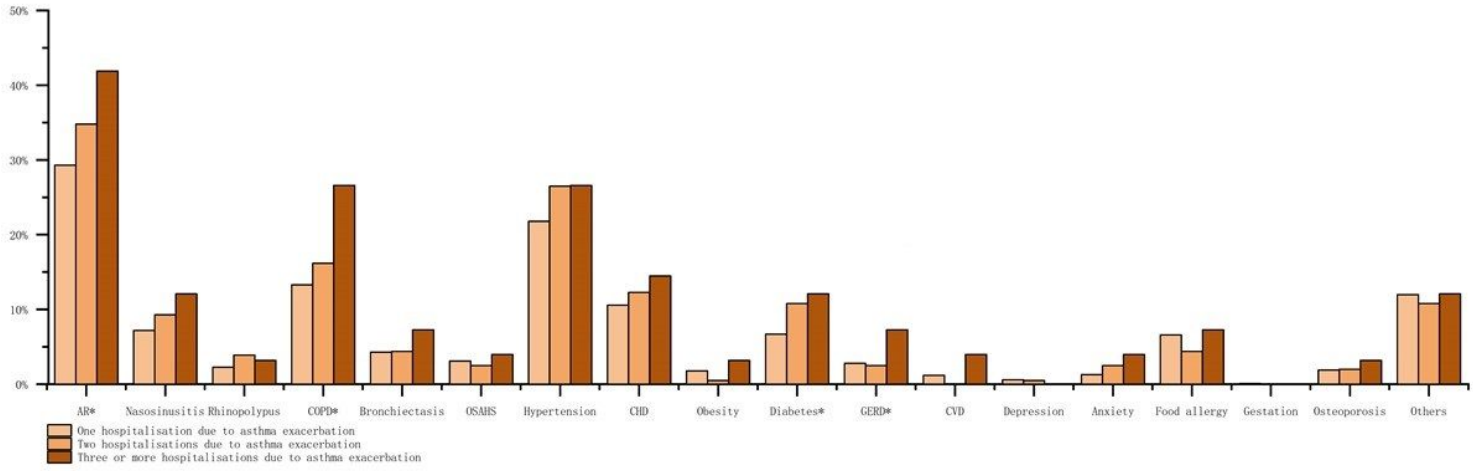

Figure 2

Impact of comorbidities on H-AX frequency during the past year

Data are presented as percentage.

*Data with statistical significance

AR, allergic rhinitis; COPD, chronic obstructive pulmonary disease; OSAHS, obstructive sleep apnea-hypopnea syndrome; CHD, Coronary heart disease; GERD, gastroesophageal reflux disease; CVD, Cerebrovascular disease.