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Coexisting chronic conditions associated with mortality and morbidity in adult patients with asthma

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Abstract

Objective—Many asthma patients suffer from chronic conditions other than asthma. We investigated the specific contribution of common comorbidities on mortality and morbidity in adult asthma.

Methods—In an observational study of adults with incident asthma identified between 1999 and 2003 using National Veterans Affairs and Centers for Medicare and Medicaid Services encounter databases (n=25,975, follow-up 3.0±1.7 years), association between 13 most prevalent comorbidities (hypertension, ischemic heart disease (IHD), osteoarthritis, rheumatoid arthritis, diabetes, mental disorders, substance/drug abuse, enlarged prostate, depression, cancer, alcoholism, HIV, and heart failure) and 4 conditions previously associated with asthma (sleep apnea, gastroesophageal reflux disease (GERD), rhinitis, and sinusitis) and mortality, hospitalizations and asthma exacerbations were assessed using multivariate regression analyses adjusted for other clinically important covariates.

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Author's contributions

KS led the design and conduct of the study, participated in the analysis and drafted the manuscript and take the responsibility for the integrity of the work in this manuscript. KO assisted the conduct of the study and data analysis. BB performed statistical analyses and contributed to the writing of the manuscript. DHA and MC participated in the conduct and analysis of the study and contributed to the writing of the manuscript. TAL guided the design and conduct of the study by KS, participated in the analysis and writing of the manuscript. All authors read, edited and approved the final manuscript.

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Results—HIV followed by alcoholism and mental disorders among 18–45 years old, and heart failure, diabetes, IHD, and cancer among those ≥65 years old were associated with an increased risk of all-cause mortality. Many conditions were associated with increased risk for all-cause hospitalizations, but the increased risk was consistent across all ages for mental disorders. For asthma exacerbations, mental disorder followed by substance abuse and IHD were associated with increased risk among those 18–45 years old, and chronic sinusitis, mental disorder, and IHD among those ≥65 years old. GERD was associated with decreased risk for asthma exacerbation in all ages.

Conclusions—Many comorbidities are associated with poor outcome in adult asthmatics and their effect differs by age. Mental disorders are associated with increased risk of mortality and morbidity across ages.

Keywords

observational study; Veterans; outcome research; comorbidities; mental disorders

INTRODUCTION

The prevalence of patients with multiple coexisting chronic conditions has been increasing with advances in treatment for chronic diseases and an aging population [1]. One in four elderly individuals suffer from multiple morbidities and even among younger adults (20–44 year old), 11–16% are reported as having multiple chronic conditions [2,3]. Therefore, management of patients with multiple chronic conditions presents a major challenge to healthcare systems worldwide [3,4].

Asthma is one of the most prevalent respiratory diseases, affecting more than 24.6 million people across all ages in the United States in 2009 [5]. Despite its prevalence across all ages, previous asthma clinical trials have mainly focused on children or younger adults without comorbidities. In adults, the focus on comorbidities has been primarily on the individual contributions of those diseases with a known association with asthma, such as rhinosinusitis, gastroesophageal reflux disease (GERD), sleep apnea, obesity, and mental disorders [6]. To date, population-based studies have investigated the prevalence of comorbidities in asthma patients compared to non-asthma population [7,8], but there is a paucity of data on the specific contribution of common comorbidities on the outcomes of adult asthma patients in real life. In addition, recognition of the specific contribution of common coexisting conditions on overall and asthma-related outcomes would be an important step in assisting clinicians to manage asthma patients with multi-comorbidities. Therefore, we investigated whether common comorbidities were associated with increased mortality and morbidity in adult asthma patients using the Veterans Affairs (VA) healthcare national database.

MATERIALS AND METHODS

Study design

We performed a cohort study using national VA inpatient, outpatient, pharmacy, and mortality databases, supplemented with data from the Centers for Medicare and Medicaid Services (CMMS). Informed Consent and HIPAA waivers were approved and local

Institutional Review Boards approved the study. This study was conducted in accordance with the amended Declaration of Helsinki.

Cohort selection

The original cohort was formed for a published study which evaluated the effects of respiratory medications on outcomes in patients with incident diagnosis of obstructive airway disease [9]. Therefore, the cohort in this study only included incident cases. For our study, we included patients who received a primary or secondary diagnosis of asthma (International Classification of Diseases, 9th Revision [ICD-9] codes, 493, 493.0, 493.1, 493.9) at two or more outpatient visits within 12 months or were admitted to the hospital with a primary diagnosis of asthma between October 1999 and September 2003. The patients had to have been seen at the VA for at least 1 year prior the first diagnosis of asthma and have received respiratory medications. Patients with a co-existing diagnosis of chronic obstructive pulmonary disease (COPD) were excluded. The patients were followed up in average 3.0 ± 1.7 (sd) years.

Coexisting chronic conditions

Presence of comorbidities was determined by having an ICD-9 inpatient or outpatient diagnosis code for a condition any time during the 1-year period prior to the date of the initial asthma diagnosis. We chose to include 13 most prevalent comorbidities in this study cohort (hypertension, ischemic heart disease [IHD], osteoarthritis, rheumatoid arthritis, diabetes, mental disorders, substance/drug abuse, enlarged prostate, depression, cancer, alcoholism, human immunodeficiency virus [HIV] infection, and heart failure) in our analysis to assess the individual effect of the most common chronic conditions. In addition, four conditions known to complicate asthma control (sleep apnea, GERD, rhinitis, and sinusitis) [10–13] were also included. Detailed definition for each diagnosis is provided in the supplement. Individuals without a diagnosis for any of these conditions were categorized into a “non-comorbid” group, which also included those with less common co-existing diseases which were not included in our analysis.

Outcomes

We assessed the association between the comorbidities and four outcomes: 1) all-cause mortality, 2) all-cause hospitalizations, 3) asthma hospitalizations, and 4) asthma exacerbations. For mortality, we identified all deaths due to all causes that occurred during the study period using the Veterans Affairs Vital Status database, which captures 98% of the veteran deaths by combining VA, Medicare, and Social Security Administration mortality data [14]. These outcomes were captured using VA national inpatient and outpatient dataset. CMMS data was also used to capture non-VA encounters on those who were also enrolled in CMMS. Definition of the asthma specific outcome is provided in the supplement.

Statistical analysis

Separate analyses were performed for all 4 outcomes by three age strata. Logistic regression and negative binomial regression were used to estimate adjusted odds ratios (ORs) for risk associated with all-cause mortality and rate ratios (RR) for risk associated with other

outcomes compared to those without the comorbidity of interest. All covariates were identified 1-year prior to the date of initial asthma diagnosis using the same databases that identified comorbidities and clinically important covariates were included in the regression models (details for adjustment methods available in supplement). Each of the regression models individually included the 17 comorbidities listed above. All of the models were built using a forward selection technique that utilized covariate adjustment and fit was assessed using the Bayesian information criterion. All analyses were performed using Stata/MP 11.2 for Windows (StataCorp, College Station, Texas).

RESULTS

Patient population

25,975 patients with incident asthma were included (Table 1). 32% were 18–45 years old, 46% were 46–64 years old, and 22% were over 65 years of age. The majority of the cohort was men and a total of 1,194 (5%) deaths occurred during the follow-up period. Within the cohort, 27% had one or more hospitalization during follow-up. In regards to their asthma, 15% had one or more hospitalization for asthma, whereas 62% did not have any asthma exacerbation during follow-up. In the cohort, 61% were dispensed inhaled corticosteroids (ICS).

Prevalence of coexisting chronic conditions

The pattern of the prevalent coexisting condition differed by age group (Table 2). Depression was the most common condition in 18–45 age group, whereas hypertension was more common in patients above 46 years of age. Mental disorders (excludes depression and includes schizophrenia, delusional disorders, non-organic psychoses, and bipolar disorders) and substance abuse were more common in younger population, whereas cancer and IHD were more common in the older group.

All-cause mortality and hospitalizations

Several comorbidities were associated with an increased risk of all-cause mortality compared to those without these chronic conditions (Table 3-1): in 18–45 year olds, HIV had the most impact (OR 3.64) followed by alcoholism (OR 3.50) and mental disorders (OR 1.80); in 46–64 year olds, diabetes (OR 2.05) followed by alcoholism (OR 1.65), cancer (OR 1.56), IHD (OR 1.48) and mental disorders (OR 1.48); and in over 65 year of age, heart failure (OR 1.42) followed by diabetes (OR 1.37), IHD (OR 1.36) and cancer (OR 1.29). Many comorbidities were associated with an increased risk of all-cause hospitalizations (Table 3-2). Mental disorders were associated with increased the risk of hospitalizations in all ages (IR 2.24 in ages 18–45, IR 1.84 in ages 46–64, 1.43 in age 65 and above). Depression was associated with increased the risk of hospitalization in patients less than 65 year old, but not in older patients. GERD was associated with lower risk of all-cause mortality (OR 0.32 in ages 18–45, OR 0.59 in ages 46–64) and hospitalization (IR 0.77 in ages 18–45, IR 0.86 in ages 46–64) among those patients less than 65 years of age.

Asthma specific hospitalizations and exacerbations

Mental disorders were associated with the increased risk of asthma-specific hospitalizations in patients in all ages (IR 2.05 in age 18–45, 1.81 in ages 46–64, 1.47 in ages 65 and above). Similarly, in age 46–64, mental disorder had slightly lower IR than HIV. Depression, substance abuse, alcoholism, and HIV were associated with increased risk of asthma hospitalizations in less than 65 year old, whereas only mental disorder was associated with increased risk in age 65 and above (Table 3--3). With respect to asthma exacerbations (Table 3-4), mental disorders were again associated with increased risk in all ages (IR 1.44 for ages 18–45, IR 1.28 for ages 46–64, IR 1.39 for ages 65 and above). In addition, substance abuse, followed by IHD, was associated with increased risk in those 18–45 years old and chronic sinusitis followed by IHD among those patients greater than 65 years old.

Similar to all-cause mortality and hospitalization, having GERD was associated with decreased risk of asthma-related events across all ages by 13–28%. Chronic sinusitis decreased risk of asthma hospitalization in age less than 65 year old by 28–29%.

Effect of multiple comorbidities

We further assessed the effect of having more than one of these 17 conditions on the outcomes (Table 4). Compared to those without any of the 17 conditions, the risks for all-cause hospitalization and asthma hospitalization were increased as number of chronic conditions rose. The risk for mortality and asthma exacerbation did not differ among those with and without chronic conditions after adjustments.

DISCUSSION

We have made several observations about the impact of specific comorbidities on mortality and morbidity in adult asthma: 1) common comorbidities are associated with poor outcome in adults with asthma and their effect differs by age, 2) mental disorders were associated with an increased risk of mortality and morbidity across ages, 3) depression was associated with an increased risk of asthma-related morbidity in patients less than 64 year old, but not in older patients, and 4) GERD was associated with a decreased risk of asthma-related events in all ages.

Among patients with asthma, there is a high prevalence of coexisting rhinosinusitis, GERD, sleep apnea, obesity, and mental disorders [6,11,13,15–16]. Many studies have investigated the prevalence of these diseases and the impact of treating these conditions on underlying asthma control [6]. However, the impact of more common coexisting diseases not associated with asthma has been less well studied. Several population studies have investigated the prevalence of common diseases in adult asthma patients compared to non-asthma population. Soriano et al. evaluated the rates of comorbidities in 7,931 asthma patients in the UK General Practice Research Database [7]. The prevalence of respiratory infection, fractures, and angina was higher in asthma patients as a whole compared to general population, whereas in individuals >65 years old, the prevalence of cataract, osteoporosis, and myocardial infarction were also increased. Cazzola et al. reported that cardiovascular disease, depression, diabetes, dyslipidemia, osteoporosis, and rhinosinusitis were slightly

more prevalent in asthma, whereas GERD and allergic rhinitis were much more prevalent in asthma patients compared to non-asthma population in 909,638 adult patients using an administrative database of general practitioners in Italy [8].

However, we are not aware of any previous study up-to-date that has evaluated the specific contribution of the coexisting chronic conditions on all-cause poor outcomes (mortality and healthcare utilizations) and specifically on asthma-related outcome in asthma patients. Our large dataset with complete records of inpatient and outpatient visits, and pharmacy data allowed us to perform such analysis. We evaluated risks for poor outcomes in asthma patients with and without 17 conditions (13 most prevalent comorbidities and 4 conditions with known association with asthma) and demonstrated that many conditions are associated with worse outcomes in adults with asthma and the effect of the comorbidity as it differs by age.

It is not too surprising that many of those chronic conditions with overall poor clinical prognosis, such as IHD, cancer, and HIV, were found to be associated with an increased risk of all-cause mortality and hospitalizations. However, the most important finding we observed was that mental disorders were associated with increased the risk of mortality and morbidity not only in younger adults, but across ages. Psychiatric disorders are common in asthma patients [6] and can be found in difficult-to-treat asthma patients up to 49% [16]. Severe asthma patients who have psychological dysfunction are at much higher risk for healthcare utilization and asthma exacerbations compared to those without [17]. More recently in a meta-analysis of 18 studies, Hutter et al. demonstrated that healthcare utilizations and cost were substantially increased in adult asthma patients with mental comorbidities [18]. Our study, which included a larger population than this meta-analysis, confirmed the association between mental disorders and mortality and hospitalizations in adult asthma patients. Moreover, we demonstrated that mental disorders increased the risk of mortality and morbidity across the ages and that depression increased the risk of morbidity in younger patients.

The association of mental disorders and depression with mortality and hospitalizations is not unexpected, but the relationship to asthma-related hospitalizations is less clear. There are several possible explanations. First, asthma patients with mental disorder/or depression may have difficulty in self-management of asthma leading to adverse outcomes from their asthma. It has been shown that patients with psychological disturbance were less adherent with their asthma treatment [19] and had decreased coping skills with deteriorating asthma symptoms [20]. Second, there may be a direct biological mechanism that links asthma and mental disorders [21]. Some of the possible pathways include alteration of hypothalamic pituitary adrenal axis [22,23], increase in oxidative stress [24,25], and autonomic nervous system dysregulation [26,27]. When symptoms suggestive of clinically significant mental disorders are present in asthma patients, an appropriate psychiatric evaluation and referral to a specialist should be sought. A Cochrane meta-analysis evaluating psychological interventions in adults with asthma was not able to find convincing benefit of those interventions on asthma outcomes [28]. It was outside of the scope of our study to adequately assess the effect of the treatment of mental disorders, so we would await further studies to test the efficacy of active management of the co-morbid mental disease in asthma

patients. An ongoing randomized control trial in a large primary care organization in the Netherlands evaluating the effect of management of depression and anxiety in patients with airway disease [29] may provide further insight.

To our surprise, the presence of GERD was protective for not only all-cause outcomes, but also for asthma-specific outcomes across all ages. The exact explanation for this observation is not known, but there are several possibilities. First, it is possible that those patients with GERD and asthma may be “healthier” than those without GERD. However, the number of comorbid conditions in those with GERD was not significantly different from in those without (data not shown), so we were not able to demonstrate data to support this possibility from the dataset available to us. Secondary, it is possible that treatment for GERD (namely proton pump inhibitor: PPI) has a positive impact on the outcomes we examined in a *long-term* follow up. In our study, a large proportion of those with the diagnosis of GERD (77%) were on PPI therapy.

GERD is common in asthma patients and can be seen in up to 80% of patients [15,30]. The use of PPI has *not* generally been shown to be effective for improving asthma control in a randomized control trial setting. Neither of the previous systematic reviews for studies in asthmatics with *symptomatic* GERD [31,32] and as well as two recent trials both in adult and pediatric asthma patients with *asymptomatic* GERD have shown improvement of asthma control with use of PPI [33,34]. However, the duration of these clinical trials were mostly less than 6 months, which may not be enough to observe benefit on severe adverse events such as ours in long-term follow up. In addition, those previous studies of PPI use in asthma were conducted in highly selected asthma patients with minimal comorbidities. It is possible that PPI may provide direct benefit through its GI protective effects in asthma patients in our study with multiple comorbidities and multiple medications. Further study in other populations with asthma is needed to confirm and expand this finding.

In our study, we did not find that presence of OSA or rhinitis was associated with increased asthma exacerbations. OSA has been shown to be highly prevalent [11], and associated with recurrent asthma exacerbations in severe asthmatics [35]. Patients with OSA have worse daytime and nocturnal asthma symptoms [36]. Many mechanisms have been proposed including increased systemic inflammation [37], hyperreactivity [38], neuromechanical reflex bronchoconstriction and cardiac dysfunction [39]. Rhinitis is also prevalent in asthma patients and shown to be associated with worse asthma control [12–13]. The upper and lower airways share the same epithelial cell lining, so asthma and rhinosinusitis may represent one systemic disease manifested in different sites (“one airway”) [40]. There are several possible explanations for the lack of association in OSA and asthma related outcome in our study in contrast to other studies. In our study using administrative dataset, we were not able to directly assess symptoms of asthma control and measure asthma exacerbations which were not severe enough for the patient to seek medical attention. Our outcome might not have been sensitive enough to detect the difference in asthma control in patients with OSA or rhinitis. In addition, although we do not know the true disease severity of asthma in our study population, the baseline characteristics of the patient population indicate that majority of the patients have mild disease in which presence of OSA or rhinitis may not have had an impact large enough to be detected with our study outcomes. Lastly, our

analysis was adjusted for presence of each of the 17 chronic conditions as well as other clinically important covariates, so true association in these two conditions with asthma outcome may not be actually present after adjusting for confounding factors.

There are several limitations to our study. Our study was performed in the VA population, in which the majority of the patients are men with lower socioeconomic status. So, the results may not be generalized to other populations. However, we believe that our study took advantage of the strength of observational studies using VA national data by studying large number of individuals suffering from multiple coexisting conditions who we frequently encounter in real life. Another limitation is that we classified the chronic conditions based on ICD-9 codes available at the entry of the study and it is possible that the individual may have been misclassified due to errors in coding or due to the subsequent development of these conditions during the follow-up time. We also only included total of 17 comorbidities by diagnosis code in our analysis, so were not able to assess contribution of other conditions, such as obesity or tobacco use. In addition, we performed our analysis only in those with asthma to evaluate the relative impact of these comorbidities within asthma patients. Therefore, comparison of the impact of comorbidities with those without asthma or with other respiratory disease (i.e. COPD) was not the objective of the current study. Lastly, as in all other observational study using administrative data, although we attempt to adjust our analysis as much as possible to focus on the contribution of the comorbidities, the associations we observed may be confounded by other unmeasured factors, such as socioeconomic status, environmental factors and severity of asthma.

CONCLUSION

We demonstrated that several comorbidities are associated with poor outcome in adults with asthma and their effect differs by age. Mental disorders increase the risk of mortality and morbidity across ages, and GERD was associated with a decreased risk. Further investigation is needed to assess whether evaluation and treatment of the mental disorder would reduce the morbidity and mortality. Identification and adequate treatment of comorbidities should be an important part of management of adult asthma patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: Prevalence and trend over the last 20 years. *Eur J Gen Pract.* 2008; 14(Suppl 1):28–32. [PubMed: 18949641]
2. van den Akker M, Buntinx F, Metsemakers JF, Roos S, Knottnerus JA. Multimorbidity in general practice: Prevalence, incidence, and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol.* 1998; 51(5):367–375. [PubMed: 9619963]

3. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet*. 2012; 380(9836):37–43. [PubMed: 22579043]
4. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. *JAMA*. 2012; 307(23):2493–2494. [PubMed: 22797447]
5. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. *Natl Health Stat Report*. 2011; (32):1–14. [PubMed: 21355352]
6. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J*. 2009; 33(4):897–906. [PubMed: 19336592]
7. 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(4):2099–2107. [PubMed: 16236861]
8. Cazzola M, Calzetta L, Bettoncelli G, Novelli L, Cricelli C, Rogliani P. Asthma and comorbid medical illness. *Eur Respir J*. 2011; 38(1):42–49. [PubMed: 21177843]
9. Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med*. 2008; 149(6):380–390. [PubMed: 18794557]
10. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, Rabe KF, Bel EH. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J*. 2005; 26(5): 812–818. [PubMed: 16264041]
11. Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemiere C, Pepe C, et al. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma. *J Allergy Clin Immunol*. 2009; 124(2):371–376. [PubMed: 19560194]
12. Ponte EV, Franco R, Nascimento HF, Souza-Machado A, Cunha S, Barreto ML, Naspitz C, et al. Lack of control of severe asthma is associated with co-existence of moderate-to-severe rhinitis. *Allergy*. 2008; 63(5):564–569. [PubMed: 18394130]
13. Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG. Allergic rhinitis and sinusitis in asthma: Differential effects on symptoms and pulmonary function. *Chest*. 2006; 130(2):429–435. [PubMed: 16899841]
14. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr*. 2006; 4:2. [PubMed: 16606453]
15. Field SK, Underwood M, Brant R, Cowie RL. Prevalence of gastroesophageal reflux symptoms in asthma. *Chest*. 1996; 109(2):316–322. [PubMed: 8620699]
16. Heaney LG, Conway E, Kelly C, Gamble J. Prevalence of psychiatric morbidity in a difficult asthma population: Relationship to asthma outcome. *Respir Med*. 2005; 99(9):1152–1159. [PubMed: 16085217]
17. ten Brinke A, Ouwerkerk ME, Zwinderman AH, Spinhoven P, Bel EH. Psychopathology in patients with severe asthma is associated with increased health care utilization. *Am J Respir Crit Care Med*. 2001; 163(5):1093–1096. [PubMed: 11316641]
18. Hutter N, Knecht A, Baumeister H. Health care costs in persons with asthma and comorbid mental disorders: A systematic review. *Gen Hosp Psychiatry*. 2011; 33(5):443–453. [PubMed: 21831446]
19. Bosley CM, Fosbury JA, Cochrane GM. The psychological factors associated with poor compliance with treatment in asthma. *Eur Respir J*. 1995; 8(6):899–904. [PubMed: 7589375]
20. Miles JF, Garden GM, Tunnicliffe WS, Cayton RM, Ayres JG. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: A case-control study. *Clin Exp Allergy*. 1997; 27(10):1151–1159. [PubMed: 9383255]
21. Van Lieshout RJ, Bienenstock J, MacQueen GM. A review of candidate pathways underlying the association between asthma and major depressive disorder. *Psychosom Med*. 2009; 71(2):187–195. [PubMed: 19073754]
22. Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, et al. A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci U S A*. 2003; 100(4):1920–1925. [PubMed: 12578963]
23. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: Relevance to pathophysiology and treatment. *Biol Psychiatry*. 2001; 49(5):391–404. [PubMed: 11274650]

24. Mak JC, Chan-Yeung MM. Reactive oxidant species in asthma. *Curr Opin Pulm Med*. 2006; 12(1): 7–11. [PubMed: 16357572]
25. Yamaguchi T, Shioji I, Sugimoto A, Yamaoka M. Psychological stress increases bilirubin metabolites in human urine. *Biochem Biophys Res Commun*. 2002; 293(1):517–520. [PubMed: 12054631]
26. Lewis MJ, Short AL, Lewis KE. Autonomic nervous system control of the cardiovascular and respiratory systems in asthma. *Respir Med*. 2006; 100(10):1688–1705. [PubMed: 16524708]
27. Miller BD, Wood BL. Influence of specific emotional states on autonomic reactivity and pulmonary function in asthmatic children. *J Am Acad Child Adolesc Psychiatry*. 1997; 36(5):669–677. [PubMed: 9136502]
28. Yorke J, Fleming SL, Shuldham CM. Psychological interventions for adults with asthma. *Cochrane Database Syst Rev*. 2006; 25(1):CD002982. [PubMed: 16437449]
29. Pommer AM, Pouwer F, Denollet J, Pop VJ. Managing co-morbid depression and anxiety in primary care patients with asthma and/or chronic obstructive pulmonary disease: Study protocol for a randomized controlled trial. *Trials*. 2012; 13:6. [PubMed: 22236488]
30. Harding SM, Guzzo MR, Richter JE. 24-h esophageal pH testing in asthmatics: Respiratory symptom correlation with esophageal acid events. *Chest*. 1999; 115(3):654–659. [PubMed: 10084471]
31. Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. *Cochrane Database Syst Rev*. 2003; (2):CD001496. [PubMed: 12804410]
32. Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: A systematic review. *Thorax*. 2001; 56(3):198–204. [PubMed: 11182012]
33. Mastrorade JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, Wise RA. Efficacy of esomeprazole for treatment of poorly controlled asthma. *N Engl J Med*. 2009; 360(15): 1487–1499. [PubMed: 19357404]
34. Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, et al. Lansoprazole for children with poorly controlled asthma: A randomized controlled trial. *JAMA*. 2012; 307(4): 373–381. [PubMed: 22274684]
35. ten Brinke A, Sterk PJ, Masclee AA, Spinhoven P, Schmidt JT, Zwinderman AH, Rabe KF, et al. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J*. 2005; 26:812–818. [PubMed: 16264041]
36. Teodorescu M, Polomis DA, Hall SV, Teodorescu MC, Gangnon RE, Peterson AG, Xie A, et al. Association of obstructive sleep apnea risk with asthma control in adults. *Chest*. 2010; 138:543–550. [PubMed: 20495105]
37. Mehra R, Redline S. Sleep apnea: a proinflammatory disorder that coaggregates with obesity. *J Allergy Clin Immunol*. 2008; 121:1096–1102. [PubMed: 18466782]
38. Lin CC, Lin CY. Obstructive sleep apnea syndrome and bronchial hyperreactivity. *Lung*. 1995; 173:117–126. [PubMed: 7715253]
39. Alkhalil M, Schulman E, Getsy J. Obstructive sleep apnea syndrome and asthma: what are the links? *J Clin Sleep Med*. 2009; 5:71–78. [PubMed: 19317386]
40. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol*. 2003; 111:1171–1183. quiz 1184. [PubMed: 12789212]

Table 1

Patient characteristics

Characteristics	All Ages (n = 25,975)	Ages 18 – 45 (n = 8,364)	Ages 46 – 64 (n = 11,823)	Ages 65+ (n = 5,788)
Men, n (%)	21,271 (81.9%)	5,744 (68.7%)	9,995 (84.5%)	5,532 (95.6%)
Age, avg (sd)	53.2 (14.4)	37.4 (6.3)	54.4 (5.1)	73.6 (5.7)
Race, n %				
Race – White	15,020 (57.8%)	3,923 (46.9%)	6,750 (57.1%)	4,347 (75.1%)
Race – Black	4,853 (18.7%)	2,069 (24.7%)	2,191 (18.5%)	593 (10.2%)
Race – Hispanic	6,102 (23.5%)	384 (4.6%)	729 (6.2%)	447 (7.7%)
Race – Other	448 (1.7%)	133 (1.6%)	221 (1.9%)	94 (1.6%)
Race – Unknown	4,094 (15.8%)	1,855 (22.2%)	1,932 (16.3%)	307 (5.3%)
Follow-up years, avg (sd)	3.0 (1.7)	3.2 (1.7)	2.9 (1.7)	2.9 (1.7)
Follow-up health care utilization				
Mean # of outpt clinic visits per yr., avg (sd)	22.3 (30.1)	21.0 (31.3)	23.5 (31.8)	21.7 (24.0)
Mean # of hospitalizations per yr., avg (sd)	0.6 (1.7)	0.5 (1.7)	0.6 (1.7)	1.0 (1.9)
Mean # of asthma hospitalizations per yr., avg (sd)	0.2 (0.8)	0.2 (0.9)	0.2 (0.8)	0.3 (0.8)
Hospitalizations, n (%)				
0	19,030 (73.3%)	6,654 (79.5%)	8,909 (75.4%)	3,467 (59.9%)
1+	6,945 (26.7%)	1,710 (20.4%)	2,914 (24.6%)	2,321 (40.1%)
Asthma hospitalizations, n (%)	3,795 (14.6%)	1,045 (12.5%)	1,586 (13.4%)	1,164 (20.1%)
Follow-up Asthma exacerbations, n (%)				
0	16,151 (62.2%)	4,909 (58.7%)	7,619 (64.4%)	3,623 (62.6%)
1	5,780 (22.3%)	1,969 (23.5%)	2,488 (21.0%)	1,323 (22.9%)
2	2,064 (7.9%)	746 (8.9%)	906 (7.7%)	412 (7.1%)
3+	1,980 (7.6%)	740 (8.8%)	810 (6.9%)	430 (7.4%)
Follow-up respiratory medications, n (%)				
SABA	22,848 (88.0%)	7,760 (92.8%)	10,449 (88.4%)	4,639 (80.1%)
LABA	6,036 (23.2%)	1,940 (23.2%)	2,743 (23.2%)	1,353 (23.4%)
ICS	15,888 (61.2%)	5,056 (60.4%)	7,207 (61.0%)	3,625 (62.6%)
Ipratropium	3,445 (13.3%)	829 (9.9%)	1,660 (14.0%)	956 (16.5%)
Theophylline	1,452 (5.6%)	275 (3.3%)	682 (5.8%)	495 (8.6%)
Montelukast	2,456 (9.5%)	826 (9.9%)	1,126 (9.5%)	504 (8.7%)
Deaths, n (%)	1,194 (4.6%)	125 (1.5%)	420 (3.6%)	649 (11.2%)

Definition of Abbreviations: n=number, avg=average, sd=standard deviation, yr=year, #=number, pt=patient, SABA=Short-Acting Beta-Agonists, LABA=Long-Acting Beta Agonists, ICS= inhaled corticosteroid.

Table 2

Prevalent coexisting chronic conditions by age group

Ages 18 – 45		Ages 46 – 64		Ages 65+	
(n = 8,364)	n (%)	(n = 11,823)	n (%)	(n = 5,788)	n (%)
Depression	1,619 (19.4%)	Hypertension	4,843 (41.0%)	Hypertension	3,616 (62.5%)
Hypertension	1,341 (16.0%)	Depression	2,190 (18.5%)	IHD ^a	1,656 (28.6%)
GERD	768 (9.2%)	Diabetes	1,940 (16.4%)	Cancer ^b	1,451 (25.1%)
Osteoarthritis	756 (9.0%)	Osteoarthritis	1,929 (16.3%)	Enlarged prostate	1,339 (23.1%)
Alcoholism	689 (8.2%)	GERD	1,613 (13.6%)	Diabetes	1,333 (23.0%)
Mental disorders ^c	676 (8.1%)	IHD ^a	1,182 (10.0%)	Osteoarthritis	1,313 (22.7%)
Substance abuse ^d	559 (6.7%)	Cancer ^b	1,120 (9.5%)	GERD	1,035 (17.9%)
Sinusitis	523 (6.3%)	Alcoholism	815 (6.9%)	Heart failure	516 (8.9%)
Diabetes	415 (5.0%)	Mental disorders ^c	768 (6.5%)	Depression	468 (8.1%)
Cancer ^b	382 (4.6%)	Sinusitis	768 (6.5%)	Rhinitis	393 (6.8%)
Rhinitis	366 (4.4%)	Enlarged prostate	623 (5.3%)	Sinusitis	307 (5.3%)
Sleep apnea	202 (2.4%)	Rhinitis	623 (5.3%)	Sleep apnea	177 (3.1%)
IHD ^a	161 (1.9%)	Substance abuse ^d	533 (4.5%)	Mental disorders ^c	162 (2.8%)
HIV	77 (0.9%)	Sleep apnea	445 (3.8%)	Rheumatoid arthritis	101 (1.7%)
Rheumatoid arthritis	47 (0.6%)	Heart failure	229 (1.9%)	Alcoholism	81 (1.4%)
Enlarged prostate	39 (0.5%)	Rheumatoid arthritis	159 (1.3%)	Substance abuse ^d	18 (0.3%)
Heart failure	34 (0.4%)	HIV	84 (0.7%)	HIV	5 (0.1%)
No conditions	3,962 (47.4%)	No conditions	3,177 (26.9%)	No conditions	745 (12.9%)

Definition of Abbreviations: n=number, GERD=Gastroesophageal reflux disease, IHD=Ischemic heart disease, HIV=Human immunodeficiency virus.

^a Includes ICD-9 codes for '428.xx';

^b Non-melanoma;

^c Includes schizophrenia, delusional disorders, non-organic psychoses & bipolar disorders;

^d Includes hallucinogen, barbiturate, cocaine, or amphetamine abuse.

Table 3-1

Adjusted odds ratio for all-cause mortality stratified by age

	Ages 18 – 45 ^a	Ages 46 – 64 ^b	Ages 65 ^c
Prior Conditions	(n = 8,364)	(n = 11,823)	(n = 5,788)
Hypertension	1.09 (0.68–1.75)	1.00 (0.81–1.25)	0.75 (0.62–0.90)^d
IHD	1.43 (0.48–4.27)	1.48 (1.09–2.01)^d	1.36 (1.11–1.66)^d
Osteoarthritis	1.09 (0.59–2.00)	0.78 (0.58–1.04)	1.10 (0.89–1.35)
Rheumatoid arthritis	1.18 (0.15–9.58)	0.97 (0.43–2.19)	1.48 (0.85–2.58)
Diabetes	0.47 (0.18–1.23)	2.05 (1.48–2.83)^d	1.37 (1.12–1.67)^d
Mental disorders	1.80 (1.07–3.03)^d	1.48 (1.03–2.10)^d	1.31 (0.81–2.11)
Substance/drug abuse	0.55 (0.29–1.07)	1.32 (0.86–2.03)	1.04 (0.23–4.78)
Enlarged prostate	2.05 (0.26–16.45)	0.70 (0.43–1.14)	0.81 (0.66–1.00)
Depression	0.92 (0.58–1.45)	0.99 (0.76–1.30)	0.96 (0.69–1.32)
Cancer (non-melanoma)	0.64 (0.26–1.57)	1.56 (1.15–2.10)^d	1.29 (1.06–1.55)^d
Alcoholism	3.50 (2.01–6.09)^d	1.65 (1.14–2.39)^d	1.43 (0.76–2.67)
HIV	3.64 (1.34–9.87)^d	1.65 (0.68–3.99)	-
Heart failure	0.51 (0.06–4.22)	1.51 (0.93–2.43)	1.42 (1.09–1.85)^d
Sleep apnea	0.24 (0.03–1.80)	0.81 (0.48–1.36)	0.73 (0.44–1.23)
GERD	0.32 (0.13–0.80)^d	0.59 (0.41–0.85)^d	0.95 (0.75–1.19)
Chronic sinusitis	0.66 (0.28–1.55)	0.60 (0.36–1.01)	0.68 (0.44–1.05)
Rhinitis	0.74 (0.25–2.14)	0.89 (0.54–1.47)	0.92 (0.64–1.33)

Definition of Abbreviations: n=number, IHD=Ischemic heart disease, HIV=Human immunodeficiency virus GERD=Gastroesophageal reflux disease.

^a Adjusted model includes hospitalizations, glucocorticoids & diuretics.

^b Adjusted model includes gender, glucocorticoids, digoxin, lipid-lowering agents, diuretics, & oral hypoglycemics.

^c Adjusted model includes glucocorticoids, digoxin, lipid-lowering agents, diuretics, & NSAIDs.

^d p<0.05 (in bold)

Table 3-2

Adjusted incident rate ratio for all-cause hospitalizations stratified by age

	Ages 18 – 45 ^a	Ages 46 – 64 ^b	Ages 65+ ^c
Prior Conditions	(n = 8,364)	(n = 11,823)	(n = 5,788)
Hypertension	0.99 (0.85–1.15)	0.94 (0.85–1.03)	0.99 (0.89–1.09)
IHD	0.86 (0.61–1.23)	1.15 (1.00–1.31)	1.12 (1.01–1.25)^d
Osteoarthritis	0.89 (0.74–1.07)	1.13 (1.01–1.26)^d	1.08 (0.97–1.19)
Rheumatoid arthritis	1.17 (0.62–2.18)	1.54 (1.15–2.05)^d	1.31 (0.97–1.77)
Diabetes	1.13 (0.86–1.47)	1.13 (0.99–1.29)	1.18 (1.05–1.32)^d
Mental disorders	2.24 (1.88–2.68)^d	1.84 (1.60–2.12)^d	1.43 (1.13–1.82)^d
Substance/drug abuse	1.30 (1.03–1.63)^d	2.00 (1.65–2.42)^d	1.55 (0.76–3.17)
Enlarged prostate	1.28 (0.62–2.67)	1.10 (0.92–1.30)	1.01 (0.92–1.12)
Depression	1.30 (1.13–1.50)^d	1.22 (1.10–1.35)^d	1.04 (0.89–1.22)
Cancer (non-melanoma)	1.14 (0.90–1.45)	1.14 (1.00–1.31)	1.13 (1.03–1.25)^d
Alcoholism	1.56 (1.26–1.92)^d	1.64 (1.40–1.93)^d	1.13 (0.79–1.62)
HIV	1.88 (1.16–3.03)^d	1.63 (1.08–2.46)^d	2.03 (0.59–7.02)
Heart failure	1.58 (0.82–3.04)	1.48 (1.15–1.90)^d	1.12 (0.96–1.30)
Sleep apnea	1.30 (0.94–1.81)	1.13 (0.93–1.38)	0.89 (0.70–1.13)
GERD	0.82 (0.68–0.99)^d	0.86 (0.76–0.97)^d	0.96 (0.85–1.08)
Chronic sinusitis	0.77 (0.61–0.97)^d	0.87 (0.73–1.03)	1.08 (0.90–1.30)
Rhinitis	0.71 (0.53–0.95)^d	0.86 (0.71–1.04)	0.98 (0.82–1.16)

Definition of Abbreviations: n=number, IHD=Ischemic heart disease, HIV=Human immunodeficiency virus, GERD=Gastroesophageal reflux disease.

^a Adjusted model includes race, outpatient visits, prior hospitalizations, mental health visits, glucocorticoids, β -blockers, calcium channel blockers, nitrates, diuretics, ACE inhibitors, histamine antagonists, PPIs, insulin, & NSAIDs.

^b Adjusted model includes race, outpatient visits, primary care visits, glucocorticoids, digoxin, β -blockers, calcium-channel blockers, nitrates, lipid-lowering agents, diuretics, histamine antagonists, PPIs, & insulin.

^c Adjusted model includes race, prior hospitalizations, primary care visits, glucocorticoids, digoxin, β -blockers, calcium-channel blockers, nitrates, lipid-lowering agents, diuretics, histamine antagonists, PPIs, insulin, anti-arrhythmias and NSAIDs.

^d p<0.05 (in bold)

Table 3-3

Adjusted incident rate ratio for asthma-related hospitalizations stratified by age

	Ages 18 – 45 ^a	Ages 46 – 64 ^b	Ages 65+ ^c
Prior Conditions	(n = 8,364)	(n = 11,823)	(n = 5,788)
Hypertension	0.92 (0.76–1.12)	0.91 (0.80–1.03)	1.02 (0.89–1.16)
IHD	0.77 (0.49–1.20)	1.00 (0.83–1.21)	1.13 (0.97–1.32)
Osteoarthritis	0.82 (0.65–1.04)	1.13 (0.98–1.31)	0.93 (0.80–1.08)
Rheumatoid arthritis	1.14 (0.51–2.54)	1.23 (0.82–1.85)	1.33 (0.86–2.06)
Diabetes	1.24 (0.92–1.67)	1.09 (0.93–1.28)	1.12 (0.97–1.30)
Mental disorders	2.05 (1.65–2.54)^d	1.81 (1.50–2.19)^d	1.47 (1.04–2.08)^d
Substance/drug abuse	1.50 (1.13–1.99)^d	1.80 (1.41–2.30)^d	2.15 (0.80–5.75)
Enlarged prostate	1.69 (0.69–4.16)	0.82 (0.64–1.05)	0.97 (0.84–1.13)
Depression	1.39 (1.17–1.65)^d	1.21 (1.05–1.39)^d	1.03 (0.81–1.29)
Cancer (non-melanoma)	1.10 (0.81–1.48)	1.15 (0.96–1.39)	1.07 (0.93–1.24)
Alcoholism	1.49 (1.14–1.95)^d	1.64 (1.32–2.02)^d	0.68 (0.37–1.25)
HIV	2.13 (1.19–3.82)^d	1.91 (1.11–3.30)^d	3.54 (0.76–16.55)
Heart failure	1.31 (0.58–2.96)	1.11 (0.78–1.59)	1.02 (0.81–1.27)
Sleep apnea	1.37 (0.92–2.04)	1.21 (0.92–1.58)	0.89 (0.63–1.28)
GERD	0.72 (0.56–0.91)^d	0.79 (0.67–0.94)^d	0.82 (0.69–0.98)^d
Chronic sinusitis	0.72 (0.53–0.97)^d	0.71 (0.55–0.91)^d	1.30 (1.00–1.69)
Rhinitis	0.54 (0.36–0.81)^d	0.77 (0.58–1.02)	0.89 (0.68–1.16)

Definition of Abbreviations: n=number, IHD=Ischemic heart disease, HIV=Human immunodeficiency virus, GERD=Gastroesophageal reflux disease.

^a Adjusted model includes race, exacerbations, prior hospitalizations, glucocorticoids, calcium channel blockers, nitrates, diuretics, & PPIs.

^b Adjusted model includes race, exacerbations, primary care visits, glucocorticoids, digoxin, nitrates, diuretics, histamine antagonists, & PPIs.

^c Adjusted model includes race, exacerbations, glucocorticoids, nitrates, anti-arrhythmias, diuretics, & PPIs.

^d p<0.05 (in bold)

Table 3-4

Adjusted incident rate ratio for asthma exacerbations stratified by age

	Ages 18 – 45 ^a	Ages 46 – 64 ^b	Ages 65+ ^c
Prior Conditions	(n = 8,364)	(n = 11,823)	(n = 5,788)
Hypertension	0.97 (0.88–1.06)	0.94 (0.87–1.01)	1.00 (0.91–1.10)
IHD	1.27 (1.01–1.60)^d	1.06 (0.94–1.19)	1.15 (1.03–1.27)^d
Osteoarthritis	0.77 (0.68–0.87)^d	1.04 (0.95–1.13)	0.86 (0.77–0.96)^d
Rheumatoid arthritis	0.64 (0.40–1.02)	0.77 (0.59–1.00)	1.18 (0.87–1.60)
Diabetes	1.15 (0.98–1.35)	1.01 (0.92–1.11)	1.00 (0.90–1.11)
Mental disorders	1.44 (1.27–1.63)^d	1.28 (1.13–1.44)^d	1.39 (1.09–1.78)^d
Substance/drug abuse	1.30 (1.11–1.52)^d	1.30 (1.11–1.52)^d	1.44 (0.71–2.92)
Enlarged prostate	0.86 (0.51–1.45)	0.87 (0.75–1.00)	1.02 (0.92–1.14)
Depression	1.07 (0.97–1.17)	1.09 (1.01–1.19)^d	1.07 (0.91–1.26)
Cancer (non-melanoma)	1.08 (0.93–1.26)	0.99 (0.89–1.11)	1.02 (0.92–1.13)
Alcoholism	1.16 (1.00–1.34)	1.29 (1.13–1.48)^d	1.15 (0.78–1.70)
HIV	1.05 (0.76–1.44)	1.06 (0.75–1.51)	2.07 (0.65–6.59)
Heart failure	1.36 (0.85–2.17)	1.15 (0.91–1.44)	1.14 (0.97–1.34)
Sleep apnea	1.22 (0.98–1.52)	1.06 (0.90–1.26)	0.87 (0.67–1.14)
GERD	0.87 (0.77–0.99)^d	0.84 (0.76–0.93)^d	0.83 (0.74–0.94)^d
Chronic sinusitis	0.98 (0.85–1.13)	0.89 (0.78–1.01)	1.29 (1.08–1.55)^d
Rhinitis	0.77 (0.65–0.93)^d	1.15 (1.00–1.33)	0.93 (0.78–1.12)

Definition of Abbreviations: n=number, IHD=Ischemic heart disease, HIV=Human immunodeficiency virus, GERD=Gastroesophageal reflux disease.

^a Adjusted model includes race, prior exacerbations, glucocorticoids, lipid-lowering agents, PPIs, & NSAIDs.

^b Adjusted model includes race, prior exacerbations, primary care visits, glucocorticoids, anti-arrhythmias, lipid-lowering agents, diuretics, & NSAIDs.

^c Adjusted model includes race, prior exacerbations, glucocorticoids, diuretics, and NSAIDs.

^d p<0.05 (In bold).

Table 4

Adjusted odds and incident rate ratios for number of chronic conditions on outcomes

Number of cluster conditions	All-Cause Mortality	All-Cause Hospitalization	Asthma-Related Hospitalization	Asthma Exacerbations
One condition	1.20 (0.98–1.46)	1.18 (1.08–1.28)	1.08 (0.97–1.20)	0.89 (0.84–0.94)
Two conditions	1.18 (0.96–1.45)	1.45 (1.32–1.59)	1.29 (1.15–1.44)	0.95 (0.89–1.01)
Three conditions	1.32 (1.06–1.63)	1.86 (1.68–2.06)	1.51 (1.34–1.71)	0.97 (0.90–1.04)
Four conditions	1.29 (1.00–1.65)	2.27 (2.02–2.55)	1.63 (1.41–1.88)	1.04 (0.95–1.14)
Five conditions	1.24 (0.92–1.68)	2.22 (1.91–2.56)	1.69 (1.40–2.03)	1.04 (0.92–1.17)
Six or more conditions	1.04 (0.72–1.49)	2.85 (2.41–3.37)	1.96 (1.58–2.45)	0.94 (0.81–1.09)

Models adjusted for age, race, gender, prior health care utilization, region of country, ipratropium and ICS exposure, glucocorticoids, digoxin, nitrates, calcium channel blockers, diuretics, PPIs, histamine antagonists & NSAIDs.