PLOS | ONE

RESEARCH ARTICLE

Impact of Age and Sex on Outcomes and Hospital Cost of Acute Asthma in the United States, 2011-2012

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Citation: Zein JG, Udeh BL, Teague WG, Koroukian SM, Schlitz NK, Bleecker ER, et al. (2016) Impact of Age and Sex on Outcomes and Hospital Cost of Acute Asthma in the United States, 2011-2012. PLoS ONE 11(6): e0157301. doi:10.1371/journal.pone.0157301

Editor: Stelios Loukides, University of Athens, GREECE

Received: April 12, 2016

Accepted: May 26, 2016

Published: June 13, 2016

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Data Availability Statement: Data from the Severe Asthma Research Program (SARP), funded and managed by the National Institute of Health. Due to legal restrictions, qualified researchers can request access to the data by contacting Ms. Noel, Patricia (NIH/NHLBI). Email: noelp@nhlbi.nih.gov. The HCUP Nationwide Inpatient Sample (NIS) is a set of longitudinal hospital inpatient databases included in the HCUP family. These databases are created by AHRQ through a Federal-State-Industry partnership. Email: hcup@ahrq.gov.

Abstract

Background

Worldwide, asthma is a leading cause of morbidity, mortality and economic burden, with significant gender and racial disparities. However, little attention has been given to the independent role of age on lifetime asthma severity and hospitalization. We aimed to assess the effect of age, gender, race and ethnicity on indicators of asthma severity including asthma related hospitalization, mortality, hospital cost, and the rate of respiratory failure.

Methods

We analyzed the 2011 and 2012 Healthcare Cost and Utilization Project- National Inpatient Sample (NIS). We validated and extended those results using the National Heart, Lung, and Blood Institute-Severe Asthma Research Program (SARP; 2002–2011) database. Severe asthma was prospectively defined using the stringent American Thoracic Society (ATS) definition.

Funding: SCE received funding from the National Institute of Health-National Heart, Lung, and Blood Institute: HL109250, HL081064, HL69170, HL103453, U10 HL109250, and UL1TR000439. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Results

Hospitalization for asthma was reported in 372,685 encounters in 2012 and 368,528 in 2011. The yearly aggregate cost exceeded $2 billion. There were distinct bimodal distributions for hospitalization age, with an initial peak at 5 years and a second at 50 years. Likewise, this bimodal age distribution of patients with severe asthma was identified using SARP. Males comprised the majority of individuals in the first peak, but women in the second. Aggregate hospital cost mirrored the bimodal peak distribution. The probability of respiratory failure increased with age until the age of 60, after which it continued to increase in men, but not in women.

Conclusions

Severe asthma is primarily a disease of young boys and middle age women. Greater understanding of the biology of lung aging and influence of sex hormones will allow us to plan for targeted interventions during these times in order to reduce the personal and societal burdens of asthma.

Introduction

Asthma is a chronic health condition associated with significant health and economic burden to patients, their families, and society. It affects 25.7 million people; 7.0 million children under the age of 18 years. The incidence of asthma is increasing. In 1980 it was 3.6%, increasing to 8.2% by 2009 [1, 2]. This increased asthma incidence is of particular concern given that asthma is a significant cause of morbidity and utilization of healthcare resources across the lifespan. In 2010, asthma resulted in 1.8 million emergency department (ED) visits and 439,000 asthma-related hospitalizations.

Severe asthma accounts for the majority of healthcare costs due to hospitalizations and ED visits, and is associated with the highest asthma related mortality [3]. While asthma is the leading cause of ED visits and the third cause of hospitalization in children aged 1 to 17 years [4, 5], data obtained from the Severe Asthma Research Program (SARP) [6] identified that severe asthma patients were older than patients with mild to moderate asthma [6]. Even after adjustment for many age-related comorbidities, older asthmatics were 2.7 times more likely to have "severe asthma" as compared to young adult asthma patients [7]. Gender difference in asthma incidence, prevalence and severity are also seen [1, 2]. Asthma is more prevalent in boys 4 to 14 years compared to girls (11.5 vs. 9.9%). However, after puberty, asthma becomes more prevalent and severe in women [8]. Interestingly, a reversal of the gender switch occurs with menopause, when asthma becomes once again more severe in older male adults [7]. While the distribution of asthma prevalence is uniform across the ages, little is known regarding the influence of age and gender on the prevalence of severe asthma in these patients[8].

Here, we assessed the effect of age and its influence by gender and race on indicators of asthma severity such as asthma related hospitalization and cost, hospital mortality, and the rate of respiratory failure in two administrative databases NIS 2011 and 2012. We compared these results with age and gender-dependent risk of a well characterized severe asthma cohort using the National Heart, Lung, and Blood Institute- Severe Asthma Research Program.

Methods

In this study, data was abstracted from the 2011 and 2012 Nationwide Inpatient Sample (NIS). The NIS is included in the Healthcare Cost and Utilization Project (HCUP) family. It is created

by the Agency for Healthcare Research and Quality's (AHRQ) through a Federal-State-Industry partnership. The database is a 20% weighted sample of all United States (US) hospital discharges, constituting more than 7 million discharges annually. A data user agreement was signed with the Agency for Healthcare Research and Quality's (AHRQ).

Framework and Study Population

To analyze the impact of aging on asthma severity, adjustments were made for age related comorbidities, gender and race which are known to impact asthma severity [9, 10] [S1 Fig]. In each visit, up to 25 diagnoses are reported in NIS using the International Classification of Disease, ninth revision- Clinical Modification (ICD9_CM codes). DX1, reflects the principal (primary) admitting diagnosis. DX2 to DX25 reflect the 24 reported secondary diagnoses in NIS. The NIS Severity Measures File list up to 29 comorbid conditions for each visit [S1 Table].

The ICD9-CM codes of 493.xx were used to identify patients admitted with a principal diagnosis (DX1) of asthma [S1 Appendix] [11]. Patients were excluded if they had a secondary diagnosis of chronic obstructive pulmonary disease (COPD), bronchiolitis with Respiratory Syncytial Virus (RSV), were active or past smokers, or if they had a chronic lung disease diagnosed as a comorbidity [S1 Appendix and S2 Fig]. Additionally, infants were excluded due to the frequent misdiagnosis of asthma in infants with wheezing. The impact of these patient group exclusions were tested with sensitivity analysis. Moreover, we cross-checked our HCUP analysis using extensively and precisely characterized asthma in the National Heart, Lung, and Blood Institute (NHLBI) Severe Asthma Research program (SARP) between 2002 to 2011. A written informed consent was obtained from all adults, or from the parents of minor participants. The project and the informed consent were approved by the Institutional Review Board at all 10 SARP sites enrolling participants [6], which includes the Cleveland Clinic Institutional Review Board (IRB), Cleveland, OH; Case Western Reserve University IRB, Cleveland, OH; the IRB at Wake Forest University, Winston-Salem, NC; the IRB for health Sciences Research at the University of Virginia, Charlottesville, VA, the IRB at the University of Wisconsin, Madison, WI; University of Pittsburgh IRB, Pittsburgh, PA; The Human Research Protection Office (HRPO) at the Washington University, St. Louis, MO; Partners Human Research Committee at the Brigham and Women's Hospital, Boston MA; the University of Texas Medical Branch IRB, Galveston, TX; Emory IRB, at Emory University School of Medicine, Atlanta, GA; and the Imperial College Research Ethics Committee (ICREC), at the National Heart and Lung Institute, Imperial College, London, UK. To be enrolled in the study, all adult participants provided a written informed consent. The informed consent as well as the study protocol were approved by all local IRBs.

Hospitalization and Outcome Variables

NIS includes variables; diagnosis, weekend admission, month of admission, payment source, urban vs rural location of patients' residence, national quartiles for median household income by ZIP code, hospital geographic region (Northeast, Midwest, South and West), hospital length of stay, hospital disposition, and hospital charges. Using this data and applying cost to charge ratios, hospital mortality, respiratory failure, and services rendered and related costs were identified.

Analysis

Using bootstrapping, unadjusted comparisons for continuous variables were analyzed. Two-sided p values <0.05 were considered significant. National estimates were produced by applying the "weight" variable to the data. All other analyses were performed using the unweighted

NIS asthma data. To test the effect of aging on mortality and respiratory failure, we fitted a logistic regression model. The initial model included age, gender, race, history of gastro-esophageal reflux disease, quartiles for median household income, admission month, weekend admission, payer information, and a modified Elixhauser comorbidity index[12, 13]. The Elixhauser comorbidity index summarizes disease burden and predicts hospital mortality. The final model was used to plot the curve of the risk adjusted probability of hospital mortality and respiratory failure. A restricted cubic spline model with 3 knots was fitted to better describe the nonlinear relationship between age and outcomes measures such as mortality and respiratory failure [14]. The descriptive statistics and the logistic regression were conducted using R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria

Sensitivity analyses

Although the fitted logistic regressions ensured variable selection decisions, the results needed to be validated with new data. Therefore, we used the 2012 databases to build the models, and the 2011 databases for validation. Importantly, in order to externally validate the reproducibility of those results, we used SARP I&II databases. SARP enrolled participants between 2002 and 2011 and was designed to study severe asthma [6]. In contrast to HCUP where ICD9 codes were used to identify asthma, SARP prospectively collected a cohort where asthma severity (severe and non-severe asthma) was classified as defined by the American Thoracic Society [15]. In order to meet the definition of severe asthma, one or both major criteria and two minor criteria was required. The 2 major criteria include continuous or near continuous treatment with oral corticosteroids, or the need for high-dose inhaled corticosteroids therapy. The 7 minor criteria include the daily need for a controller medication in addition to inhaled corticosteroids, the daily need for short-acting beta-agonist use, persistent airway obstruction, one or more urgent care visits for asthma per year, three or more oral corticosteroid "bursts" per year, lung function deterioration with less than 25% reduction in oral or inhaled corticosteroid dose, and a previous history of near fatal asthma [15].

We anticipated two additional potential sources of bias. The first originating from the misdiagnosis of asthma in children younger than 1 year and the second resulting from mislabeling RSV bronchiolitis and COPD as asthma and vice versa. In order to account for such potential problems we analyzed the data initially after the exclusion of children younger than 1 year, and patients listed with COPD, RSV bronchiolitis or tobacco use as a secondary diagnosis, and subsequently compared those result to those obtain from the original data without any exclusions. Likewise, in order to reproduce those results, similar analysis was performed using the NIS 2011 database. Furthermore, the use of SARP obviated these biases, because active smokers and asthma patients with a smoking history that exceeded 5 pack-years were excluded. All SARP participants underwent lengthy testing in order to confirm asthma diagnosis, including spirometry and methacholine challenge testing. Children in SARP were diagnosed and characterized by pediatric asthma specialists.

Results

The bimodal distribution of asthma hospitalization

Using ICD9-CM codes, we identified 79,810 asthma hospitalizations in the NIS 2011 and 74,110 in NIS 2012 database. National estimates produced by applying the "weight" variable to the initial data indicate that asthma resulted in 372,685 hospitalizations, 1,090 deaths (0.3%) with an aggregate cost of $ 2,231,112,607 in 2012 [S2 Table]. After excluding patients younger than 1 year and those with secondary diagnosis of COPD, smoking addiction, and RSV

Table 1. Demographics of patient hospitalized for asthma.

Characteristic		NIS 2011	NIS 2012	SARP
Number of encounters in the database		8,023,590	7,296,968	1,361
Number of asthma hospitalizations		48,941	45,670	237
Age (years)		40 [8,61]	35 [7, 60]	34 [24, 49]
Female gender (%)		30,703 (63.0)	27,228 (59.6)	141(59.5%)
Race (%)				
	White	20,263 (41.4)	18,730 (43.0)	98 (41)
	Black	13,658 (27.9)	13,891 (31.9)	114 (48)
	Hispanic	6,993 (14.3)	7,661 (17.6)	16 (17)
	Asian or Pacific Islander	924 (1.9)	1103 (2.5)	5 (2)
	Native American	359 (0.7)	314 (0.7)	0 (0)
	Others	1,791 (3.7)	1,827 (4.2)	6 (2)
Gastroesophageal reflux Disease (%)		8,247 (16.9)	6,853 (15.0)	90 (41)
Primary expected payer (%)				
	Medicare	14,825 (30.4)	12,026 (26.4)	
	Medicaid	15,138 (31.0)	16,346 (35.9)	
	Private including HMO	14,404 (29.5)	12,720 (27.9)	
	Self-pay	2,837 (5.8)	2,846 (6.2)	
	No charge	242 (0.5)	220 (0.5)	
	Other	1,369 (2.8)	1,420 (3.1)	
Median household income. (%)				
	$1–$38,999	17,509 (36.7)	17,050 (38.5)	
	$39,000–$47,999	11,230 (23.5)	10,643 (24.1)	
	$48,000–62,999	10,841 (22.7)	9,064 (20.5)	
	$63,000 or more	8,158 (17.1)	7,496 (16.9)	

NIS indicates National Inpatient Sample; SARP, Severe Asthma Research Program

doi:10.1371/journal.pone.0157301.t001

bronchiolitis, only 48,941 patients from NIS2011 and 45,670 from NIS 2012 were used for analysis [Table 1]. The average hospital length of stay was 3 days [Table 2]. Asthma hospitalization was higher in young children and in middle age adults [Fig 1]. This bimodal distribution was identical in NIS 2011 and NIS 2012 databases [Fig 1A and 1B].

The role of gender and race on asthma related hospitalization and cost

Although, more hospitalizations were generally reported among women than men [Table 1], there were significant gender differences across the lifespan of asthmatics. Asthma related hospitalizations were most prevalent among young boys (age 1 to 10 years) and middle-aged women (age 40 to 60 years) [Fig 2A and S3 Fig]. This bimodal age-gender distribution was seen in 2011 and 2012 databases, and in SARP [S3 and S4 Figs], and remained evident among all races in the NIS populations. The age of onset of the second peak was impacted by race and ethnicity [Fig 2B]. Specifically, the age of hospitalization varied among race and ethnic background among adult asthmatics (age older than 18) hospitalized in 2012 from a mean of 51.5 years in African Americans to a mean age of 64.4 years in Asians ($p<0.0001$) [S3 Table].

The role of age on asthma related respiratory failure and mortality

Respiratory failure was reported in 4,172 (8.5%) and 4,449 (9.7%) patients hospitalized for asthma in the 2011 and 2012 NIS databases respectively [Table 2]. The probability of risk

Table 2. Clinical outcome of patients hospitalized for asthma.

Outcome		NIS 2011	NIS 2012
Disposition of patient (%)			
	Discharged home	42267 (86.6)	40248 (88.1)
	Transfer to short-term hospital	455 (0.9)	401 (0.9)
	Other transfers	2145 (4.4)	1636 (3.6)
	Home health care	3174 (6.5)	2717 (5.9)
	Against medical advice	638 (1.3)	555 (1.2)
	Hospital deaths	149 (0.3)	129 (0.3)
Respiratory failure (%)		4172 (8.5)	4449 (9.7)
Hospital length of stay (days)*		2.00 [2.00, 4.00]	2.00 [1.00, 4.00]
Total hospital charges (US $)*		13131 [7685, 23138]	13397 [7817, 23597]
Total hospital cost (US $)*		4106 [2565, 6621]	4099 [2559, 6675]

NIS indicates National Inpatient Sample

doi:10.1371/journal.pone.0157301.t002

adjusted hospital mortality and respiratory failure was plotted as a function of age [Fig 3]. The risk of respiratory failure increased by 34% [adjusted OR (95CI) 1.34 (1.30–1.39)] for each 10 years increment in age until the age of 60 years. Afterward the risk did not significantly increase [adjusted OR (95CI) 0.98 (0.95–1.02)]. This plateau in risk of respiratory failure after age of 60 was due to a lower probability of respiratory failure among women compared to men [S5 Fig].

Similar to the risk of respiratory failure, the adjusted probability of death increases by 47% [adjusted OR (95CI) 1.47 (1.31–1.66)] for each 10 years increment in age [Fig 3B]. While a higher number of older women died of asthma compared to men [S6A Fig], there were almost twice as many total women hospitalized for asthma. Therefore, the mortality rates among hospitalized men and women were not significantly different [OR (95CI) 1.36 (0.94–1.96) for women vs. men] [S6B Fig].

Results from SARP

Among the 1,361 asthma patients enrolled in SARP, 583 patients met the American Thoracic Society definition of severe asthma and 237 patients had required hospitalization during the year prior to their visit. The SARP age distribution for severe asthma and hospitalization mirrored the bimodal distribution seen in NIS 2011 and NIS 2012 [Fig 1C and 1D]. The slight attenuation of the initial peak in SARP may reflect the fact that SARP did not enroll children younger than 6 years [Fig 1].

The role of age on asthma related hospital cost

Hospitalization cost increased with age, with females having higher cost [S7 Fig and S4 Table]. The average hospitalization cost in 2012 was $6,875 for an asthma patient who did not develop respiratory failure. It was $14,839 for an asthmatic who developed respiratory failure and $29,043 for an individual requiring intubation and mechanical ventilation [expressed as Median (IQR) in S5 Table]. Aggregate hospital cost followed a bimodal distribution, similar to the bimodal peak of severe asthma, and was highest between the age of 1 to 10 years and after the age of 40 years [S7 Fig].

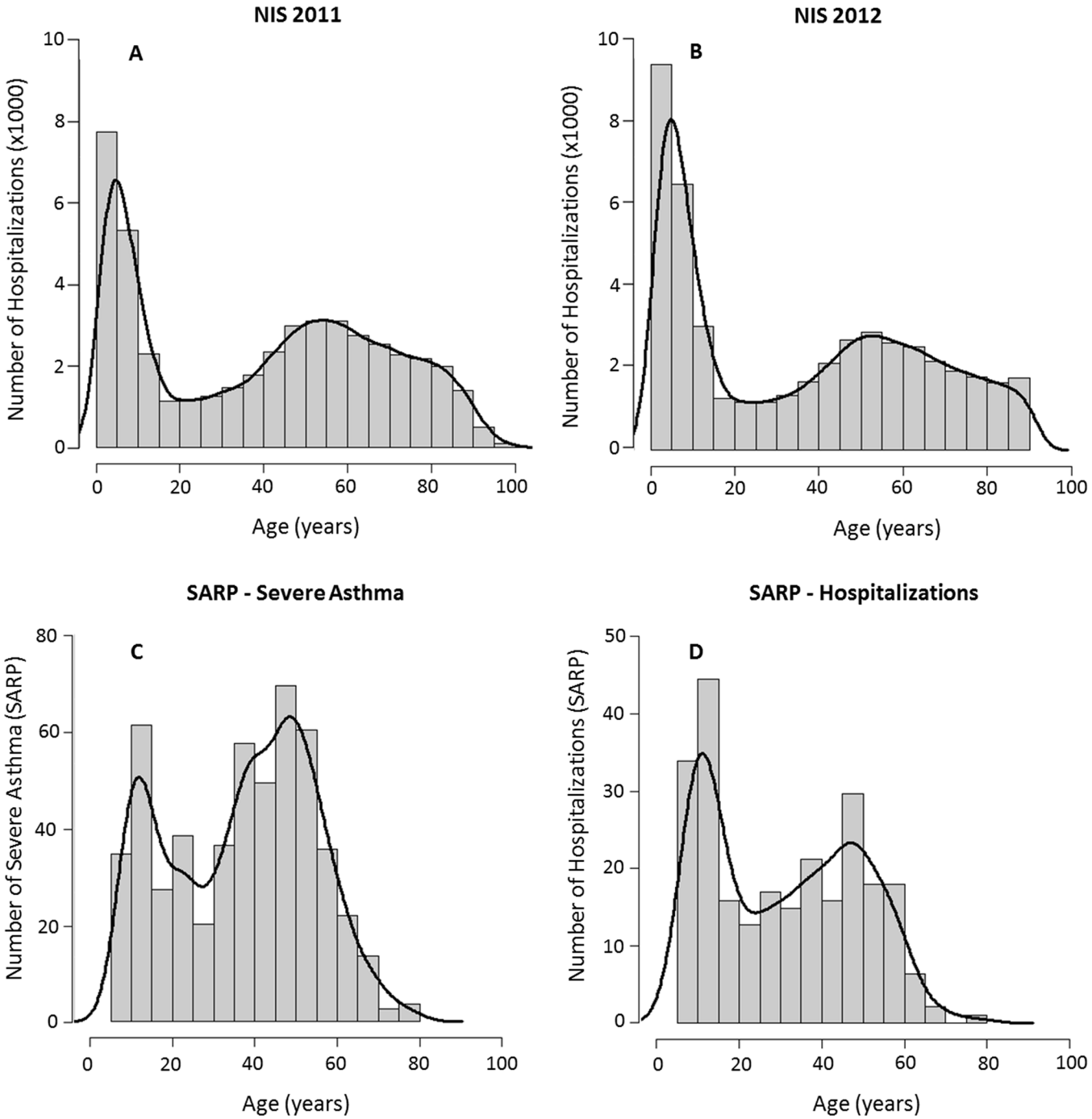

Fig 1. Histogram with smoothed density estimate of age distribution of asthma related hospitalizations in the United States in 2011 (Panel A) and 2012 (Panel B). Panel C and Panel D reflect the age distribution of severe asthma and asthma hospitalization in the Severe Asthma Research Program (SARP) database. All 3 databases show a bimodal age distribution of severe asthma.

doi:10.1371/journal.pone.0157301.g001

Discussion

The principal finding of this study is that the age distribution of severe asthma and asthma hospitalization is bimodal, consistent with the hypothesis that asthma is more severe in young boys and middle age women. This bimodal distribution of severe asthma is in contrast with the

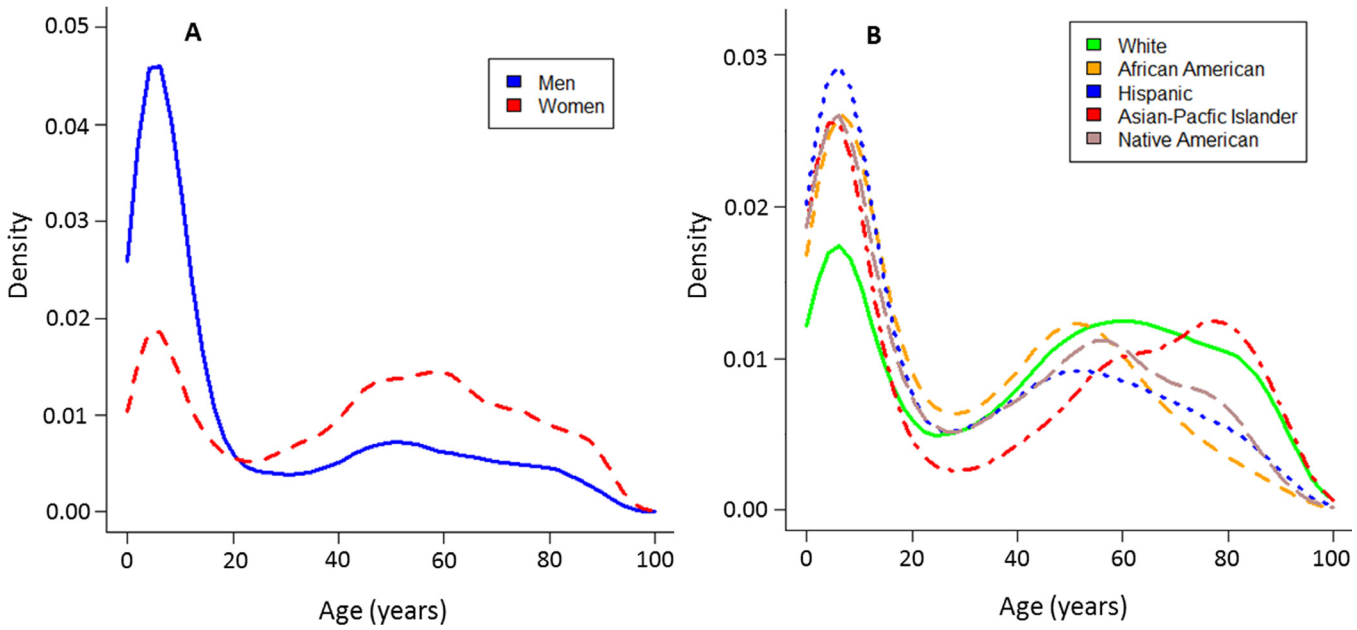

Fig 2. Density plots of the distribution of asthma hospitalizations stratified by gender and race. Panel A shows that asthma hospitalization is more frequent among young boys and middle age women. Panel B shows a bi-modal distribution of asthma severity across different races. Panel A and B are abstracted from NIS 2012.

doi:10.1371/journal.pone.0157301.g002

age distribution of asthma prevalence which does not change appreciably across the ages[8]. The bimodal distribution of asthma severity was confirmed using SARP, a well characterized prospectively collected and strictly defined cohort of non-severe and severe asthmatic patients' ages 6 to 80 years.

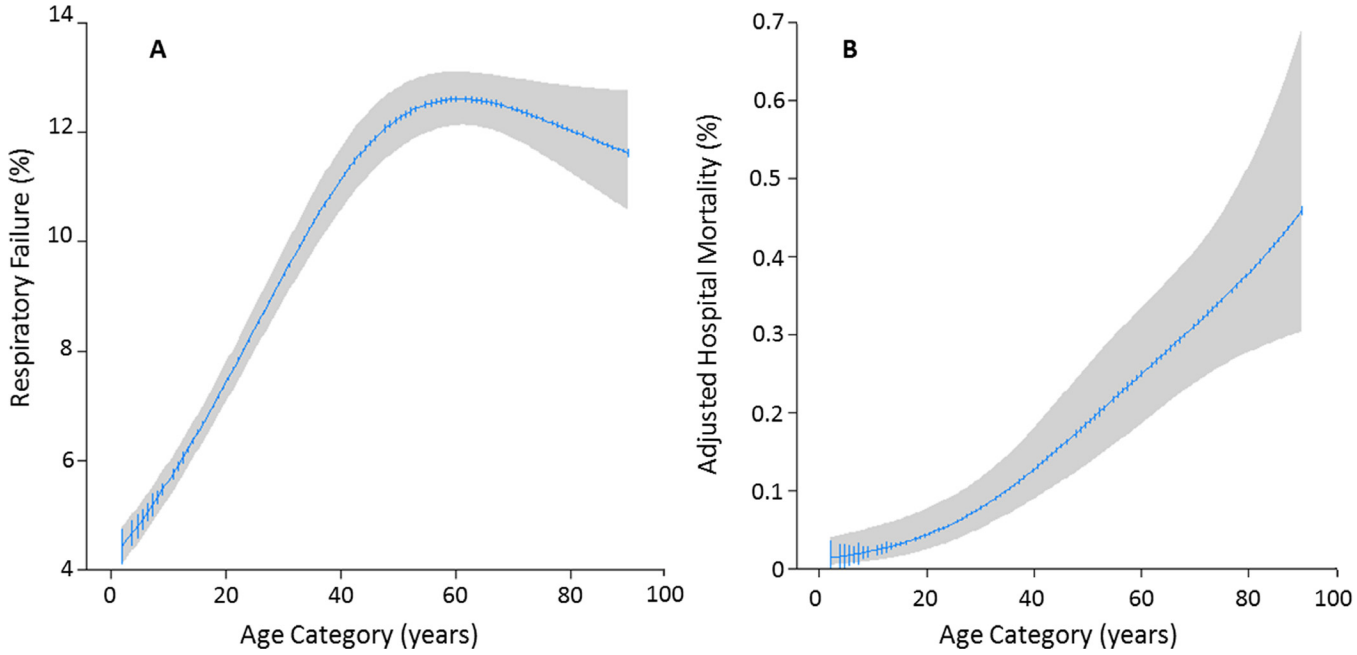

Fig 3. Risk-adjusted probabilities of asthma related hospital mortality (Panel A) and respiratory failure (Panel B) as a function of age using the NIS 2012 database. The probabilities were calculated by fitting a logistic regression using a restricted cubic spline function for age. The 95% CIs are indicated by the gray area around the fitted line.

doi:10.1371/journal.pone.0157301.g003

These findings strongly support gender differences in asthma severity throughout the life course. Asthma is more prevalent in boys than in girls during childhood [16–18], but in adolescence, asthma becomes more severe and prevalent in girls [19, 20]. This shift is attributed to changes in hormonal milieu or environmental exposures [21–23]. In line with this, the rate of asthma related hospitalization was higher among young boys and middle-aged women in this study, supporting the theory that asthma is modulated by sex hormones. Additionally, the rate of respiratory failure was found to be lower among older women compared to men. Such improvement can be attributed to menopause and supports the reversal of the well-described gender switch that occurs at puberty [7].

The role of age on asthma related health cost is important. While less than 10% of asthmatics have severe disease, this group accounts for more than 50% of all asthma-related total health care costs[24–26]. Conversely, as the world is aging, the number of people older than 60 years is projected to double between 2007 and 2050 [27]. This will create a significant burden on the healthcare system and society worldwide. As such, investigating preventable determinants of lung aging that contribute to severe asthma will become clinically and economically vital. This study provides a comprehensive analysis of hospitalization cost while taking into account the age-gender interaction and adjusting for race and age related comorbidities. The findings that asthma is more severe and expensive with children and older adults, suggest that an improved approach to asthma therapy is needed. For example, managing tobacco addiction, obesity, GERD and other age related comorbidities will be increasingly important. While mean hospitalization cost is important for individual patients, aggregate hospital cost is paramount to society and national healthcare policymakers. Our data help to identify high risk groups, such as young boys and middle age women, who can be targeted for close outpatient monitoring, asthma education and aggressive medical therapy.

HCUP databases provide a unique opportunity to analyze hospital mortality and cost. While Medicare and Medicaid databases provide accurate information regarding senior and non-privileged participants, HCUP-NIS samples all individuals admitted to a hospital in the US. This helps lowering the selection bias. Furthermore, for a disease with a very low mortality such as asthma (0.3% per hospitalization) [28], large databases are needed to detect any differences in mortality risk factors. On the other hand, HCUP does not provide any clinical or medication data, and therefore may be subject to biased results. In this context, secondary databases run the risk of not measuring all the necessary variables and risk factors [29] or missing and misclassifying important measurements [30]. Therefore, the accuracy of administrative data depend on the correct identification and documentation of the disease in the patient chart, a task that is not consistently fulfilled by clinicians [31, 32]. For example, while GERD may be under-reported in HCUP, the primary outcomes listed here are not influenced by the clinician. Mortality, hospital length of stay and hospital cost are well recorded and accurately reported to HCUP. Furthermore, in order to increase the Diagnosis-Related Group (DRG) and hospital charges, the diagnosis of respiratory failure is also less likely to be under reported. Even taking these limitations into account, observational databases continue to be useful in making accurate predictions for individual patients [33]. Importantly, the specificity of disease ascertainment through administrative claim-based data was reported to be substantially higher than 90% for most conditions but sensitivities is usually reported below 60% [34]. This fact supports the accuracy of the diagnosis of asthma in the HCUP database.

In order to minimize bias, we have provided a robust description of the data and diagnostic codes used, focusing on the sampling methods and the inclusion and exclusion criteria. We also took into consideration the unique characteristics of the database, how it was generated and the variables it measures [35, 36]. HCUP is an administrative claim-based database. The data are limited by a lack of clinical information, including physiological, radiological or

laboratory testing results. Additionally, no information is available regarding medication use or compliance. Therefore it was not possible to use standard definitions to define asthma severity such as the one recommended by the American Thoracic Society Workshop on Refractory Asthma [15], or to use information on asthma related quality of life such as the one provided using the Asthma Quality of Life Questionnaire (AQLQ) [37]. To address such limitations, other markers of asthma severity, such as rate of asthma related hospitalization, hospital mortality, hospital length of stay, monetary cost and the rate of respiratory failure were used as indicators for severe asthma. Additionally, we used the NIS 2012 to fit our models and the NIS 2011 database to validate them. Most importantly, in order to externally validate and confirm the results we used the NHLBI SARP database which recruited patients over a 10 years period using strictly defined criteria for severe asthma. The analysis duplication and results validation provide a measure of reassurance that the findings are robust and true across all databases.

In summary, asthma is most severe in young males and middle aged women. In these populations, it results in the highest hospitalization rates, mortality, respiratory failure, and aggregate cost. A global multisystem approach to the health of the young and the elderly is needed in order to improve asthma control and lower cost. Moreover, we report for the first time that asthma severity decreases dramatically, though transiently, in young adulthood. Understanding the determinants of this decrease may prove important clues to help flatten the severe asthma risk curve across the entire age spectrum.

Supporting Information

S1 Appendix. ICD-9 CM Codes used in the analysis.
(DOCX)

S1 Fig. Conceptual framework.
(DOCX)

S2 Fig. Patient selection for assessment of asthma related hospital outcome.
(DOCX)

S3 Fig. Distribution of asthma related hospitalizations stratified by gender.
(DOCX)

S4 Fig. Density plot of age distribution stratified by gender using of patient with severe asthma (Panel C) or hospitalized from asthma during the previous year (Panel D) using the Severe Asthma Research Program (SARP I&II).
(DOCX)

S5 Fig. Plot of the probably of asthma related respiratory failure as a function of age and stratified by gender using NIS data.
(DOCX)

S6 Fig. Distribution of asthma related hospital mortality stratified by gender.
(DOCX)

S7 Fig. Mean and aggregate hospital cost as a function of age in 2012.
(DOCX)

S1 Table. Data Elements in the 2011 and 2012 NIS Disease Severity Measures Files.
(DOCX)

S2 Table. National Statistics of Asthma Related ED visit and Hospitalizations.
(DOCX)

S3 Table. Estimated hospital cost and charges by gender and respiratory failure abstracted from the NIS databases.
(DOCX)

S4 Table. Estimated hospital cost and charges by gender and age category abstracted from the NIS databases.
(DOCX)

S5 Table. Estimated hospital cost and charges by gender and respiratory failure abstracted from the NIS databases.
(DOCX)

Acknowledgments

Contributors

Members of the Severe Asthma Research Program (SARP I&II) are: Suzy Comhair, Eugene Bleecker, William Busse, William Calhoun, Mario Castro, Anne Fitzpatrick, Elliot Israel, W. Gerald Teague, Sally Wenzel, Fernando Holguin, Benjamin Gaston, and Serpil Erzurum.

Author Contributions

Conceived and designed the experiments: JGZ BLU WGT SMK NKS ERB WBB WJC MC SAC AMF EI SEW FH BMG SCE. Performed the experiments: JGZ BLU SMK SCE. Analyzed the data: JGZ SCE. Contributed reagents/materials/analysis tools: JGZ BLU WGT SMK NKS ERB WBB WJC MC SAC AMF EI SEW FH BMG SCE. Wrote the paper: JGZ BLU SCE. Provided administrative and technical support: ERB WBB WJC MC SAC AMF EI SEW BMG SCE.

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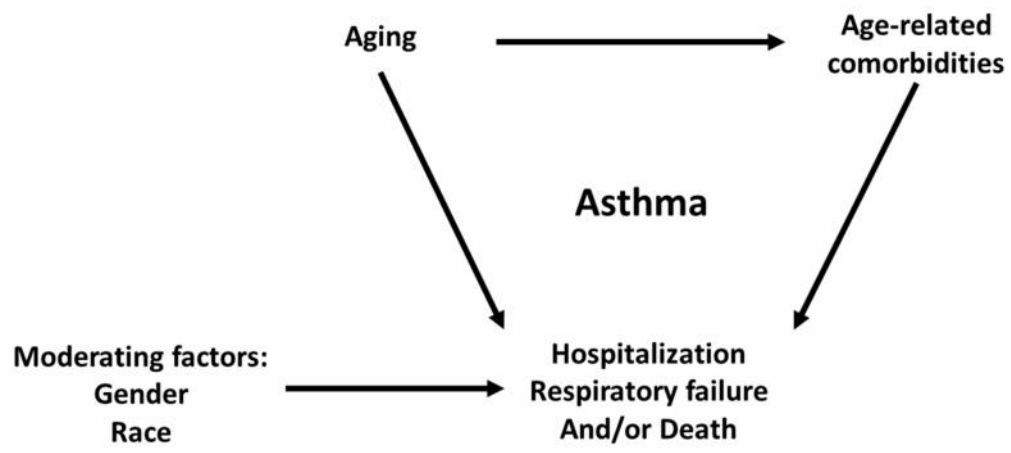
S1 Appendix. ICD-9 CM Codes used in the analysis

		ICD-9 CM code
Asthma Diagnosis:		
	Extrinsic asthma unspecified:	493.00
	Extrinsic asthma with status asthmaticus	493.01
	Extrinsic asthma with (acute) exacerbation:	493.02
	Intrinsic asthma unspecified:	493.10
	Intrinsic asthma with status asthmaticus:	493.11
	Intrinsic asthma with (acute) exacerbation:	493.12
	Chronic obstructive asthma unspecified:	493.20
	Chronic obstructive asthma with status asthmaticus:	493.21
	Chronic obstructive asthma with (acute) exacerbation:	493.22
	Cough variant asthma:	493.82
	Asthma unspecified:	493.90
	Asthma unspecified type with status asthmaticu	493.91
	Asthma unspecified with (acute) exacerbation:	493.92
Gastroesophageal Reflux Disease (GERD) Diagnosis:		
	Reflux esophagitis:	530.11
	Esophageal reflux:	530.81
Respiratory Syncytial Virus (RSV) Related Bronchiolitis Diagnosis.		
	Respiratory syncytial virus:	079.6
	Acute bronchiolitis due to respiratory syncytial virus:	466.11
Chronic Obstructive Pulmonary Disease (COPD):		
	Emphysematous bleb	492.0
	Other emphysema	492.8
	Chronic airway obstruction not elsewhere classified	496
	Obstructive chronic bronchitis without exacerbation	491.20
	Obstructive chronic bronchitis with (acute) exacerbation	491.21
	Obstructive chronic bronchitis with acute bronchitis	491.22
Diagnosis of Respiratory Failure and Arrest:		
	Acute respiratory failure	518.81
	Chronic respiratory failure	518.83
	Acute and chronic respiratory failure	518.84
	Respiratory arrest	799.1
Tobacco Use Disorder		
	Nondependent tobacco use disorder:	305.1
	Personal history of tobacco use:	v15.82

S1 Fig. Conceptual framework. Aging is associated with worse clinical outcome, such as higher hospitalization rate, respiratory failure and mortality higher age-related. This association is in part mediated by age related comorbidities such as obesity, congestive heart failure, malignancy, and gastro esophageal reflux disease which in turn result in, morbidity and mortality. Additionally, other moderating factors such as gender, race can impact asthma severity and subsequently clinical outcome.

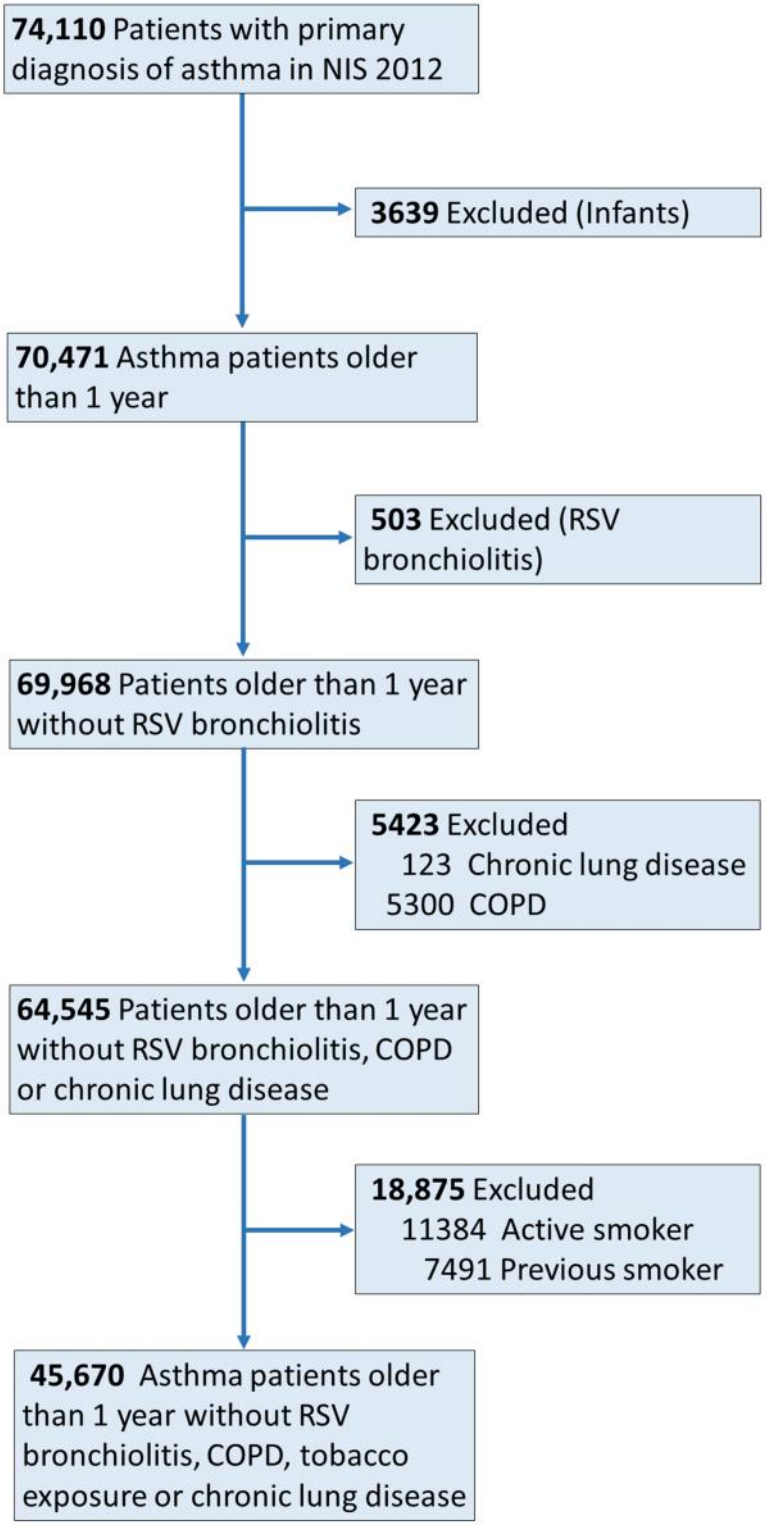


S1 Table. Data Elements in the 2011 and 2012 NIS Disease Severity Measures Files.

Comorbidities	**HCUP Code**
Acquired Immunodeficiency Syndrome (AIDS)	CM_AIDS
Alcohol abuse	CM_ALCOHOL
Deficiency anemia	CM_ANEMDEF
Rheumatoid Arthritis/Collagen Vascular Disease (RA/CTD)	CM_ARTH
Blood loss	CM_BLDLOSS
Congestive Heart Failure (CHF)	CM_CHF
Chronic lung disease*	CM_CHRNLUNG
Coagulopathy	CM_COAG
Depression	CM_DEPRESS
Diabetes (DM)	CM_DM
Diabetes with Chronic complications	CM_DMCX
Drug abuse	CM_DRUG
Hypertension (combine uncomplicated and complicated)	CM_HTN_C
Hypothyroidism	CM_HYPOTHY
Liver disease	CM_LIVER
Lymphoma	CM_LYMPH
Fluid and electrolyte disorders	CM_LYTES
Metastatic cancer	CM_METS
Other neurological disorders	CM_NEURO
Obesity	CM_OBESE
Paralysis	CM_PARA
Peripheral vascular Disorders	CM_PERIVASC
Psychosis	CM_PSYCH
Pulmonary circulation disorder	CM_PULMCIRC
Renal failure	CM_RENLFAIL
Solid tumor without metastasis	CM_TUMOR
Peptic ulcer disease excluding bleeding	CM_ULCER
Valvular heart disease (VHD)	CM_VALVE
Weight loss	CM_WGHTLOSS

*patients with chronic lung diseases were excluded from this analysis as detailed in the method section of the manuscript.

S2 Fig. Patient selection for assessment of asthma related hospital outcome.

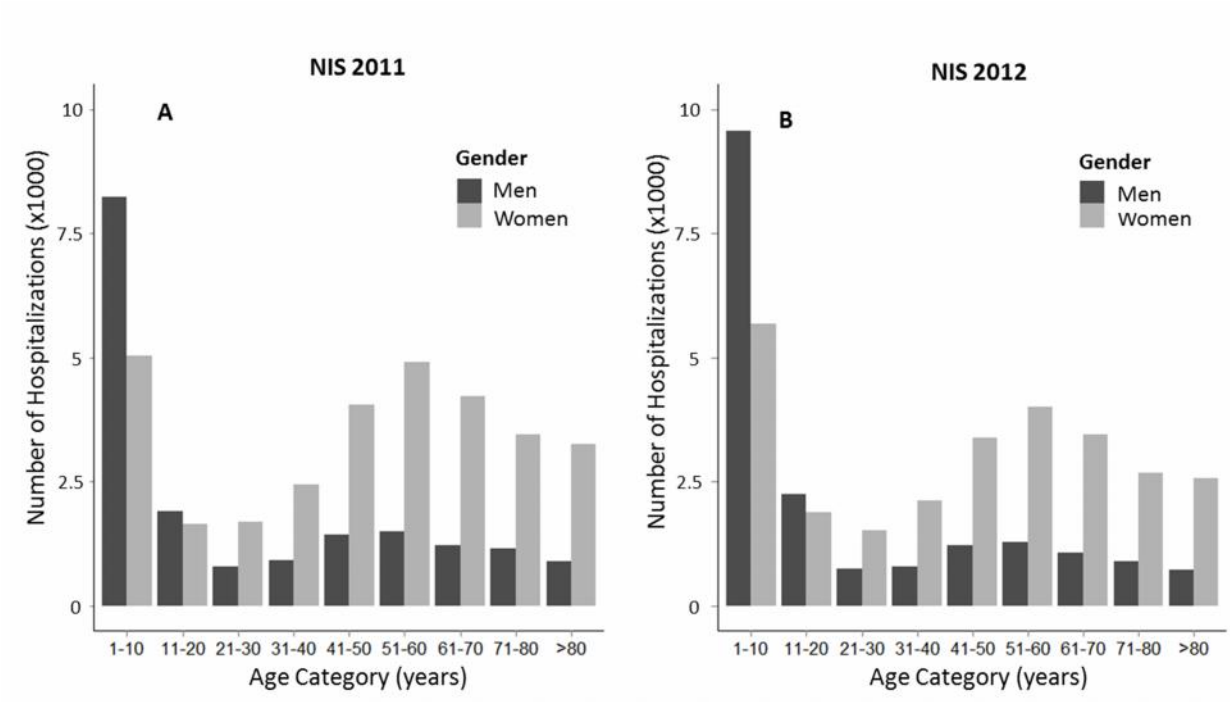


RSV indicates Respiratory Syncytial Virus; COPD, Chronic Obstructive Pulmonary Disease.

S2 Table. National Statistics on Asthma Hospitalizations.

	2011	**2012**
Total number of hospitalization	368,528	372,685
Female gender (%)	232,970 (63)	226,915 (61)
Length of Stay , days (mean)	3.4	3.2
Length of stay, days (median)	3.0	2.0
Charges, $ (mean)	20,756	21,512
Charges, $ (median)	13,926	14,350
Cost, $ (mean)	5,907	5,981
Cost, $ (median)	4,336	4,380
Aggregate Charges, $	7,649,167,168	8,017,199,720
Aggregate Cost, $	2,176,015,890	2,231,112,607
In-Hospital Deaths	1,088 (0.30%)	1,090 (0.29%)

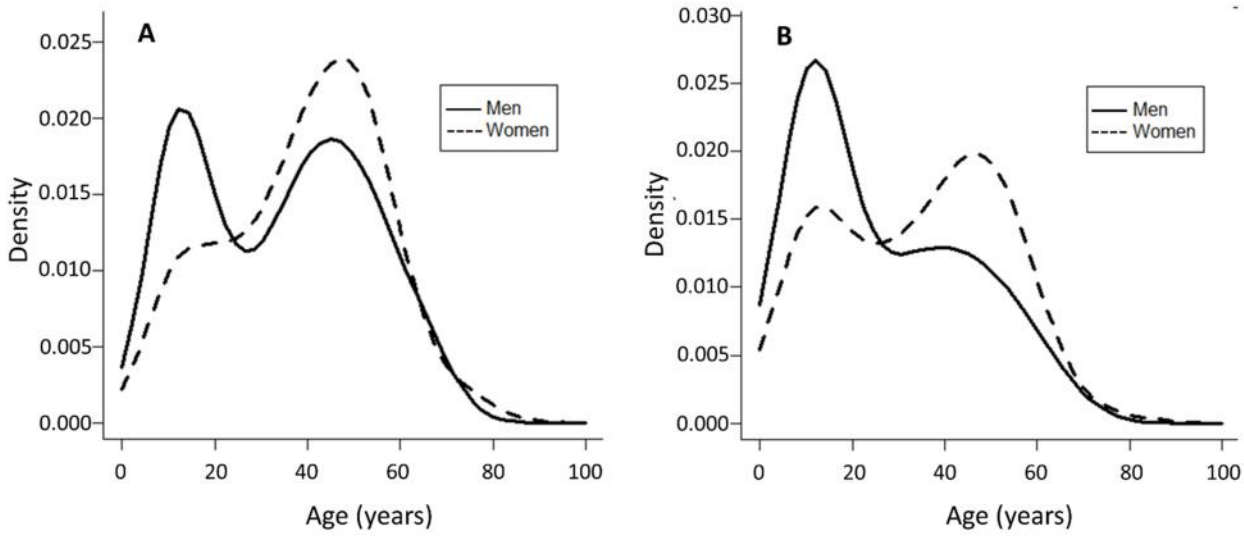
S3 Fig. Distribution of asthma related hospitalizations stratified by gender. Panels A and B reflect hospitalizations in 2011 and 2012 respectively.



S3 Table. Racial differences in mean age among adult 18 years and older hospitalized in 2012.

	Mean difference (Years)	**95% CI**	**p value**
African American vs. White	-8.65	-9.36; -7.93	<0.000
Hispanic vs. White	-4.80	-5.71; -3.88	<0.000
Asians or Pacific Islander vs. White	5.15	3.15; 7.15	<0.000
Native American vs. White	-4.33	-8.12; -0.54	<0.016
Hispanic vs. African American	3.85	2.87; 4.84	<0.000
Asian or Pacific Islander vs. African American	13.80	11.76; 15.83	<0.000
Native American vs. African American	4.32	0.51; 8.13	<0.017
Asian or Pacific Islander vs. Hispanic	9.94	7.83; 12.05	<0.000
Native American vs. Hispanic	0.47	-3.38; 4.32	0.997
Native American vs. Asian or Pacific Islander	-9.47	-9.36; -7.93	<0.000

S4 Fig. Density plot of age distribution stratified by gender using of patient with severe asthma (Panel C) or hospitalized from asthma during the previous year (Panel D) using the Severe Asthma Research Program (SARP I&II). The attenuation of early peak is SARP I&II could be related to the fact that SARP did not recruit children younger than 6 years.



S4 Table. Estimated hospital cost and charges by gender and age category abstracted from the NIS databases.

		Total Charges ($)		Total Cost ($)	
NIS data	**Age (years)**	**Men**	**Women**	**Men**	**Women**
2012					
	<1	8653 [5447-14456]	8871 [5363-14903]	2655 [1722-4212]	2653 [1768-4243]
	1-10	9475 [5796-15486]	10106 [6141-16617]	2823 [1886-4528]	3009 [1991-4898]
	11-20	11579 [6829-19978]	11830 [7111-20876]	3454 [2234-5837]	3584 [2305-5851]
	21-30	11542 [7038-18381]	13190 [7959-21402]	3501 [2394-5291]	3891 [2634-5909]
	31-40	13276 [8139-21318]	14273 [8511-23755]	3879 [2629-5929]	4284 [2879-6595]
	41-50	15188 [8982-25313]	15898 [9598-26322]	4504 [3022-6877]	4763 [3188-7188]
	51-60	15804 [9627-26936]	17951 [10741-30403]	4857 [3265-7290]	5345 [3544-8036]
	61-70	18301 [11269-30768]	19259 [11469-31798]	5414 [3729-8288]	5774 [3868-8755]
	71-80	18880 [11610-31619]	20108 [11974-34609]	5497 [3826-8578]	5978 [4002-9223]
	>80	20543 [12038-35976]	20862 [12441-35757]	5982 [4011-9497]	6229 [4241-9487]
2011					
	<1	7840 [4912-12870]	8062 [5156-13709]	2514 [1679-3899]	2555 [1662-4130]
	1-10	8411 [5399-13320]	8912 [5529-14841]	2616 [1792-4042]	2881 [1942-4538]
	11-20	10280 [6482-17553]	10465 [6526-17233]	3315 [2190-5152]	3359 [2257-5232]
	21-30	10959 [6977-18216]	12293 [7584-20324]	3419 [2292-5330]	3710 [2562-5630]
	31-40	13055 [8051-21901]	13492 [8380-22235]	3836 [2671-5957]	4136 [2814-6376]
	41-50	14095 [8854-23847]	15418 [9430-26208]	4353 [2931-6455]	4686 [3133-7183]
	51-60	17011 [10064-27732]	16958 [10166-29113]	5042 [3323-7536]	5191 [3484-7958]
	61-70	18022 [10644-30174]	18570 [11003-30943]	5446 [3609-8348]	5694 [3770-8670]
	71-80	19171 [11187-32253]	20051 [11967-34575]	5815 [3962-8761]	5987 [4027-9137]
	>80	20139 [11446-33970]	20120 [12054-34314]	6140 [4080-9192]	6129 [4140-9381]

Results are reported as median and Interquartile Range (median[IQR])

S5 Fig. Plot of the probably of asthma related respiratory failure as a function of age and stratified by gender using NIS data.

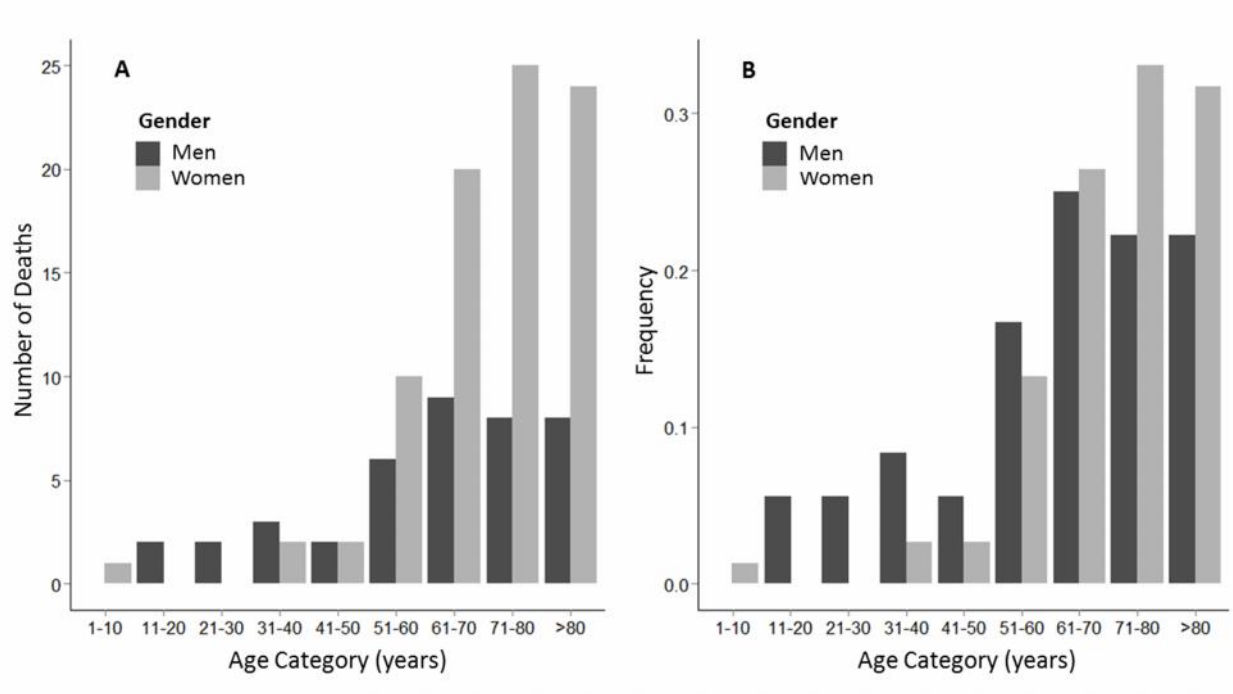
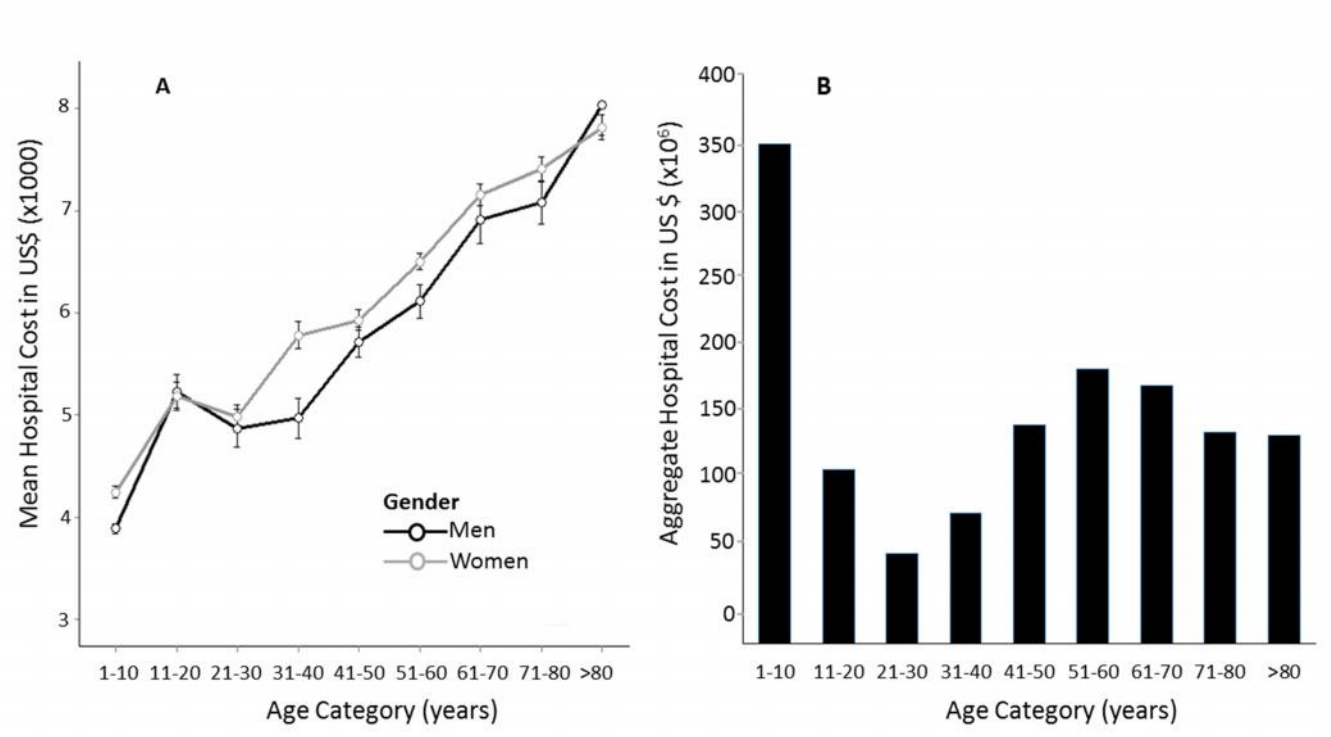
The association between age and the probability of respiratory failure is demonstrated by applying a LOWESS (Locally Weighted Scatterplot Smoother) smoother in the overall population. The relationship between age and probability of respiratory failure resembles a spline with an inflection point at the age of 60 years (Panel A). The stratification by gender shows the probability of asthma severity is higher in men than women after age 60 (Panel B).

S5 Table. Estimated hospital cost and charges by gender and respiratory failure abstracted from the NIS databases.

		Total Charges ($)		Total Cost ($)	
NIS data	**Outcome**	**Men**	**Women**	**Men**	**Women**
2012					
	No Respiratory Failure	11708 [6945-20089]	25319 [14848-41178]	3570 [2271-5711]	4499 [2907-6998]
	Respiratory Failure	19651 [11387-36304]	40305 [22557-72471]	6193 [3882-10455]	6926 [4442-11318]
	Requiring Mechanical Ventilation	59422 [31795-109338]	62423 [37565-108267]	17176 [10312-32479]	18619 [11306-28369]
2011					
	No Respiratory Failure	11262 [6754-19514]	14537 [8647-25094]	3522 [2248-5659]	4515 [2915-7044]
	Respiratory Failure	21040 [11557-40131]	22212 [12816-41108]	6334 [3853-10994]	6700 [4314-11409]
	Requiring Mechanical Ventilation	67888 [36915-127068]	69643 [41251-127368]	19482 [10818-33630]	21029 [12531-36749]

Results are reported as median and Interquartile Range (median[IQR])

S6 Fig. Distribution of asthma related hospital mortality stratified by gender. Panels A: The number of deaths from asthma as a function of age stratified by gender. Panel B: reflect the frequency of hospital mortality stratified by gender. Overall more women older than 50 years died with asthma in the hospital. Correcting for the higher hospitalization rate among older women compared to men, the difference in the frequency of asthma related hospital mortality is smaller among older men and women.



S7 Fig. Mean and aggregate hospital cost as a function of age in 2012. Panel A: Mean and Standard Error plot of asthma related hospitalization cost across age categories stratified by gender showing than mean hospitalization cost increases with age and is higher in women compared to men. Panel B reflect the aggregate hospital cost across age categories also showing the bimodal distribution of aggregate cost. Panel A and B are abstracted from NIS 2012.