BMJ Open

Trends in asthma hospital admissions and mortality in Kuwait, 2000 to 2014: a national retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021244
Article Type:	Research
Date Submitted by the Author:	18-Dec-2017
Complete List of Authors:	Ziyab, Ali; Kuwait University Faculty of Medicine, Community Medicine Abul, Adnan; Kuwait University Faculty of Medicine, Community Medicine
Keywords:	Epidemiology < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, Asthma Hospitalization, Asthma Mortality

Trends in asthma hospital admissions and mortality in Kuwait, 2000 to 2014: a national retrospective study

Authors: Ali H. Ziyab[1], Adnan T. Abul[1,2]

Affiliations:

[1] Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait

[2] Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait

Corresponding author:

Ali H. Ziyab, PhD

Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait.

P. O. Box 24923

Safat 13110, Kuwait

Tel: (+965) 24636545

Fax: (+965) 25338948

Email: aziyab@hsc.edu.kw

Word count: 3,709 words

ABSTRACT

Objectives: To examine trends in asthma hospitalization and mortality rates from 2000 to 2014 in Kuwait according to sex, age, and nationality.

Methods: For this nationwide, retrospective observational study, data from hospital discharge records and death certificates listing asthma as the primary reason for hospitalization or mortality were obtained from the National Center for Health Information database using ICD-10 codes J45 and J46. Annual asthma hospitalization and mortality rates were estimated using the respective mid-year population estimates as denominators. Trends in stratified and adjusted (for sex, age, and nationality) hospitalization and mortality rates were examined. Poisson regression models were applied to test for linear trends overtime and estimate adjusted rate ratios (aRR) and 95% confidence intervals (CI).

Results: During the 15-year study period, a total of 43,652 hospitalizations and 484 deaths due to asthma exacerbations were identified. The average annual adjusted rates of asthma hospitalization and mortality were estimated to be 134.9 (95% CI: 131.8, 138.1) and 2.1 (95% CI: 1.8, 2.4) per 100,000 population, respectively. Hospitalization rates decreased by 49.5% in the total population (from 180.8 to 91.3 admissions per 100,000 population between 2000 and 2014, $P_{trend} < 0.001$). Adjusted mortality rate decreased from 4.1 to 0.9 deaths per 100,000 population between 2000 and 2014; a 77.6% decrease ($P_{trend} < 0.001$). Kuwaiti nationals compared to non-Kuwaiti subjects had higher risk of asthma hospitalization (aRR = 1.83, 95% CI: 1.75, 1.92). Among children aged ≤ 19 years, the risk of hospitalization was higher in boys compared to girls; however, among adults, women experienced more hospitalizations than men.

Conclusions: Asthma hospitalization and mortality rates have substantially decreased between 2000 and 2014 in Kuwait, with persisting differences between genders, age groups, and citizens vs. non-citizens. The observed decreasing trends in Kuwait are in agreement with global trends.

Strengths and limitations of this study

- This study provided, at a national level, a comprehensive perspective on trends and disparities in hospitalizations and mortality related to asthma exacerbations in Kuwait over a 15-year period.

- Although data analyzed in the current report were obtained from the National Center for Health Information database using ICD-10 codes J45 and J46, misclassification of asthma-related hospitalizations or deaths is inevitable in epidemiological studies based on routinely collected data, which could either underestimate or overestimate the frequency.

- Lack of information on ethnicity/race of patients is a further limitation to our study.

INTRODUCTION

Asthma is the most common inflammatory chronic disorder of the lungs that affects children and adults. Globally, it was estimated in 2015 that 358 million people suffer from asthma, which reflects a 12.6% increase in asthma prevalence compared to 1990.[1] Whereas, asthma-related mortality, causing 397,000 deaths in 2015, decreased by 26.7% between 1990 and 2015.[1] The International Study of Asthma and Allergies in Childhood (ISAAC) revealed the existence of both between and within countries variations in the prevalence of asthma.[2] For instance, among children aged 13 to 14 years old, the 12-month prevalence of asthma symptoms ranged from 3.4% to 31.2%.[3] In Westernized countries, asthma is usually seen in around 10% of the general population.[4] Hence, due to the elevated prevalence, morbidity, and mortality, asthma is considered a global public health problem.

The major pathophysiological hallmarks that contribute to the complex heterogeneity of the clinical manifestations of asthma include recurrent airway inflammation, variable airway obstruction, and bronchial hyper-responsiveness.[5] Asthma exacerbations, defined as "a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome", have been graded in severity from mild to severe and in some instances as life-threatening.[6 7] Exacerbations requiring emergency department visits and hospitalizations are associated with substantial morbidity, medical expenditures, and economic as well as social burden on individuals and families.[6 8] In principle, asthma exacerbations are preventable events in the presence of high quality health care, patient awareness and compliance, and optimal asthma management.

In Kuwait, the burden of asthma is comparable to what is observed in Western nations. For instance, 7.6% and 15.6% of schoolchildren aged 13 to 14 years reported current wheeze and ever doctor-diagnosed asthma, respectively.[9] A recent study showed that 11.9% of university students in Kuwait suffer from asthma.[10] Annually, asthma management and treatment cause a considerable financial burden, costing $207 million with hospital admissions accounting for 43% of the total direct costs for asthma treatment in Kuwait.[11] During the period from 1992 to 1994, the annual rate of asthma hospitalization and mortality in Kuwait were estimated to be 205 admissions and 1.59 deaths per 100,000 population, respectively.[12] Given the ongoing improvements in asthma therapeutic and management strategies, we hypothesized that asthma hospitalizations and mortality to have decreased; however, there has been no recent efforts to assess temporal trends in Kuwait. Therefore, this study sought to describe trends in asthma hospital admissions and mortality according to sex, age, and nationality in Kuwait between 2000 and 2014 using national hospital discharge records and death certificates.

METHODS

Study setting

Kuwait, a small country with a total approximate area of 18,000 km^2, is located in the Arabian Peninsula with sandy desert covering its landscape. Generally, the climate in Kuwait is arid with extreme hot temperatures during summer and mild-cool weather in winter and frequent dust storms that occur throughout the year.[13] As of June 2017, the total population was estimated to be around 4.4 million. The population of Kuwait can be divide into two separate communities, namely citizens of Kuwait (Kuwaitis) and labor migrants/expatriates (non-Kuwaitis). Kuwaitis make around 30% (1.3 million) of the population, whereas non-Kuwaitis constitute about 70% (3.1 million) of the population. The majority of the non-Kuwaitis are of Asian ethnicity (1.8 million) and Arab ethnicity (1.2 million). Demographically, the majority of expatriates are males (65%), poorly educated (70% with less than secondary level education), and relatively young (83% aged between 15 and 60 years old).[14] Hence, distorting the demographic distribution of this population towards male and working-age predominance.

Health care services in Kuwait are divided into primary, secondary, and tertiary care. There are six public general hospitals, providing secondary level care, across Kuwait equipped with child and adult emergency departments. Moreover, at a smaller scale, some private hospitals provide emergency care services.

Study design, data sources, and outcomes

In this nationwide, retrospective observational study, we analyzed data from hospital discharge records and death certificates on asthma for the period from January 1, 2000 to December 31,

2014. Public and private hospitals across the state of Kuwait are required to report health and vital statistics and data on regular bases to the National Center for Health Information (NCHI) at the Ministry of Health. In this study, data was collected from all hospital discharge records and death certificates listing asthma as the primary reason for admission or death using ICD-10 (International Classification of Diseases, Tenth Revision) codes: J45 (asthma, including predominantly allergic asthma, non-allergic asthma, mixed asthma, asthma unspecified) and J46 (status asthmaticus). In the data extraction process, we included all anonymized asthma-related hospital admission episodes or mortality and collected data on age, sex, and nationality using the NCHI database. If a person has been hospitalized several times for asthma, we counted and considered all admissions per-person as independent events. Annual mid-year population estimates, total and stratified according to sex, age, and nationality, were obtained from the Public Authority for Civil Information, Kuwait. Ethical approval was obtained from the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait.

Statistical analysis

Counts of asthma hospital admissions and deaths resembled the unit of analysis. Five age groups were defined: < 5 years, 5 to 19 years, 20 to 44 years, 45 to 64 years, and ≥ 65 years. Annual and average annual rates of asthma hospital admissions and mortality per 100,000 population were estimated for the 15-year study period (from January 1, 2000 to December 31, 2014) for the total population and stratified according to age group, sex, and nationality. In trend analysis, using calendar year as the exposure variable of interest, annual changes in rates of asthma hospital admissions and mortality were examined. Moreover, percent change (PC) in hospitalization rates comparing the years 2000 and 2014 were calculated as follows: PC = [((rate in 2014 – rate in

2000)/rate in 2000) x 100]. Poisson regression models, with log link function, were used to calculate overall as well as stratified model-adjusted rates and adjusted rate ratios (aRR) and their corresponding 95% confidence intervals (CI) using the GENMOD procedure in SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Regression-based adjustments for age, sex, and nationality were considered when estimating rates and rate ratios. In all regression models, we treated the observed counts of asthma-related hospitalizations/mortality in each year as the outcome variable and the corresponding denominator (i.e., logarithm of mid-year population counts) as an offset term. Additionally, sex- and age-standardized asthma hospital admission rates for the total population and stratified according to nationality were calculated using weights from the World Health Organization (WHO) new World Standard Population.[15] The STDRATE procedure in SAS 9.4 was used to compute directly sex- and age-standardized rates. All statistical analyses were conducted using SAS 9.4. The statistical significance level was set to $\alpha = 0.05$ for all association and trend analyses.

RESULTS

Characteristics and trends of asthma hospital admissions

During the 15-year study period, a total of 43,652 hospital admissions due to asthma exacerbations were identified from hospital discharge records in Kuwait. Of the total hospital admissions, 23,784 (54.5%) were among males, 27,959 (64.1%) were among Kuwaiti individuals, and 18,405 (42.1%) were among children aged < 5 years old (Table 1). The sex, age, and nationality model-adjusted average annual rate of asthma hospital admissions was estimated to be 134.9 (95% CI: 131.8, 138.1) per 100,000 population. On average, significantly higher rates of hospitalizations was observed among females compared to males (159.3 vs. 114.3 admissions per 100,000 population per year, $P < 0.001$) and Kuwaiti nationals compared to non-Kuwaiti subjects (182.5 vs. 99.8 admissions per 100,000 population per year, $P < 0.001$). Averaged annual hospitalization rates were highest among children aged < 5 years (426.5 admissions per 100,000 population) and in adults aged ≥ 65 years (405.1 admissions per 100,000 population), whereas individuals aged 20 to 44 years had the lowest average annual hospitalization rate of 34.6 admissions per 100,000 population (Table 1).

Trend analysis showed that asthma hospitalization rates decreased from 180.8 to 91.3 admissions per 100,000 population between 2000 and 2014 in the total population (a 49.5% decrease [95% CI: 44.2, 54.3], $P_{trend} < 0.001$; Figure 1, Table 2). Significantly decreasing trends were observed in both sexes, with reductions in admissions rates between 2000 and 2014 amounting to 51.8% in females (from 221.8 to 106.9 admissions per 100,000 population, $P_{trend} < 0.001$) and 47.6% in males (from 148.5 to 77.9 admissions per 100,000 population, $P_{trend} < 0.001$).

Moreover, decreasing trends in hospital admission rates were observed in most subgroups stratified according to sex, nationality, and age group (Figure 2). For instance, most pronounced decreases in hospitalization rates between 2000 and 2014 among both Kuwaiti males and females were observed among those aged 5 to 19 years old (decrease of 63.1% in males and 70.2% in females, $P_{trend} < 0.001$) when compared to other age groups. Whereas, non-Kuwaiti males aged < 5 (49.0% decrease, $P_{trend} < 0.001$) and ≥ 65 (49.2% decrease, $P_{trend} < 0.001$) years experienced the highest decreases in hospitalization rates. Among non-Kuwaiti females, those aged 45 to 64 years had a 64.8% decrease in asthma hospital admissions between 2000 and 2014 ($P_{trend} < 0.001$; Figure 2).

Associations between nationality and asthma hospitalization rates

In regard to nationality disparity in asthma hospitalization, Kuwaiti nationals compared to non-Kuwaiti subjects had higher risk of asthma hospital admission in the total population (aRR = 1.83, 95% CI: 1.75, 1.92). Moreover, our analysis showed that both males and females of Kuwaiti nationality had higher asthma hospitalization rates compared to non-Kuwaitis across all age groups (see online supplementary table S1). Overall, Kuwaiti males had 1.81 (95% CI: 1.69, 1.94) times the risk of hospitalization compared to non-Kuwaiti males. Similarly, Kuwaiti females had 1.88 (95% CI: 1.72, 2.06; see online supplementary table S1) times the risk of hospitalization compared to non-Kuwaiti females.

Sex differences in asthma hospitalization rates

Overall, females had higher risk of asthma hospitalization compared to males (aRR = 1.39, 95% CI: 1.33, 1.46). However, the sex ratio of asthma hospitalization varied significantly across age

groups (Figure 3). Among children aged ≤ 19 years, the risk of hospital admission for asthma was significantly lower in females compared to males (age < 5 years: $RR_{female\ vs.\ male}$ = 0.58, 95% CI: 0.54, 0.63; age 5 to 19 years: $RR_{female\ vs.\ male}$ = 0.56, 95% CI: 0.51, 0.62). On the contrary, among those aged ≥ 20 years, asthma hospitalization was significantly higher in females compared to males. For instance, among those aged 20 to 44 years old, females had 1.99 (95% CI: 1.76, 2.26) times the risk of hospitalization compared to males. These sex and age specific trends where similar for Kuwaiti and non-Kuwaiti subjects (Figure 3).

Characteristics and trends of asthma mortality

A total of 484 asthma deaths were identified over the 15-year study period in Kuwait (Table 1). The average annual adjusted asthma mortality rate was estimated to be 2.1 (95% CI: 1.8, 2.4) deaths per 100,000 population per year. The risk of asthma mortality was higher among females compared to males (aRR = 1.41, 95% CI: 1.19, 1.68) and Kuwaitis compared to non-Kuwaitis (aRR = 1.29, 95% CI: 1.06, 1.56). However, sex-stratified analysis showed that the risk of asthma mortality is similar between Kuwaiti females and non-Kuwaiti females (aRR = 0.85, 95% CI: 0.67, 1.08). In contrast, Kuwaiti males had 1.99 (95% CI: 1.48, 2.68) times the risk of asthma mortality compared to non-Kuwait males. In regard to age, asthma mortality rate was highest among those aged ≥ 65 years old (27.7 deaths per 100,000 population per year; Table 1).

Across the study period, deaths due to asthma showed statistically significant decreasing trends (P_{trend} < 0.001, Figure 4). In the total population, asthma mortality rate decreased from 4.1 to 0.9 deaths per 100,000 population between 2000 and 2014 (Table 2); translating to a 77.6% (95% CI: 58.9, 87.8) reduction in mortality related to asthma exacerbations. Among males, asthma

mortality rate decreased from 4.1 to 0.45 deaths per 100,000 population between 2000 and 2014. Whereas, among females, asthma mortality rate reduced from 4.3 to 1.4 deaths per 100,000 population between 2000 and 2014. Hence, the magnitude of reduction in mortality rate was higher among males (89.0% decrease) compared to females (67.4% decrease).

DISCUSSION

The purpose of this study was to examine national trends in hospitalization and mortality due to asthma exacerbations in Kuwait using data from hospital discharge records and death certificates. This retrospective analysis of national data showed substantial reductions in asthma hospital admission and mortality rates in Kuwait between 2000 and 2014. Decreases in asthma hospital admissions and mortality rates over the 15-year study period were evident in both sexes, across different age groups, and among Kuwaiti nationals and non-Kuwaiti subjects. On average, females compared to males and Kuwaitis compared to non-Kuwaitis had higher rates of asthma hospitalization and mortality. Children aged < 5 years and adults aged ≥ 65 years had significantly higher hospitalization rates compared to other age groups. Asthma mortality rate among subjects aged ≥ 65 years was pronouncedly elevated in comparison to those aged < 65 years. The observed decreasing trends in hospitalization and mortality rates might be, in part, explained by improved management strategies and treatments and accessibility to high quality health care services.

Up to our knowledge, there has been no recent investigations characterizing trends in asthma hospital admissions and mortality in Kuwait. A previous report estimated asthma hospitalization and mortality rates in Kuwait during two three-year periods: from 1987-to-1989 and 1992-to-1994.[12] In 1994, asthma hospital admission and mortality rates were estimated to be 231.2 admissions and 1.36 deaths per 100,000 population, respectively.[12] In 2014, the latest year in the current analysis, there were 91.3 admissions and 0.9 death per 100,000 population due to asthma-related exacerbations. Hence, this comparison clearly shows substantial reductions, specifically in asthma hospitalization, between 1994 and 2014 in Kuwait.

A main finding in this report is that the estimated asthma hospital admission rate in the total population has reduced markedly from 180.8 admissions per 100,000 population in 2000 to 91.3 admissions per 100,000 population in 2014; translating to a 49.5% decrease. These declining trends were evident in both sexes, different age groups, and Kuwaiti nationals and non-Kuwaiti subjects. Similar declining trends have been observed in different global regions.[16] For instance, between 1997 and 2011 in Costa Rica, asthma hospital admission rate decreased by 53%, with reductions observed among males and females as well as children and adults.[17] Similar to our findings, reports from the United States, Spain, Finland, and Norway have shown significant decreasing trends in asthma hospitalization among the pediatric population.[18-21] A report from the United Kingdom, looking at trends in asthma hospitalization over a 50-year period from 1955 to 2004, indicated that asthma hospital admissions increased until late 1980s and have been declining thereafter.[22] Similarly, a comprehensive report investigating trends in pediatric asthma hospital admissions in developed countries, showed a peak in asthma hospitalizations around 1989-1990 and subsequently progressive declining trends.[23]

In regard to trends in asthma mortality, the current report showed that mortality related to asthma exacerbations has decreased by 77.6% (95% CI: 58.9, 87.8) between 2000 and 2014 in Kuwait. In a global analysis of data from 188 countries, age-standardized asthma mortality rate decreased by 58.8% (95% CI: 39.0, 69.0) between 1990 and 2015.[1] Another study based on data from 46 countries, investigating trends in asthma mortality between 1993 and 2012, showed reductions in asthma deaths between 1993 and 2006, with no further changes from 2006 through to 2012.[24] These international data further support the observed substantial decreases in asthma morality in Kuwait.

To this ends, at a global level, the decreasing trends in asthma hospital admission and mortality rates over the past few decades can be explained, at least in part, by important changes in asthma medical care. These include developments in the pharmacological selectivity and delivery of adrenergic and corticosteroid drugs.[22] Specifically, the wide availability and utilization of long-term asthma control medications, such as inhaled corticosteroids. Moreover, the development of international, regional, and local asthma management guidelines have also contributed to reducing asthma exacerbations and burden. The Global Initiative for Asthma (GINA), established in 1993, has continuously been developing evidence-based strategies for managing and preventing asthma that have been serving the international community at large.[25] Collectively, improved therapeutics that are accessible and quality-assured coupled with patient education and accessibility to quality health care services have contributed to the declining trends in asthma hospitalizations and mortality.

Across the 15-year study period, sex-, age-, and nationality-based disparities in asthma hospitalizations and mortality were observed. Overall, hospital admission rates were higher among females compared to males. However, these sex-based differences were found to vary across age-groups. Among subjects aged ≤ 19 years old, males experienced more asthma hospitalizations compared to females; whereas, among adults, this observation is switched, where asthma hospitalizations become more frequent among females compared to males. Such observations have been reported in previous investigations.[26 27] Studies adjusting for the effect of potential confounders (e.g., obesity, smoking, race) and comorbidities (e.g. chronic obstructive pulmonary diseases), concluded that the age-stratified sex differences in asthma hospitalizations persisted even after adjustments.[28-30] Hence, indicating that causes of such disparities are

multifactorial. Hormonal factors have been speculated to differentially predispose males and females to disease development.[31] For instance, estrogen and progesterone were shown to alter pulmonary function and modify airway responsiveness.[32] However, the exact mechanisms underlying the age-stratified sex disparity in hospitalizations due to asthma exacerbations are not fully elucidated.

Preschool children aged < 5 years and adults aged ≥ 65 years had, on average, higher asthma hospitalization rates (426.5 and 405.1 admissions per 100,000 population, respectively) over the study period than all other age groups; an observation that has been previously reported.[33 34] However, careful interpretation of these age-specific rates should be exercised since diagnosis of asthma in early childhood is challenging[25] and diagnostic overlap of asthma with acute bronchitis and bronchiolitis may occur,[35] which could contribute to the high hospitalization rates observed among preschool children. Among older adults, diagnostic substitution of chronic obstructive pulmonary disease for asthma may occur, leading to the observed elevated asthma hospital admission rates.

Geographical as well as racial/ethnic variations in asthma prevalence, hospital admissions, and mortality have been reported.[3 34] For instance, in the United States, African-Americans had higher asthma hospitalization and mortality rates compared to white subjects.[36] In the Scottish population, South Asians compared to Scottish white subjects had higher rates of asthma hospitalization.[37] The current analysis demonstrated differences in asthma hospitalization rates based on nationality, with Kuwaiti nationals compared to non-Kuwaiti subjects having higher risk of asthma hospitalization. Although this nationality-based variation can be explained, in

part, by the different racial/ethnic background of Kuwaiti and non-Kuwaiti subjects, other factors cannot be excluded. The different sex and age structure of the two populations (non-Kuwaitis mainly being of male gender and working age) could highly confound the observed nationality-based variations. However, both model adjusted rates (see online supplementary table S1) and sex- and age-standardized rates (see online supplementary table S2) showed that Kuwaiti nationals have higher risk of asthma hospitalization and compared to non-Kuwait subjects. Thus, the different sex- and age-structure of the two populations (Kuwaiti and non-Kuwait population) did not explain the observed nationality-based disparity. On the other hand, accessibility to health care, quality of care and treatment, patient education, and social, behavioral, and environmental aspects could be some of the underlying factors for the observed nationality-based differences.[38]

This investigation provided, at a national level, a comprehensive understanding of trends and disparities in hospitalizations and mortality related to asthma exacerbations in Kuwait over a 15-year period. Nonetheless, we acknowledge some limitations, including misclassification of asthma-related hospitalizations or deaths, which is inevitable in epidemiological studies based on routinely collected data, such as data from hospital discharge records and death certificates. Such misclassification could either underestimate or overestimate the frequency of asthma hospitalizations and mortality. However, this is unlikely to fully account for the observed long-term declining trends and the sex-, nationality-, and age-based differences. Moreover, throughout the study period, there were no changes in the ICD disease-coding or coding rules; hence, avoiding the influence of diagnostic shift or procedural changes. Although governmental and private hospitals are required to report health and vital statistics to the NCHI, private hospitals

tend not to fully comply with reporting requirements, which might lead to underestimating the burden of asthma hospitalizations and mortality. However, underreporting, if any, by private hospitals does not directly impact the reported trends. Another limitation is the inability of identifying multiple/repeated hospitalizations for each patient during the same year or over the study period due to the anonymous nature of the analyzed data.

A further limitation is that the analyzed data did not include information on race/ethnicity of patients, which has been shown to be an important factor in asthma hospitalizations and deaths.[37] Rather, information on nationality (Kuwait vs. non-Kuwaiti), a variable that could partially account for the race/ethnicity effect, was available and analysis comparing the two population groups showed that Kuwaiti nationals have higher hospitalization and mortality rates compared to non-Kuwait subjects. On the other hand, a recent report have concluded that caution should be practiced when interpreting declining trends in mortality rates in countries with high influx of migrant workforce, as the case in Kuwait, since such trends could be, in part, attributed to the healthy worker/migrant effect.[39] Although our findings are susceptible to such bias, results of stratified analysis showed that the declining trends in asthma hospital admission and mortality rates were similar in Kuwaiti and non-Kuwaiti subjects (see online supplementary table S2 and figure S1). Hence, the healthy worker/migrant effect does not explain the observed decreasing trends.

In conclusion, this study provided a national perspective on trends and burden of hospital admissions and mortality related to asthma exacerbations in Kuwait between 2000 and 2014. Trend analysis indicated that hospitalization and mortality rates have significantly decreased

over the 15-year study period. The decreasing trends were evident in both sexes, all age groups, and among Kuwaiti nationals and non-Kuwait subjects. Improvements in clinical care and development of targeted interventional strategies could further reduce rates of hospital admissions and mortality related to asthma exacerbations. Nevertheless, sex-, age-, and nationality-based differences in asthma hospitalization and mortality persisted across the study period. Therefore, future etiologic research is needed to address factors underlying such disparities and gaps in knowledge.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Contributors

AHZ: conceived and designed the epidemiologic study, contributed to acquisition of data, analyzed and interpreted the data, and drafted the manuscript. ATA: conceived and designed the epidemiologic study, interpreted the data, and revised the manuscript. All authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by all authors.

Ethics approval

The study was approved by the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait.

Patient consent

Not applicable.

Data sharing statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request at: aziyab@hsc.edu.kw.

Acknowledgements

We would like to thank staff at the National Center for Health Information, Ministry of Health, Kuwait for providing the analyzed data in this manuscript. Specifically, we thank Dr. Fahad Al-Khalifa, Dr. Ali Sadek, and Dr. Gamal Makboul for their cooperation and support.

REFERENCES

1. Collaborators GBDCRD. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:691-706.

2. Asher MI, Montefort S, Bjorksten B*, et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.

3. Lai CK, Beasley R, Crane J*, et al.* Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64:476-83.

4. Holgate ST, Wenzel S, Postma DS*, et al.* Asthma. *Nat Rev Dis Primers* 2015;1:15025.

5. Martinez FD, Vercelli D. Asthma. *Lancet* 2013;382:1360-72.

6. Fuhlbrigge A, Peden D, Apter AJ*, et al.* Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012;129(Suppl 3):S34-48.

7. Sears MR. Epidemiology of asthma exacerbations. *J Allergy Clin Immunol* 2008;122:662-8.

8. Pawankar R, Canonica GW, Holgate ST*, et al.* Allergic diseases and asthma: a major global health concern. *Curr Opin Allergy Clin Immunol* 2012;12:39-41.

9. Owayed A, Behbehani N, Al-Momen J. Changing prevalence of asthma and allergic diseases among Kuwaiti children. An ISAAC Study (Phase III). *Med Princ Pract* 2008;17:284-9.

10. Ziyab AH. Prevalence and Risk Factors of Asthma, Rhinitis, and Eczema and Their Multimorbidity among Young Adults in Kuwait: A Cross-Sectional Study. *BioMed Res Int* 2017;2017:10.

11. Khadadah M. The cost of asthma in Kuwait. *Med Princ Pract* 2013;22:87-91.

12. Abul AT, Nair PC, Behbehanei NA*, et al.* Hospital admissions and death rates from asthma in Kuwait during pre- and post-Gulf War periods. *Ann Allergy Asthma Immunol* 2001;86:465-8.

13. Al-Awadhi JM, Alshuaibi AA. Dust fallout in Kuwait city: deposition and characterization. *Sci Total Environ* 2013;461-462:139-48.

14. De Bel-Air F. The demographic and economic framework of migration in Kuwait: Gulf Labour Market and Migration (GLMM) programme of the Migration Policy Center (MPC) and the Gulf Research Center (GRC), 2013.

15. Ahmad OB, Boschi-Pinto C, Lopez AD*, et al.* Age standardization of rates: a new WHO standard - GPE Discussion Paper Series: 31 EIP/GPE/EBD. *Geneva: World Health Organization* 2001.

16. The Global Asthma Report 2014. *Global Asthma Network* 2014; Auckland, New Zealand.

17. Soto-Martinez M, Avila L, Soto N, *et al.* Trends in hospitalizations and mortality from asthma in Costa Rica over a 12- to 15-year period. *J Allergy Clin Immunol Pract* 2014;2:85-90.

18. Hasegawa K, Tsugawa Y, Brown DF, *et al.* Childhood asthma hospitalizations in the United States, 2000-2009. *J Pediatr* 2013;163:1127-33 e3.

19. de Miguel-Diez J, Jimenez-Garcia R, Hernandez-Barrera V, *et al.* National trends in hospital admissions for asthma exacerbations among pediatric and young adult population in Spain (2002-2010). *Respir Med* 2014;108:983-91.

20. Saynajakangas O, Valmari P, Tuuponen T, *et al.* Trends in hospitalization for childhood asthma in Finland in 1996-2004. *Acta Paediatr* 2007;96:919-23.

21. Mikalsen IB, Skeiseid L, Tveit LM, *et al.* Decline in admissions for childhood asthma, a 26-year period population-based study. *Pediatr Allergy Immunol* 2015;26:750-5.

22. Anderson HR, Gupta R, Strachan DP, *et al.* 50 years of asthma: UK trends from 1955 to 2004. *Thorax* 2007;62:85-90.

23. Chawla J, Seear M, Zhang T, *et al.* Fifty years of pediatric asthma in developed countries: how reliable are the basic data sources? *Pediatr Pulmonol* 2012;47:211-9.

24. Ebmeier S, Thayabaran D, Braithwaite I, *et al.* Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). *Lancet* 2017;390:935-45.

25. Bateman ED, Hurd SS, Barnes PJ*, et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.

26. Chen Y, Stewart P, Johansen H*, et al.* Sex difference in hospitalization due to asthma in relation to age. *J Clin Epidemiol* 2003;56:180-7.

27. Schatz M, Clark S, Camargo CA, Jr. Sex differences in the presentation and course of asthma hospitalizations. *Chest* 2006;129:50-5.

28. Lin RY, Ji R, Liao W. Age dependent sex disproportion in US asthma hospitalization rates, 2000-2010. *Ann Allergy Asthma Immunol* 2013;111:176-81.

29. Chasm RM, Pei YV, Pallin DJ*, et al.* Sex differences in risk of hospitalization among emergency department patients with acute asthma. *Ann Allergy Asthma Immunol* 2015;115:70-2 e1.

30. Goto T, Tsugawa Y, Camargo CA, Jr.*, et al.* Sex differences in the risk of hospitalization among patients presenting to US emergency departments with asthma exacerbation, 2010-2012. *J Allergy Clin Immunol Pract* 2016;4:149-51.

31. Klein SL. Immune cells have sex and so should journal articles. *Endocrinology* 2012;153:2544-50.

32. Haggerty CL, Ness RB, Kelsey S*, et al.* The impact of estrogen and progesterone on asthma. *Ann Allergy Asthma Immunol* 2003;90:284-91.

33. Moorman JE, Akinbami LJ, Bailey CM. National surveillance of asthma: United States, 2001-2010. National Center for Health Statistics. *Vital Health Stat* 2012;3:1-67.

34. Mehal JM, Holman RC, Steiner CA*, et al.* Epidemiology of asthma hospitalizations among American Indian and Alaska Native people and the general United States population. *Chest* 2014;146:624-32.

35. Mansbach JM, Clark S, Teach SJ*, et al.* Children Hospitalized with Rhinovirus Bronchiolitis Have Asthma-Like Characteristics. *J Pediatr* 2016;172:202-04.

36. Gupta RS, Carrion-Carire V, Weiss KB. The widening black/white gap in asthma hospitalizations and mortality. *J Allergy Clin Immunol* 2006;117:351-8.

37. Sheikh A, Steiner MF, Cezard G*, et al.* Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. *BMC Med* 2016;14:3.

38. Shah NM, Shah MA, Behbehani J. Ethnicity, nationality and health care accessibility in Kuwait: a study of hospital emergency room users. *Health Policy Plan* 1996;11:319-28.

39. Chaabna K, Cheema S, Mamtani R. Migrants, healthy worker effect, and mortality trends in the Gulf Cooperation Council countries. *PLoS One* 2017;12:e0179711.

Table 1. Number and average annual rate of asthma hospital admissions and mortality in Kuwait, 2000 to 2014

Characteristic	Number of hospital admissions for asthma (%)	Average annual rate of hospital admissions per 100,000 population[†] (95% CI)	Number of Asthma mortalities (%)	Average annual mortality rate per 100,000 population[‡] (95% CI)
Overall	43,652 (100.0)	134.9 (131.8, 138.1)	484 (100.0)	2.1 (1.8, 2.4)
Sex				
Male	23,784 (54.5)	114.3 (110.4, 118.5)	245 (50.6)	1.8 (1.5, 2.1)
Female	19,868 (45.5)	159.3 (154.6, 164.1)	239 (49.4)	2.5 (2.1, 3.0)
Nationality				
Kuwaiti	27,959 (64.1)	182.5 (177.1, 188.1)	248 (51.2)	2.4 (2.0, 2.8)
Non-Kuwaiti	15,693 (35.9)	99.8 (96.3, 103.5)	236 (48.8)	1.9 (1.6, 2.2)
Age group (years)				
< 5	18,405 (42.1)	426.5 (413.3, 440.1)	16 (3.3)	1.4 (0.9, 2.3)
5 – 19	8,578 (19.7)	81.1 (77.5, 84.9)	21 (4.3)	0.7 (0.5, 1.1)
20 – 44	7,293 (16.7)	34.6 (33.0, 36.1)	99 (20.5)	0.6 (0.5, 0.7)
45 – 64	5,671 (13.0)	92.4 (87.4, 97.7)	124 (25.6)	2.6 (2.2, 3.1)
≥ 65	3,705 (8.5)	405.1 (377.1, 435.1)	224 (46.3)	27.7 (24.2, 31.8)

CI: confidence interval.

[†] Model-adjusted average annual hospital admission rates for asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

[‡] Model-adjusted average annual mortality rates for asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

Table 2. Annual rates and rate ratios of asthma hospital admissions and mortality in Kuwait, 2000 to 2014

Year	Number of hospital admissions for asthma	Hospital admission rate per 100,000 population† (95% CI)	Adjusted hospital admission RR‡ (95% CI)	Number of asthma mortalities	Mortality rate per 100,000 population§ (95% CI)	Adjusted mortality RR‡ (95% CI)
2000	3,004	180.8 (168.7, 193.8)	1.00 (Reference)	39	4.1 (3.0, 5.6)	1.00 (Reference)
2001	3,557	212.4 (199.3, 226.4)	1.18 (1.07, 1.29)	37	3.3 (2.4, 4.6)	0.81 (0.52, 1.25)
2002	3,755	217.7 (204.6, 231.7)	1.20 (1.10, 1.32)	51	4.9 (3.6, 6.6)	1.19 (0.79, 1.78)
2003	3,022	170.1 (158.8, 182.2)	0.94 (0.86, 1.04)	34	2.9 (2.1, 4.1)	0.71 (0.46, 1.11)
2004	2,860	154.5 (144.0, 165.9)	0.86 (0.78, 0.94)	21	2.3 (1.5, 3.5)	0.56 (0.34, 0.93)
2005	3,133	160.4 (149.9, 171.6)	0.89 (0.81, 0.97)	37	2.6 (1.8, 3.6)	0.62 (0.41, 0.96)
2006	2,819	137.2 (127.7, 147.2)	0.76 (0.69, 0.84)	43	2.5 (1.9, 3.4)	0.61 (0.40, 0.92)
2007	2,215	101.3 (93.6, 109.8)	0.56 (0.51, 0.62)	40	2.5 (1.8, 3.6)	0.60 (0.39, 0.92)
2008	2,353	103.5 (95.8, 111.8)	0.57 (0.52, 0.63)	38	2.2 (1.6, 3.0)	0.52 (0.34, 0.81)
2009	2,525	107.8 (100.0, 116.2)	0.59 (0.54, 0.66)	55	3.0 (2.3, 3.9)	0.73 (0.49, 1.08)
2010	2,629	108.3 (100.7, 116.6)	0.60 (0.54, 0.66)	32	1.9 (1.3, 2.6)	0.45 (0.29, 0.71)
2011	3,149	125.3 (117.1, 134.0)	0.69 (0.63, 0.76)	16	1.4 (0.9, 2.2)	0.33 (0.19, 0.58)
2012	2,976	113.9 (106.3, 122.0)	0.63 (0.57, 0.69)	14	0.9 (0.5, 1.4)	0.21 (0.12, 0.38)
2013	3,122	116.1 (108.5, 124.2)	0.64 (0.58, 0.71)	14	0.8 (0.5, 1.3)	0.19 (0.11, 0.34)
2014	2,533	91.3 (84.8, 98.4)	0.51 (0.46, 0.56)	13	0.9 (0.5, 1.6)	0.22 (0.12, 0.41)

RR: rate ratio; CI: confidence interval

† Model-adjusted hospital admission rates for asthma per 100,000 population were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

‡ Rate ratios compared with 2000 (the reference year) are adjusted for age, sex, and nationality.

§ Model-adjusted mortality rates due to asthma per 100,000 population were calculated using Poisson regression while adjusting for sex, nationality, and age group.

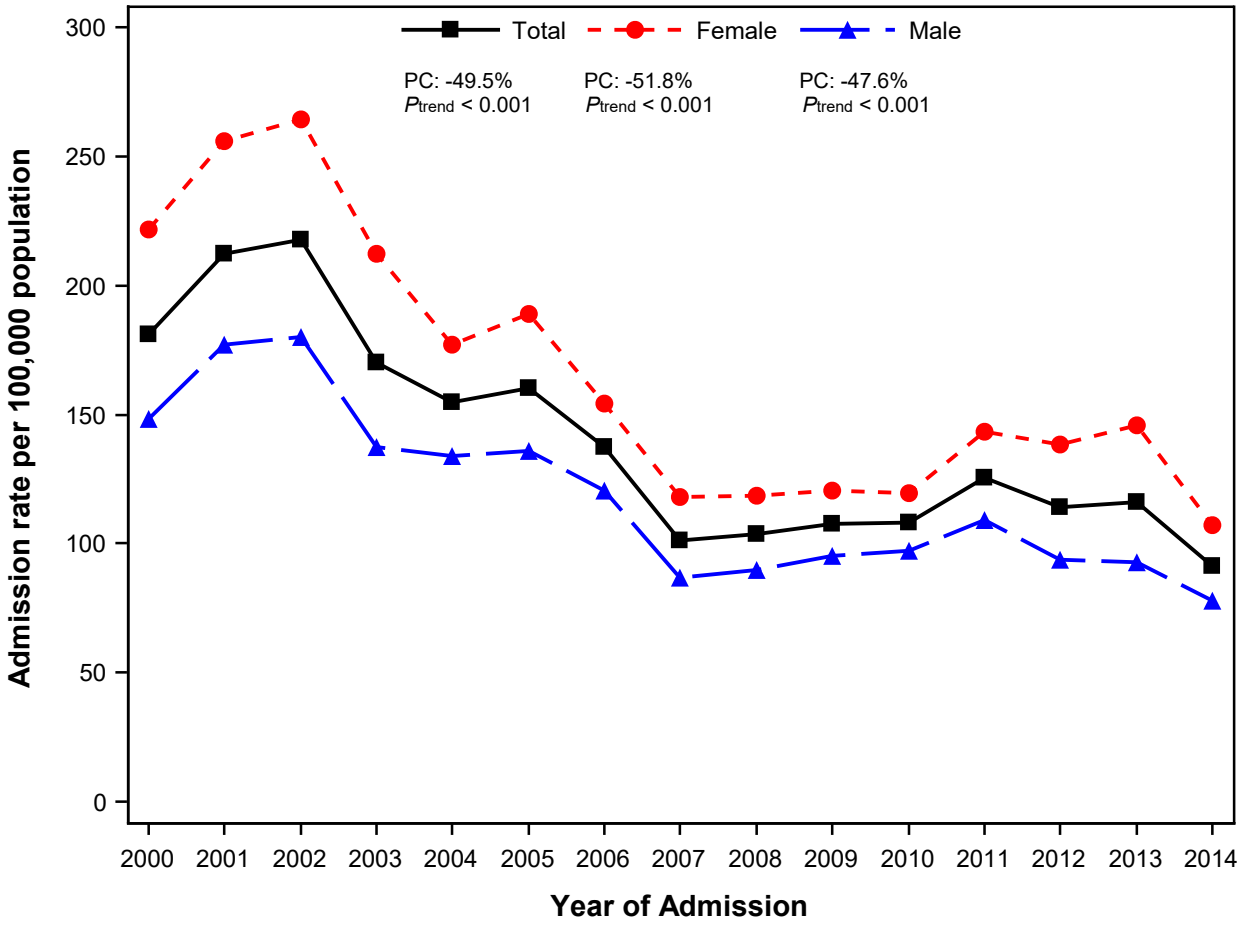
Figure Legends

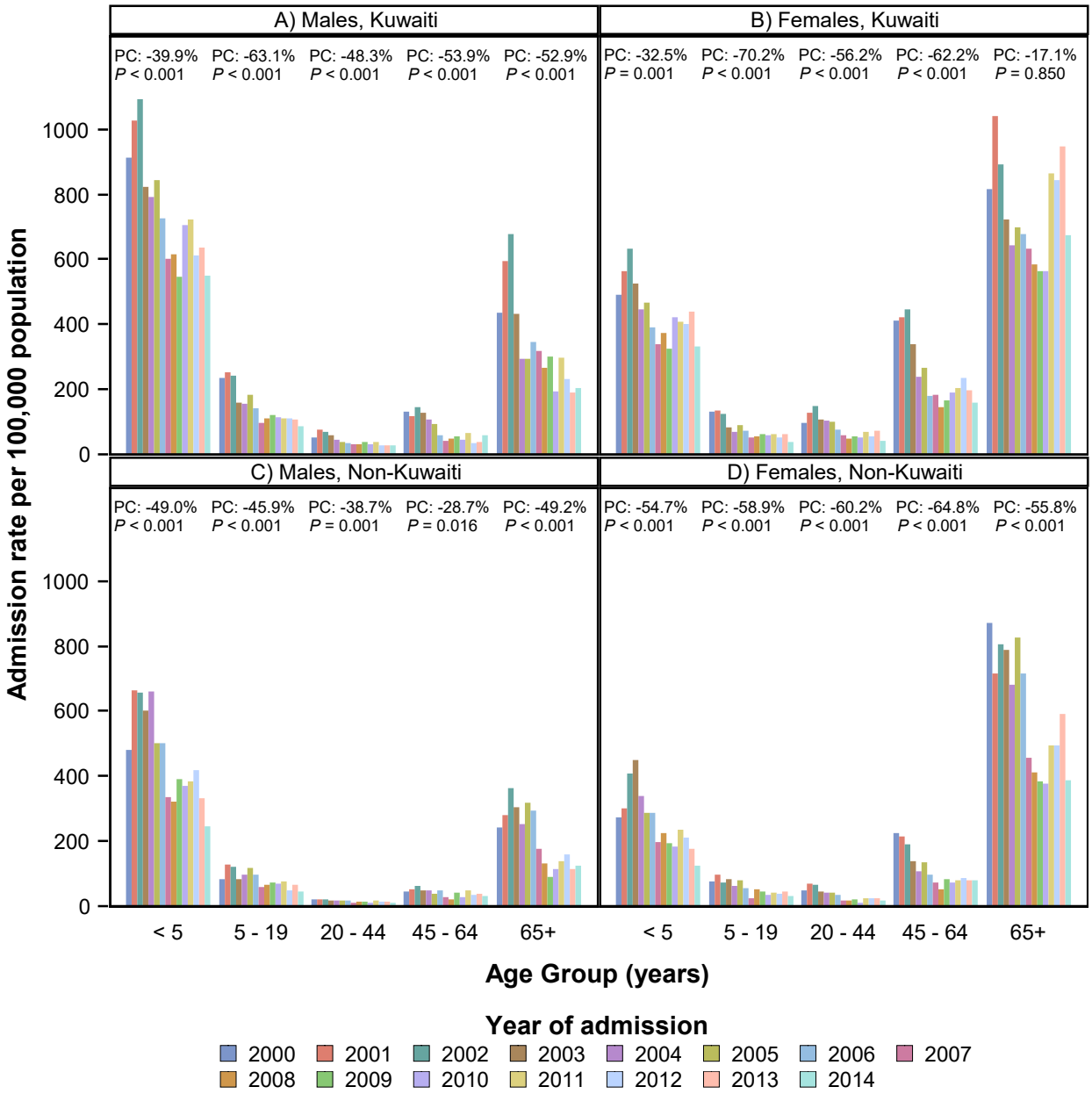
Figure 1. Trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. Admission rates for the total population and by sex are presented. Rates for the total population are sex, age, and nationality model-adjusted. The sex-stratified rates are age and nationality model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis.

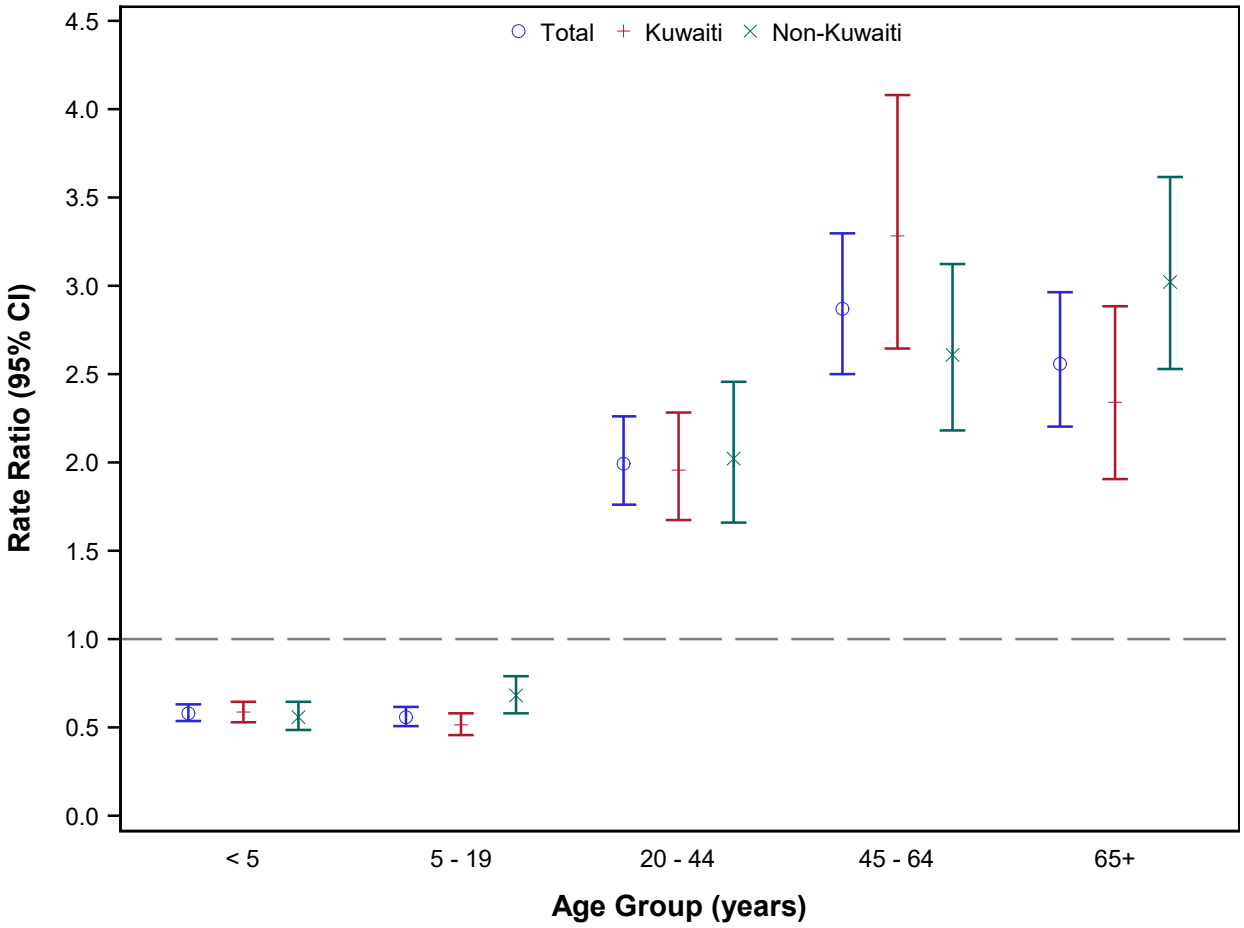
Figure 2. Age-, sex-, and nationality-specific trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. A) Rates among males of Kuwaiti nationality. B) Rates among females of Kuwaiti nationality. C) Rates among males of non-Kuwaiti nationality. D) Rates among females of non-Kuwaiti nationality. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis.

Figure 3. Rate ratios of hospital admission rates for asthma in females vs. males by age group in Kuwait, 2000 to 2014. Rate ratios comparing females to males in the total population and by nationality are presented according to age groups. Rate ratios in the total population were adjusted for nationality.

Figure 4. Rate ratios of asthma mortality rates in Kuwait, 2000 to 2014. Annual mortality rate ratios compared with 2000 (the reference year) are model-adjusted for age, sex, and nationality.


Total
Female
Male
PC: -49.5%
Ptrend < 0.001
PC: -51.8%
Ptrend < 0.001
PC: -47.6%
Ptrend < 0.001
Admission rate per 100,000 population
300
250
200
150
100
50
0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year of Admission


A) Males, Kuwaiti
PC: -39.9% P < 0.001
PC: -63.1% P < 0.001
PC: -48.3% P < 0.001
PC: -53.9% P < 0.001
PC: -52.9% P < 0.001
B) Females, Kuwaiti
PC: -32.5% P = 0.001
PC: -70.2% P < 0.001
PC: -56.2% P < 0.001
PC: -62.2% P < 0.001
PC: -17.1% P = 0.850
C) Males, Non-Kuwaiti
PC: -49.0% P < 0.001
PC: -45.9% P < 0.001
PC: -38.7% P = 0.001
PC: -28.7% P = 0.016
PC: -49.2% P < 0.001
D) Females, Non-Kuwaiti
PC: -54.7% P < 0.001
PC: -58.9% P < 0.001
PC: -60.2% P < 0.001
PC: -64.8% P < 0.001
PC: -55.8% P < 0.001
Admission rate per 100,000 population
0
200
400
600
800
1000
< 5
5 - 19
20 - 44
45 - 64
65+
Age Group (years)
Year of admission
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014


Total
Kuwaiti
Non-Kuwaiti
Rate Ratio (95% CI)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
< 5
5 - 19
20 - 44
45 - 64
65+
Age Group (years)

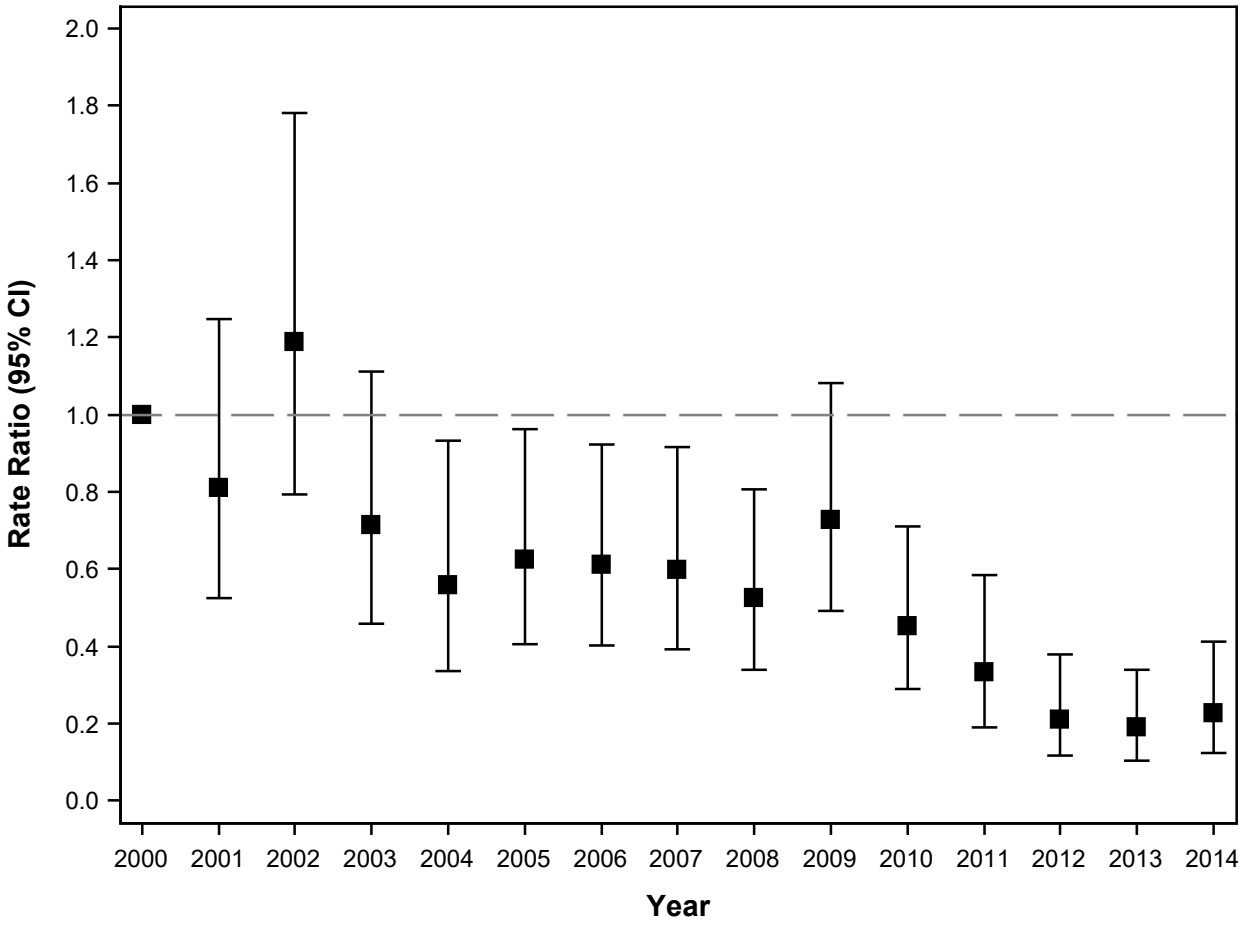

Rate Ratio (95% CI)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year

Table S1. Rates and rate ratios of hospital admissions for asthma comparing Kuwaiti and non-Kuwaiti individuals stratified by sex and age group, 2000 to 2014

	Age group (years)	Nationality	Number of hospital admissions for asthma	Average annual rate of hospital admissions per 100,000 population† (95% CI)	RR‡ (95% CI)
Males	< 5	Kuwaiti	8,318	733.5 (690.3, 779.4)	1.67 (1.49, 1.86)
		Non-Kuwaiti	3,502	440.6 (401.4, 483.7)	1.00
	5 – 19	Kuwaiti	4,077	141.5 (131.7, 152.0)	1.80 (1.57, 2.06)
		Non-Kuwaiti	1,535	78.8 (70.1, 88.4)	1.00
	20 – 44	Kuwaiti	1,061	40.0 (35.6, 44.9)	2.62 (2.27, 3.02)
		Non-Kuwaiti	2,127	15.3 (14.0, 16.6)	1.00
	45 – 64	Kuwaiti	559	73.4 (61.4, 87.8)	1.82 (1.48, 2.25)
		Non-Kuwaiti	1,510	40.3 (36.1, 44.9)	1.00
	≥ 65	Kuwaiti	720	319.9 (289.0, 354.0)	1.65 (1.39, 1.96)
		Non-Kuwaiti	375	194.2 (168.9, 223.3)	1.00
	Total	Kuwaiti	14,735	151.7 (143.9, 159.9)	1.81 (1.69, 1.94)
		Non-Kuwaiti	9,049	83.7 (79.2, 88.5)	1.00
Females	< 5	Kuwaiti	4,711	431.5 (400.8, 464.5)	1.75 (1.52, 2.01)
		Non-Kuwaiti	1,874	246.5 (219.3, 277.0)	1.00
	5 – 19	Kuwaiti	2,025	72.3 (66.5, 78.6)	1.36 (1.17, 1.57)
		Non-Kuwaiti	941	53.2 (47.1, 60.1)	1.00
	20 – 44	Kuwaiti	2,202	76.5 (67.4, 86.9)	2.50 (2.08, 3.01)
		Non-Kuwaiti	1,903	30.6 (26.7, 35.0)	1.00
	45 – 64	Kuwaiti	2,363	240.5 (217.1, 266.4)	2.27 (1.90, 2.70)
		Non-Kuwaiti	1,239	106.1 (92.2, 122.2)	1.00
	≥ 65	Kuwaiti	1,923	751.0 (683.1, 825.8)	1.33 (1.11, 1.59)
		Non-Kuwaiti	687	566.5 (483.8, 663.4)	1.00
	Total	Kuwaiti	13,224	213.2 (202.2, 224.9)	1.88 (1.72, 2.06)
		Non-Kuwaiti	6,644	113.4 (105.2, 122.3)	1.00

RR: rate ratio; CI: confidence interval

† Average annual hospital admission rates for asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models.

‡ Age- and sex- specific rate ratios comparing Kuwaiti to non-Kuwaiti individuals.

Table S2. Sex- and age-standardized rates and rate ratios of asthma hospital admissions in the total population and stratified by nationality in Kuwait, 2000 to 2014

	Sex- and age-standardized asthma hospital admission rate per 100,000 population[†] (95% CI)			
Year	**Total**	**Kuwaiti**	**Non-Kuwaiti**	**RR[‡] (95% CI)**
2000	190.6 (181.6, 199.6)	241.8 (228.8, 254.8)	138.4 (124.5, 152.4)	1.75 (1.56, 1.96)
2001	221.3 (211.8, 230.7)	278.6 (264.8, 292.3)	156.3 (143.0, 169.6)	1.78 (1.62, 1.97)
2002	224.9 (215.7, 234.1)	286.7 (273.1, 300.2)	161.2 (147.8, 174.6)	1.78 (1.62, 1.96)
2003	175.2 (167.3, 183.1)	215.5 (204.0, 226.9)	143.0 (130.5, 155.6)	1.51 (1.36, 1.67)
2004	153.5 (146.5, 160.6)	184.5 (174.3, 194.7)	129.2 (117.9, 140.6)	1.43 (1.29, 1.58)
2005	162.8 (155.6, 169.9)	194.7 (184.6, 204.9)	135.4 (123.9, 146.9)	1.44 (1.30, 1.59)
2006	140.7 (134.1, 147.2)	163.8 (154.5, 173.1)	119.8 (109.4, 130.1)	1.37 (1.23, 1.52)
2007	107.0 (101.3, 112.6)	138.6 (130.1, 147.1)	75.5 (67.7, 83.3)	1.84 (1.63, 2.07)
2008	103.9 (98.6, 109.2)	134.1 (126.1, 142.1)	74.5 (67.2, 81.8)	1.80 (1.61, 2.02)
2009	107.2 (102.0, 112.3)	136.7 (128.7, 144.7)	79.4 (72.5, 86.4)	1.72 (1.55, 1.91)
2010	106.3 (101.3, 111.3)	141.8 (134.0, 149.5)	72.2 (65.6, 78.8)	1.96 (1.77, 2.18)
2011	127.1 (121.6, 132.6)	166.6 (158.0, 175.2)	88.8 (81.6, 95.9)	1.88 (1.71, 2.07)
2012	118.3 (113.1, 123.5)	152.5 (144.5, 160.5)	84.2 (77.3, 91.1)	1.81 (1.64, 2.00)
2013	120.7 (115.6, 125.9)	158.0 (150.1, 166.0)	84.4 (77.4, 91.4)	1.87 (1.70, 2.06)
2014	93.7 (89.3, 98.2)	126.0 (119.0, 133.0)	63.6 (57.8, 69.4)	1.98 (1.78, 2.20)
Average[⁋]	136.3 (134.7, 137.9)	175.3 (172.9, 177.8)	98.8 (96.6, 101.1)	1.77 (1.73, 1.82)

RR: rate ratio; CI: confidence interval

[†] Asthma hospital admission rates per 100,000 population were sex- and age-standardized to the World Health Organization Standard Population.

[‡] Rate ratios comparing sex- and age-standardized hospital admission rates among Kuwaiti to non-Kuwaiti subjects.

[⁋] Average annual sex- and age-standardized asthma hospital admission rates per 100,000 population per year over the period from 2000 to 2014.

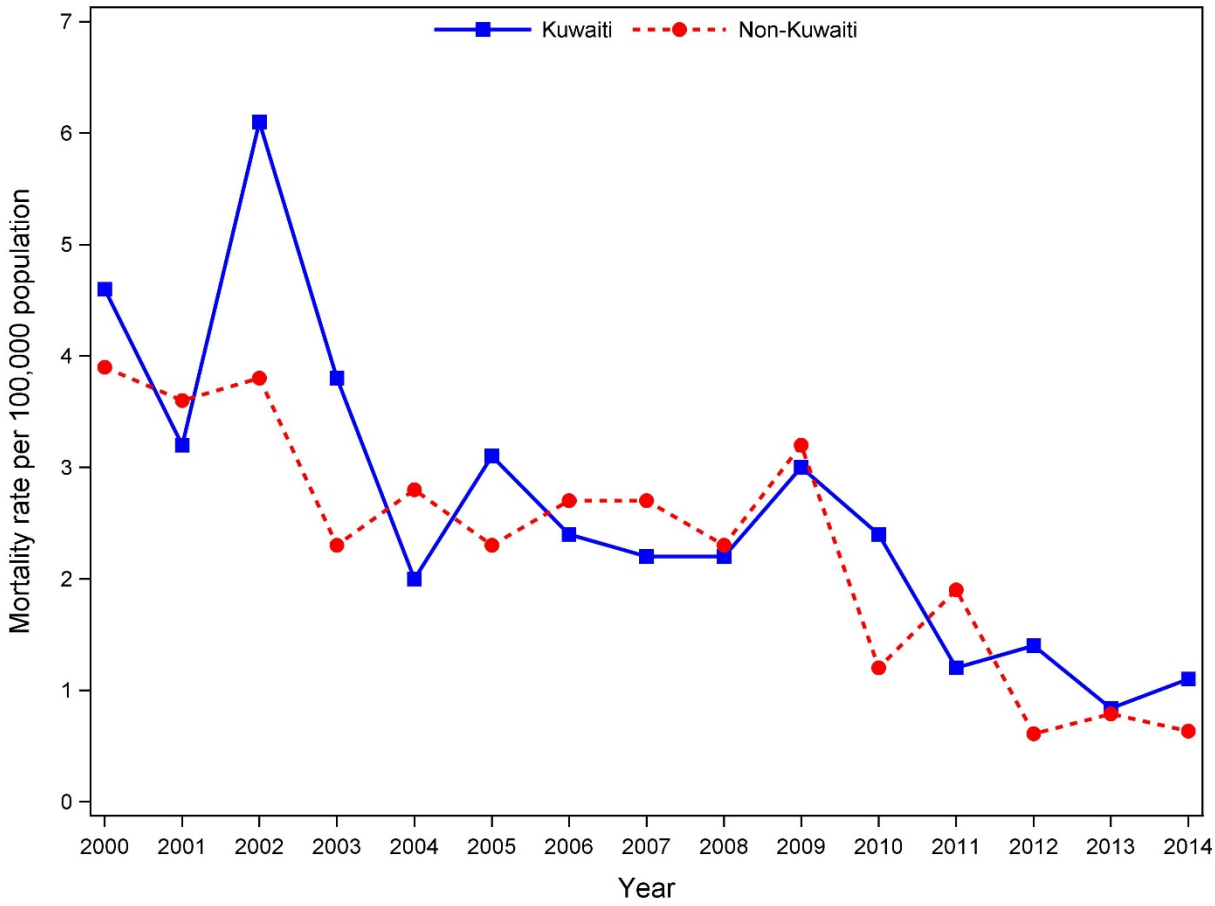


Figure S1. Nationality specific trends in annual asthma mortality rates per 100,000 population in Kuwait, 2000 to 2014. Mortality rates according to nationality (Kuwaiti vs. Non-Kuwaiti) are model-adjusted for age and sex.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends in asthma hospital admissions and mortality in Kuwait, 2000 to 2014: a national retrospective observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021244.R1
Article Type:	Research
Date Submitted by the Author:	16-Feb-2018
Complete List of Authors:	Ziyab, Ali; Kuwait University Faculty of Medicine, Community Medicine Abul, Adnan; Kuwait University Faculty of Medicine, Community Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Respiratory medicine
Keywords:	Epidemiology < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, Asthma Hospitalization, Asthma Mortality

Trends in asthma hospital admissions and mortality in Kuwait, 2000 to 2014: a national retrospective observational study

Authors: Ali H. Ziyab[1], Adnan T. Abul[1,2]

Affiliations:

[1] Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait

[2] Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait

Corresponding author:

Ali H. Ziyab, PhD

Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait.

P. O. Box 24923

Safat 13110, Kuwait

Tel: (+965) 24636545

Fax: (+965) 25338948

Email: aziyab@hsc.edu.kw

Word count: 4,483 words

ABSTRACT

Objectives: To examine trends in asthma hospitalization and mortality rates from 2000 to 2014 in Kuwait according to sex, age, and nationality.

Methods: For this nationwide, retrospective observational study, data from hospital discharge records and death certificates listing asthma as the primary reason for hospitalization or mortality were obtained from the National Center for Health Information database using ICD-10 codes J45 and J46. Annual asthma hospitalization and mortality rates were estimated using the respective mid-year population estimates as denominators. Trends in sex-, age-, and nationality-adjusted hospitalization and mortality rates were examined. Poisson regression models were applied to test for linear trends overtime and estimate adjusted rate ratios (aRR) and 95% confidence intervals (CI).

Results: During the 15-year study period, a total of 43,652 hospitalizations and 484 deaths due to asthma exacerbations were identified. The average annual adjusted rates of asthma hospitalization and mortality were estimated to be 134.9 (95% CI: 131.8, 138.1) and 2.1 (95% CI: 1.8, 2.4) per 100,000 population, respectively. Hospitalization rates decreased by 49.5% in the total population (from 180.8 to 91.3 admissions per 100,000 population between 2000 and 2014, $P_{trend} < 0.001$). Adjusted mortality rate decreased from 4.1 to 0.9 deaths per 100,000 population between 2000 and 2014; a 77.6% decrease ($P_{trend} < 0.001$). Kuwaiti nationals compared to non-Kuwaiti subjects had higher risk of asthma hospitalization (aRR = 1.83, 95% CI: 1.75, 1.92). Among children aged ≤ 19 years, the risk of hospitalization was higher in boys compared to girls; however, among adults, women experienced more hospitalizations than men.

Conclusions: Asthma hospitalization and mortality rates have substantially decreased between 2000 and 2014 in Kuwait, with persisting differences between genders, age groups, and citizens vs. non-citizens. The observed decreasing trends in Kuwait are in agreement with global trends.

Strengths and limitations of this study

- This study provided, at a national level, a comprehensive perspective on trends and disparities in hospitalizations and mortality related to asthma exacerbations in Kuwait over a 15-year period.

- Although data analyzed in the current report were obtained from the National Center for Health Information database using ICD-10 codes J45 and J46, misclassification of asthma-related hospitalizations or deaths is inevitable in epidemiological studies based on routinely collected data, which could either underestimate or overestimate the frequency.

- Lack of information on ethnicity/race of patients is a further limitation to our study.

INTRODUCTION

Asthma is the most common inflammatory chronic disorder of the lungs that affects children and adults. Globally, it was estimated in 2015 that 358 million people suffer from asthma, which reflects a 12.6% increase in asthma prevalence compared to 1990.[1] Whereas, asthma-related mortality, causing 397,000 deaths in 2015, decreased by 26.7% between 1990 and 2015.[1] The International Study of Asthma and Allergies in Childhood (ISAAC) revealed variations in the prevalence of asthma both between and within countries..[2] For instance, among children aged 13 to 14 years old, the 12-month prevalence of asthma symptoms ranged from 3.4% to 31.2%.[3] In Westernized countries, asthma is usually seen in around 10% of the general population.[4] Hence, due to the elevated prevalence, morbidity, and mortality, asthma is considered a global public health problem.

The major pathophysiological hallmarks that contribute to the complex heterogeneity of the clinical manifestations of asthma include recurrent airway inflammation, variable airway obstruction, and bronchial hyper-responsiveness.[5] Asthma exacerbations, defined as "a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome", have been graded in severity from mild to severe and in some instances as life-threatening.[6 7] Exacerbations requiring emergency department visits and hospitalizations are associated with substantial morbidity, medical expenditures, and economic as well as social burden on individuals and families.[6 8] In principle, asthma exacerbations are preventable events in the presence of high quality health care, patient awareness and compliance, and optimal asthma management.

In Kuwait, the burden of asthma is comparable to what is observed in Western nations. For instance, 7.6% and 15.6% of schoolchildren aged 13 to 14 years reported current wheeze and ever doctor-diagnosed asthma, respectively.[9] A recent study showed that 11.9% of university students in Kuwait suffer from asthma.[10] Annually, asthma management and treatment cause a considerable financial burden, costing US$207 million (United States dollar) with hospital admissions accounting for 43% of the total direct costs for asthma treatment in Kuwait.[11] During the period from 1992 to 1994, the annual rate of asthma hospitalization and mortality in Kuwait were estimated to be 205 admissions and 1.59 deaths per 100,000 population, respectively.[12] Given the ongoing improvements in asthma therapeutic and management strategies, we hypothesized that asthma hospitalizations and mortality to have decreased; however, there have been no recent efforts to assess temporal trends in Kuwait. Therefore, this study sought to describe trends in asthma hospital admissions and mortality according to sex, age, and nationality in Kuwait between 2000 and 2014 using national hospital discharge records and death certificates.

METHODS

Study setting

Kuwait, a small country with a total approximate area of 18,000 km^2, is located in the Arabian Peninsula with sandy desert covering its landscape. Generally, the climate in Kuwait is arid with extreme hot temperatures during summer and mild-cool weather in winter and frequent dust storms that occur throughout the year.[13] As of June 2017, the total population was estimated to be around 4.4 million. The population of Kuwait can be divided into two separate communities, namely citizens of Kuwait (Kuwaitis) and labor migrants/expatriates (non-Kuwaitis). Kuwaitis make around 30% (1.3 million) of the population, whereas non-Kuwaitis constitute about 70% (3.1 million) of the population. The majority of the non-Kuwaitis are of Asian ethnicity (1.8 million) and Arab ethnicity (1.2 million). Demographically, the majority of expatriates are males (65%), poorly educated (70% with less than secondary level education), and relatively young (83% aged between 15 and 60 years old).[14] Hence, distorting the demographic distribution of this population towards male and working-age predominance.

Health care services in Kuwait are divided into primary, secondary, and tertiary care. There are six public general hospitals, providing secondary level care, across Kuwait equipped with child and adult emergency departments. Moreover, at a smaller scale, some private hospitals provide emergency care services.

Study design, data sources, and outcomes

In this nationwide, retrospective observational study, we analyzed data from hospital discharge records and death certificates on asthma for the period from January 1, 2000 to December 31,

2014. Public and private hospitals across the state of Kuwait are required to report health and vital statistics data on regular bases to the National Center for Health Information (NCHI) at the Ministry of Health. In this study, data was collected from all hospital discharge records and death certificates listing asthma as the primary reason for admission or death using ICD-10 (International Classification of Diseases, Tenth Revision) codes: J45 (asthma, including predominantly allergic asthma, non-allergic asthma, mixed asthma, asthma unspecified) and J46 (status asthmaticus). In the data extraction process, we included all anonymized asthma-related hospital admission episodes or mortality and collected data on age, sex, and nationality using the NCHI database. If a person has been hospitalized several times for asthma, we counted and considered all admissions per-person as independent events. Annual mid-year population estimates, total and stratified according to sex, age, and nationality, were obtained from the Public Authority for Civil Information, Kuwait. Ethical approval was obtained from the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait.

Statistical analysis

Counts of asthma hospital admissions and deaths resembled the unit of analysis. Five age groups were defined: < 5 years, 5 to 19 years, 20 to 44 years, 45 to 64 years, and ≥ 65 years. Annual and average annual rates of asthma hospital admissions and mortality per 100,000 population were estimated for the 15-year study period (from January 1, 2000 to December 31, 2014) for the total population and stratified according to age group, sex, and nationality. In trend analysis, using calendar year as the exposure variable of interest, annual changes in rates of asthma hospital admissions and mortality were examined. Trend analysis was conducted using the total study sample and a subsample restricted to those aged between 5 and 44 years old. The rationale for

additionally examining trends in those aged 5-44 years old was to minimize the effect of misclassification of asthma hospitalization and mortality among younger and older age groups.[15] Moreover, percent change (PC) in hospitalization and mortality rates comparing the years 2000 and 2014 were calculated as follows: PC = [((rate in 2014 – rate in 2000)/rate in 2000) x 100]. Poisson regression models, with log link function, were used to calculate overall as well as stratified model-adjusted rates and adjusted rate ratios (aRR) and their corresponding 95% confidence intervals (CI) using the GENMOD procedure in SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Regression-based adjustments for age, sex, and nationality were considered when estimating rates and rate ratios. In all regression models, we treated the observed counts of asthma-related hospitalizations/mortality in each year as the outcome variable and the corresponding denominator (i.e., logarithm of mid-year population counts) as an offset term. Additionally, sex- and age-standardized asthma hospital admission rates for the total population and stratified according to nationality were calculated using weights from the World Health Organization (WHO) new World Standard Population.[16] The STDRATE procedure in SAS 9.4 was used to compute directly sex- and age-standardized rates. All statistical analyses were conducted using SAS 9.4. The statistical significance level was set to $\alpha = 0.05$ for all association and trend analyses.

RESULTS

Characteristics and trends of asthma hospital admissions

During the 15-year study period, a total of 43,652 hospital admissions due to asthma exacerbations were identified from hospital discharge records in Kuwait. Of the total hospital admissions, 23,784 (54.5%) were among males, 27,959 (64.1%) were among Kuwaiti individuals, and 18,405 (42.1%) were among children aged < 5 years old (table 1). The sex, age, and nationality model-adjusted average annual rate of asthma hospital admissions was estimated to be 134.9 (95% CI: 131.8, 138.1) admissions per 100,000 population per year. On average, significantly higher hospitalization rates were observed among females compared to males (159.3 vs. 114.3 admissions per 100,000 population per year, $P < 0.001$) and Kuwaiti nationals compared to non-Kuwaiti subjects (182.5 vs. 99.8 admissions per 100,000 population per year, $P < 0.001$). Average annual hospitalization rates were highest among children aged < 5 years (426.5 admissions per 100,000 population) and in adults aged ≥ 65 years (405.1 admissions per 100,000 population), whereas individuals aged 20 to 44 years had the lowest average annual hospitalization rate of 34.6 admissions per 100,000 population (table 1).

Trend analysis showed that asthma hospitalization rates decreased from 180.8 to 91.3 admissions per 100,000 population between 2000 and 2014 in the total population (a 49.5% decrease [95% CI: 44.2, 54.3], $P_{trend} < 0.001$; figure 1A, table 2). Significantly decreasing trends were observed in both sexes, with reductions in admissions rates between 2000 and 2014 amounting to 51.8% in females (from 221.8 to 106.9 admissions per 100,000 population, $P_{trend} < 0.001$) and 47.6% in males (from 148.5 to 77.9 admissions per 100,000 population, $P_{trend} < 0.001$; figure 1B). Similarly, decreasing trends in asthma hospitalization rates were evident among Kuwaiti and

non-Kuwaiti subjects (figure 1C). Among Kuwaiti subjects, hospitalization rate decreased from 251.0 to 128.9 admissions per 100,000 population between 2000 and 2014; representing a 48.6% reduction. Among non-Kuwaiti subjects, hospitalization rate was estimated to be 126.5 admissions per 100,000 population in 2000, and decreased to 63.2 admissions per 100,000 population in 2014; representing a 50.1% reduction.

Similar to the observed trends in the total study sample, analysis among those aged between 5 and 44 years old (referred to as subsample) showed decreasing trends in asthma hospitalization rates. In the total subsample, hospitalization rate decreased from 77.3 to 32.5 admissions per 100,000 population between 2000 and 2014; representing a 57.9% reduction (figure 1D). Sex-stratified analysis of the subsample showed that hospitalization rates have decreased between 2000 and 2014 in both females (from 83.6 to 31.5 admissions per 100,000 population, $P_{trend} < 0.001$) and males (from 71.9 to 33.0 admissions per 100,000 population, $P_{trend} < 0.001$; figure 1E). Similarly, between 2000 and 2014, decreasing trends in hospitalization rates were observed among Kuwaiti individuals (from 116.6 to 44.0 admissions per 100,000 population, $P_{trend} < 0.001$) and non-Kuwait subjects (from 48.8 to 24.2 admissions per 100,000 population, $P_{trend} < 0.001$; figure 1F).

Moreover, using the total study sample, decreasing trends in hospital admission rates were observed in most subgroups stratified according to sex, nationality, and age group (figure 2). For instance, most pronounced decreases in hospitalization rates between 2000 and 2014 among both Kuwaiti males and females were observed among those aged 5 to 19 years old (decrease of 63.1% in males and 70.2% in females, $P_{trend} < 0.001$) when compared to other age groups.

Whereas, non-Kuwaiti males aged < 5 (49.0% decrease, $P_{trend} < 0.001$) and ≥ 65 (49.2% decrease, $P_{trend} < 0.001$) years experienced the highest decreases in hospitalization rates. Among non-Kuwaiti females, those aged 45 to 64 years had a 64.8% decrease in asthma hospital admissions between 2000 and 2014 ($P_{trend} < 0.001$; figure 2).

Characteristics and trends of asthma mortality

A total of 484 asthma deaths were identified over the 15-year study period in Kuwait (table 1). Of the total deaths, 245 (50.6%) were among males, 248 (51.2%) were among Kuwaiti individuals, and 224 (46.3%) were among individuals aged ≥ 65 years old (table 1). The average annual adjusted asthma mortality rate was estimated to be 2.1 (95% CI: 1.8, 2.4) deaths per 100,000 population per year. On average, significantly higher mortality rates were observed among females compared to males (2.5 vs. 1.8 deaths per 100,000 population per year, $P < 0.001$) and Kuwaiti nationals compared to non-Kuwaiti subjects (2.4 vs. 1.9 deaths per 100,000 population per year, $P = 0.010$). Average annual mortality rate was highest among individuals aged ≥ 65 years (27.7 deaths per 100,000 population) and least among those aged 20-44 years (0.6 deaths per 100,000 population; table 1).

Across the study period, asthma mortality rates decreased from 4.1 to 0.9 deaths per 100,000 population between 2000 and 2014 in the total population; translating to a 77.6% (95% CI: 58.9, 87.8, $P_{trend} < 0.001$) reduction (figure 3A, table 2). Among males, asthma mortality rates decreased from 4.1 to 0.5 deaths per 100,000 population between 2000 and 2014. Whereas, among females, asthma mortality rates reduced from 4.3 to 1.4 deaths per 100,000 population between 2000 and 2014. Hence, the magnitude of reduction in mortality rates was higher among

males (89.0% decrease) compared to females (67.4% decrease; figure 3B). Moreover, decreasing trends between 2000 and 2014 in asthma mortality rates were evident among Kuwaiti subjects (from 4.6 to 1.1 deaths per 100,000 population, $P_{trend} < 0.001$) and non-Kuwaiti individuals (from 3.9 to 0.6 deaths per 100,000 population, $P_{trend} < 0.001$; figure 3C).

Furthermore, trends in asthma mortality were examined in a subsample restricted to those aged between 5 and 44 years old. In the total subsample, asthma mortality rates decreased from 0.6 to 0.2 deaths per 100,000 population between 2000 and 2014; representing a 61.9% reduction ($P_{trend} = 0.005$; figure 3D). Mortality rates among females aged 5-44 years old showed decreasing trends across the study period (from 0.7 to 0.3 deaths per 100,000 population, $P_{trend} = 0.005$; figure 3E). In contrast, mortality rates among males aged 5-44 years old did not demonstrate statistically significant decreasing trends ($P_{trend} = 0.207$; figure 3E). Although the decreasing trends in nationality-stratified mortality rates in the subsample did not gain statistical significance, the magnitude of reduction between 2000 and 2014 was higher among non-Kuwaiti subjects (77.9% decrease, $P_{trend} = 0.071$) compared to Kuwaiti individuals (18.4% decrease, $P_{trend} = 0.066$; figure 3F).

Associations between nationality and asthma hospitalization and mortality rates

In regard to nationality disparity in asthma hospitalization, Kuwaiti nationals compared to non-Kuwaiti subjects had higher risk of asthma hospital admission in the total population (aRR = 1.83, 95% CI: 1.75, 1.92). Moreover, our analysis showed that both males and females of Kuwaiti nationality had higher asthma hospitalization rates compared to non-Kuwaitis across all age groups (see online supplementary table S1). Overall, Kuwaiti males had 1.81 times (95% CI:

1.69, 1.94) the risk of hospitalization compared to non-Kuwaiti males. Similarly, Kuwaiti females had 1.88 times (95% CI: 1.72, 2.06; see online supplementary table S1) the risk of hospitalization compared to non-Kuwaiti females.

In regard to asthma mortality, Kuwaiti individuals compared to non-Kuwaiti subjects had higher mortality rate (aRR = 1.29, 95% CI: 1.06, 1.56). Sex-stratified analysis showed that the risk of asthma mortality is similar between Kuwaiti females and non-Kuwaiti females (aRR = 0.85, 95% CI: 0.67, 1.08). In contrast, Kuwaiti males had 1.99 times (95% CI: 1.48, 2.68) the risk of asthma mortality compared to non-Kuwait males.

Sex differences in asthma hospitalization and mortality rates

Overall, females had higher risk of asthma hospitalization compared to males (aRR = 1.39, 95% CI: 1.33, 1.46). However, the sex ratio of asthma hospitalization varied significantly across age groups (figure 4). Among children aged ≤ 19 years, the risk of hospital admission for asthma was significantly lower in females compared to males (age < 5 years: $RR_{female\ vs.\ male}$ = 0.58, 95% CI: 0.54, 0.63; age 5 to 19 years: $RR_{female\ vs.\ male}$ = 0.56, 95% CI: 0.51, 0.62). On the contrary, among those aged ≥ 20 years, asthma hospitalization risk was significantly higher in females compared to males. For instance, among those aged 20 to 44 years old, females had 1.99 times (95% CI: 1.76, 2.26) the risk of hospitalization compared to males. These sex and age specific associations were similar for Kuwaiti and non-Kuwaiti subjects (figure 4).

In general, the risk of asthma mortality was higher among females compared to males (aRR = 1.41, 95% CI: 1.19, 1.68). In age stratified analysis, mortality rates were higher among females

compared to males among those aged 5-19 years ($aRR_{female\ vs.\ male}$ = 1.51, 95% CI: 0.98, 2.32), 20-44 years ($aRR_{female\ vs.\ male}$ = 1.55, 95% CI: 1.10, 2.40), and ≥ 65 years ($aRR_{female\ vs.\ male}$ = 1.50, 95% CI: 1.06, 2.12; see online supplementary table S2).

DISCUSSION

The purpose of this study was to examine national trends in hospitalization and mortality due to asthma exacerbations in Kuwait using data from hospital discharge records and death certificates. This retrospective analysis of national data showed substantial reductions in asthma hospital admission and mortality rates in Kuwait between 2000 and 2014. Decreases in asthma hospital admissions and mortality rates over the 15-year study period were evident in both sexes, across different age groups, and among Kuwaiti nationals and non-Kuwaiti subjects. On average, females compared to males and Kuwaitis compared to non-Kuwaitis had higher rates of asthma hospitalization and mortality. Children aged < 5 years and adults aged ≥ 65 years had significantly higher hospitalization rates compared to other age groups. Asthma mortality rate among subjects aged ≥ 65 years was pronouncedly elevated in comparison to those aged < 65 years. The observed decreasing trends in hospitalization and mortality rates might be, in part, explained by improved management strategies and treatments and accessibility to high quality health care services.

Up to our knowledge, there have been no recent investigations characterizing trends in asthma hospital admissions and mortality in Kuwait. A previous report estimated asthma hospitalization and mortality rates in Kuwait during two three-year periods: from 1987-to-1989 and 1992-to-1994.[12] In 1994, asthma hospital admission and mortality rates were estimated to be 231.2 admissions and 1.36 deaths per 100,000 population, respectively.[12] In 2014, the latest year in the current analysis, there were 91.3 admissions and 0.9 deaths per 100,000 population due to asthma exacerbations. Hence, this comparison clearly shows substantial reductions, specifically in asthma hospitalization, between 1994 and 2014 in Kuwait.

A main finding in this report is that the estimated asthma hospital admission rate in the total population has reduced markedly from 180.8 admissions per 100,000 population in 2000 to 91.3 admissions per 100,000 population in 2014; translating to a 49.5% decrease. These declining trends were evident in both sexes, different age groups, and Kuwaiti nationals and non-Kuwaiti subjects. Moreover, comparable declining trends were observed in the subsample restricted to those aged 5-44 years old. Similar declining trends have been observed in different global regions.[17] For instance, between 1997 and 2011 in Costa Rica, asthma hospital admission rate decreased by 53%, with reductions observed among males and females as well as children and adults.[18] Similar to our findings, reports from the United States, Spain, Finland, and Norway have shown significant decreasing trends in asthma hospitalization among the pediatric population.[19-22] A report from the United Kingdom, looking at trends in asthma hospitalization over a 50-year period from 1955 to 2004, indicated that asthma hospital admissions increased until late 1980s and have been declining thereafter.[23] Similarly, a comprehensive report investigating trends in pediatric asthma hospital admissions in developed countries, showed a peak in asthma hospitalizations around 1989-1990 and subsequently progressive declining trends.[24]

In regard to trends in asthma mortality, the current report showed that mortality related to asthma exacerbations has decreased by 77.6% between 2000 and 2014 in Kuwait in the total study sample and by 61.9% in the 5-44 year age group. In a global analysis of data from 188 countries, age-standardized asthma mortality rate decreased by 58.8% (95% CI: 39.0, 69.0) between 1990 and 2015.[1] Another study based on data from 46 countries, investigating trends in asthma mortality between 1993 and 2012, showed reductions in asthma deaths between 1993 and 2006,

with no further changes from 2006 to 2012.[15] These international data further support the observed decreases in asthma morality in Kuwait.

To this end, at a global level, the decreasing trends in asthma hospital admission and mortality rates over the past few decades can be explained, at least in part, by important changes in asthma medical care. These include developments in the pharmacological selectivity and delivery of adrenergic and corticosteroid drugs.[23] Specifically, the wide availability and utilization of long-term asthma control medications, such as inhaled corticosteroids. Moreover, the development of international, regional, and local asthma management guidelines have also contributed to reducing asthma exacerbations and burden. The Global Initiative for Asthma (GINA), established in 1993, has continuously been developing evidence-based strategies for managing and preventing asthma that have been serving the international community at large.[25] Collectively, improved therapeutics that are accessible and quality-assured coupled with patient education and accessibility to quality health care services have contributed to the declining trends in asthma hospitalizations and mortality.

Across the 15-year study period, sex-, age-, and nationality-based disparities in asthma hospitalizations and mortality were observed. Overall, hospital admission rates were higher among females compared to males. However, these sex-based differences were found to vary across age-groups. Among subjects aged ≤ 19 years old, males experienced more asthma hospitalizations compared to females; whereas, among adults, this observation is switched, where asthma hospitalizations become more frequent among females compared to males. Such observations have been reported in previous investigations.[26 27] Studies adjusting for the effect of

potential confounders (e.g., obesity, smoking, race) and comorbidities (e.g. chronic obstructive pulmonary diseases), concluded that the age-stratified sex differences in asthma hospitalizations persisted even after adjustments.[28-30] Hormonal factors have been speculated to differentially predispose males and females to disease development.[31] For instance, estrogen and progesterone were shown to alter pulmonary function and modify airway responsiveness.[32] However, the exact mechanisms underlying the age-stratified sex disparity in hospitalizations due to asthma exacerbations are not fully elucidated.

Preschool children aged < 5 years and adults aged ≥ 65 years had, on average, higher asthma hospitalization rates (426.5 and 405.1 admissions per 100,000 population, respectively) over the study period than all other age groups; an observation that has been previously reported.[33 34] However, careful interpretation of these age-specific rates should be exercised since diagnosis of asthma in early childhood is challenging[25] and diagnostic overlap of asthma with acute bronchitis and bronchiolitis may occur,[35] which could contribute to the high hospitalization rates observed among preschool children. Among older adults, diagnostic substitution of chronic obstructive pulmonary disease for asthma may occur, leading to the observed elevated asthma hospital admission rates. Hence, as an attempt to lessen the effect of misclassification in the younger and older age groups, trends, in the current report, were additionally examined in a subsample restricted to individuals aged 5-44 years old.

Geographical as well as racial/ethnic variations in asthma prevalence, hospital admissions, and mortality have been reported.[3 34] For instance, in the United States, African-Americans had higher asthma hospitalization and mortality rates compared to white subjects.[36] In the Scottish

population, South Asians compared to Scottish white subjects had higher rates of asthma hospitalization.[37] The current analysis demonstrated differences in asthma hospitalization rates based on nationality, with Kuwaiti nationals compared to non-Kuwaiti subjects having higher risk of asthma hospitalization. We speculate that the different racial/ethnic backgrounds of Kuwaiti and non-Kuwait subjects to be one explanatory factor of the observed nationality-based variation; however, the analyzed data lacked precise information on race/ethnic groups of study subjects. Hence, we could not delineate the effect of race/ethnicity in the current report. The different sex and age structure of the two populations (non-Kuwaitis mainly being of male gender and working age) could highly confound the observed nationality-based variation. However, both model adjusted rates (see online supplementary table S1) and sex- and age-standardized rates (see online supplementary table S3) showed that Kuwaiti nationals have higher risk of asthma hospitalization compared to non-Kuwait subjects. Thus, the different sex- and age-structure of the two populations (Kuwaiti and non-Kuwait population) did not explain the observed nationality-based disparity. On the other hand, accessibility to health care, quality of care and treatment, patient education, and social, behavioral, and environmental aspects could be some of the underlying factors for the observed nationality-based differences.[38]

This investigation provided, at a national level, a comprehensive understanding of trends and disparities in hospitalizations and mortality related to asthma exacerbations in Kuwait over a 15-year period. Nonetheless, we acknowledge some limitations, including misclassification of asthma-related hospitalizations or deaths, which is inevitable in epidemiological studies based on routinely collected data, such as data from hospital discharge records and death certificates. Such misclassification could either underestimate or overestimate the frequency of asthma

hospitalizations and mortality. However, this is unlikely to fully account for the observed long-term declining trends and the sex-, nationality-, and age-based differences. Moreover, throughout the study period, there were no changes in the ICD disease-coding or coding rules; hence, avoiding the influence of diagnostic shift or procedural changes. Although governmental and private hospitals are required to report health and vital statistics to the NCHI, private hospitals tend not to fully comply with reporting requirements, which might lead to underestimating the burden of asthma hospitalizations and mortality. However, underreporting, if any, by private hospitals does not directly impact the reported trends since the Ministry of Health has not relaxed the policies and requirements of reporting health and vital statistics. Moreover, to estimate the relative contributions of public and private hospitals to the data, we used the number of beds as a proxy measure due to the lack of information on the reporting hospitals in the analyzed data. In 2014, there were 6962 (86.8%) beds in public hospitals and 1058 (13.2%) beds in private hospitals (Annual Health Report, NCHI, 2014); hence, we expect that the majority of the analyzed data was reported by public hospitals and any underreporting by private hospitals should not majorly impact results and conclusions of the current report. Another limitation is the inability of identifying multiple/repeated hospitalizations for each patient during the same year or over the study period due to the anonymous nature of the analyzed data.

A further limitation is that the analyzed data did not include information on race/ethnicity of patients, which has been shown to be an important factor in asthma hospitalizations and deaths.[37] Rather, information on nationality (Kuwaiti vs. non-Kuwaiti), a variable that could partially account for the race/ethnicity effect, was available and analysis comparing the two population groups showed that Kuwaiti nationals have higher hospitalization and mortality rates compared

to non-Kuwaiti subjects. On the other hand, a recent report have concluded that caution should be practiced when interpreting declining trends in mortality rates in countries with high influx of migrant workforce, as the case in Kuwait, since such trends could be, in part, attributed to the healthy worker/migrant effect.[39] Although our findings are susceptible to such bias, results of stratified analysis showed that the declining trends in asthma hospital admission and mortality rates were similar in Kuwaiti and non-Kuwaiti subjects (see figure 1C and figure 3C). Hence, the healthy worker/migrant effect does not explain the observed decreasing trends.

In conclusion, this study provided a national perspective on trends and burden of hospital admissions and mortality related to asthma exacerbations in Kuwait between 2000 and 2014. Trend analysis indicated that hospitalization and mortality rates have significantly decreased over the 15-year study period. The decreasing trends were evident in both sexes, all age groups, and among Kuwaiti nationals and non-Kuwaiti subjects. Improvements in clinical care and development of targeted interventional strategies could further reduce rates of hospital admissions and mortality related to asthma exacerbations. Nevertheless, sex-, age-, and nationality-based differences in asthma hospitalization and mortality persisted across the study period. Therefore, future etiologic research is needed to address factors underlying such disparities and gaps in knowledge.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Contributors

AHZ: conceived and designed the epidemiologic study, contributed to acquisition of data, analyzed and interpreted the data, and drafted the manuscript. ATA: conceived and designed the epidemiologic study, interpreted the data, and revised the manuscript. All authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by all authors.

Ethics approval

The study was approved by the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait.

Patient consent

Not applicable.

Data sharing statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request at: aziyab@hsc.edu.kw.

Acknowledgements

We would like to thank staff at the National Center for Health Information, Ministry of Health, Kuwait, for providing the analyzed data in this manuscript. Specifically, we thank Dr. Fahad Al-Khalifa, Dr. Ali Sadek, and Dr. Gamal Makboul for their cooperation and support.

REFERENCES

1. Collaborators GBDCRD. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:691-706.

2. Asher MI, Montefort S, Bjorksten B*, et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.

3. Lai CK, Beasley R, Crane J*, et al.* Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64:476-83.

4. Holgate ST, Wenzel S, Postma DS*, et al.* Asthma. *Nat Rev Dis Primers* 2015;1:15025.

5. Martinez FD, Vercelli D. Asthma. *Lancet* 2013;382:1360-72.

6. Fuhlbrigge A, Peden D, Apter AJ*, et al.* Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012;129(Suppl 3):S34-48.

7. Sears MR. Epidemiology of asthma exacerbations. *J Allergy Clin Immunol* 2008;122:662-8; quiz 69-70.

8. Pawankar R, Canonica GW, Holgate ST*, et al.* Allergic diseases and asthma: a major global health concern. *Curr Opin Allergy Clin Immunol* 2012;12:39-41.

9. Owayed A, Behbehani N, Al-Momen J. Changing prevalence of asthma and allergic diseases among Kuwaiti children. An ISAAC Study (Phase III). *Med Princ Pract* 2008;17:284-9.

10. Ziyab AH. Prevalence and Risk Factors of Asthma, Rhinitis, and Eczema and Their Multimorbidity among Young Adults in Kuwait: A Cross-Sectional Study. *BioMed Research International* 2017;2017:10.

11. Khadadah M. The cost of asthma in Kuwait. *Med Princ Pract* 2013;22:87-91.

12. Abul AT, Nair PC, Behbehanei NA*, et al.* Hospital admissions and death rates from asthma in Kuwait during pre- and post-Gulf War periods. *Ann Allergy Asthma Immunol* 2001;86:465-8.

13. Al-Awadhi JM, Alshuaibi AA. Dust fallout in Kuwait city: deposition and characterization. *Sci Total Environ* 2013;461-462:139-48.

14. De Bel-Air F. The demographic and economic framework of migration in Kuwait: Gulf Labour Market and Migration (GLMM) programme of the Migration Policy Center (MPC) and the Gulf Research Center (GRC), 2013.

15. Ebmeier S, Thayabaran D, Braithwaite I*, et al.* Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). *Lancet* 2017;390:935-45.

16. Ahmad OB, Boschi-Pinto C, Lopez AD, *et al.* Age standardization of rates: a new WHO standard - GPE Discussion Paper Series: 31 EIP/GPE/EBD. *Geneva: World Health Organization* 2001

17. The Global Asthma Report 2014. *Global Asthma Network* 2014; Auckland, New Zealand

18. Soto-Martinez M, Avila L, Soto N, *et al.* Trends in hospitalizations and mortality from asthma in Costa Rica over a 12- to 15-year period. *J Allergy Clin Immunol Pract* 2014;2:85-90.

19. Hasegawa K, Tsugawa Y, Brown DF, *et al.* Childhood asthma hospitalizations in the United States, 2000-2009. *J Pediatr* 2013;163:1127-33 e3.

20. de Miguel-Diez J, Jimenez-Garcia R, Hernandez-Barrera V, *et al.* National trends in hospital admissions for asthma exacerbations among pediatric and young adult population in Spain (2002-2010). *Respir Med* 2014;108:983-91.

21. Saynajakangas O, Valmari P, Tuuponen T, *et al.* Trends in hospitalization for childhood asthma in Finland in 1996-2004. *Acta Paediatr* 2007;96:919-23.

22. Mikalsen IB, Skeiseid L, Tveit LM, *et al.* Decline in admissions for childhood asthma, a 26-year period population-based study. *Pediatr Allergy Immunol* 2015;26:750-5.

23. Anderson HR, Gupta R, Strachan DP, *et al.* 50 years of asthma: UK trends from 1955 to 2004. *Thorax* 2007;62:85-90.

24. Chawla J, Seear M, Zhang T, *et al.* Fifty years of pediatric asthma in developed countries: how reliable are the basic data sources? *Pediatr Pulmonol* 2012;47:211-9.

25. Bateman ED, Hurd SS, Barnes PJ*, et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.

26. Chen Y, Stewart P, Johansen H*, et al.* Sex difference in hospitalization due to asthma in relation to age. *J Clin Epidemiol* 2003;56:180-7.

27. Schatz M, Clark S, Camargo CA, Jr. Sex differences in the presentation and course of asthma hospitalizations. *Chest* 2006;129:50-5.

28. Lin RY, Ji R, Liao W. Age dependent sex disproportion in US asthma hospitalization rates, 2000-2010. *Ann Allergy Asthma Immunol* 2013;111:176-81.

29. Chasm RM, Pei YV, Pallin DJ*, et al.* Sex differences in risk of hospitalization among emergency department patients with acute asthma. *Ann Allergy Asthma Immunol* 2015;115:70-2 e1.

30. Goto T, Tsugawa Y, Camargo CA, Jr.*, et al.* Sex differences in the risk of hospitalization among patients presenting to US emergency departments with asthma exacerbation, 2010-2012. *J Allergy Clin Immunol Pract* 2016;4:149-51 e2.

31. Klein SL. Immune cells have sex and so should journal articles. *Endocrinology* 2012;153:2544-50.

32. Haggerty CL, Ness RB, Kelsey S*, et al.* The impact of estrogen and progesterone on asthma. *Ann Allergy Asthma Immunol* 2003;90:284-91; quiz 91-3, 347.

33. Moorman JE, Akinbami LJ, Bailey CM. National surveillance of asthma: United States, 2001-2010. National Center for Health Statistics. *Vital Health Stat* 2012;3:1-67.

34. Mehal JM, Holman RC, Steiner CA*, et al.* Epidemiology of asthma hospitalizations among American Indian and Alaska Native people and the general United States population. *Chest* 2014;146:624-32.

35. Mansbach JM, Clark S, Teach SJ*, et al.* Children Hospitalized with Rhinovirus Bronchiolitis Have Asthma-Like Characteristics. *J Pediatr* 2016;172:202-04 e1.

36. Gupta RS, Carrion-Carire V, Weiss KB. The widening black/white gap in asthma hospitalizations and mortality. *J Allergy Clin Immunol* 2006;117:351-8.

37. Sheikh A, Steiner MF, Cezard G*, et al.* Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. *BMC Med* 2016;14:3.

38. Shah NM, Shah MA, Behbehani J. Ethnicity, nationality and health care accessibility in Kuwait: a study of hospital emergency room users. *Health Policy Plan* 1996;11:319-28.

39. Chaabna K, Cheema S, Mamtani R. Migrants, healthy worker effect, and mortality trends in the Gulf Cooperation Council countries. *PLoS One* 2017;12:e0179711.

Table 1. Number and average annual rate of asthma hospital admissions and mortality in Kuwait, 2000 to 2014

Characteristic	Number of hospital admissions for asthma (%)	Average annual rate of hospital admissions per 100,000 population[†] (95% CI)	Number of Asthma mortalities (%)	Average annual mortality rate per 100,000 population[‡] (95% CI)
Overall	43,652 (100.0)	134.9 (131.8, 138.1)	484 (100.0)	2.1 (1.8, 2.4)
Sex				
Male	23,784 (54.5)	114.3 (110.4, 118.5)	245 (50.6)	1.8 (1.5, 2.1)
Female	19,868 (45.5)	159.3 (154.6, 164.1)	239 (49.4)	2.5 (2.1, 3.0)
Nationality				
Kuwaiti	27,959 (64.1)	182.5 (177.1, 188.1)	248 (51.2)	2.4 (2.0, 2.8)
Non-Kuwaiti	15,693 (35.9)	99.8 (96.3, 103.5)	236 (48.8)	1.9 (1.6, 2.2)
Age group (years)				
< 5	18,405 (42.1)	426.5 (413.3, 440.1)	16 (3.3)	1.4 (0.9, 2.3)
5 – 19	8,578 (19.7)	81.1 (77.5, 84.9)	21 (4.3)	0.7 (0.5, 1.1)
20 – 44	7,293 (16.7)	34.6 (33.0, 36.1)	99 (20.5)	0.6 (0.5, 0.7)
45 – 64	5,671 (13.0)	92.4 (87.4, 97.7)	124 (25.6)	2.6 (2.2, 3.1)
≥ 65	3,705 (8.5)	405.1 (377.1, 435.1)	224 (46.3)	27.7 (24.2, 31.8)

CI: confidence interval.

[†] Model-adjusted average annual hospital admission rates for asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

[‡] Model-adjusted average annual mortality rates due to asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

Table 2. Annual rates and rate ratios of asthma hospital admissions and mortality in Kuwait, 2000 to 2014

Year	Number of hospital admissions for asthma	Hospital admission rate per 100,000 population† (95% CI)	Adjusted hospital admission RR‡ (95% CI)	Number of asthma mortalities	Mortality rate per 100,000 population§ (95% CI)	Adjusted mortality RR‡ (95% CI)
2000	3,004	180.8 (168.7, 193.8)	1.00 (Reference)	39	4.1 (3.0, 5.6)	1.00 (Reference)
2001	3,557	212.4 (199.3, 226.4)	1.18 (1.07, 1.29)	37	3.3 (2.4, 4.6)	0.81 (0.52, 1.25)
2002	3,755	217.7 (204.6, 231.7)	1.20 (1.10, 1.32)	51	4.9 (3.6, 6.6)	1.19 (0.79, 1.78)
2003	3,022	170.1 (158.8, 182.2)	0.94 (0.86, 1.04)	34	2.9 (2.1, 4.1)	0.71 (0.46, 1.11)
2004	2,860	154.5 (144.0, 165.9)	0.86 (0.78, 0.94)	21	2.3 (1.5, 3.5)	0.56 (0.34, 0.93)
2005	3,133	160.4 (149.9, 171.6)	0.89 (0.81, 0.97)	37	2.6 (1.8, 3.6)	0.62 (0.41, 0.96)
2006	2,819	137.2 (127.7, 147.2)	0.76 (0.69, 0.84)	43	2.5 (1.9, 3.4)	0.61 (0.40, 0.92)
2007	2,215	101.3 (93.6, 109.8)	0.56 (0.51, 0.62)	40	2.5 (1.8, 3.6)	0.60 (0.39, 0.92)
2008	2,353	103.5 (95.8, 111.8)	0.57 (0.52, 0.63)	38	2.2 (1.6, 3.0)	0.52 (0.34, 0.81)
2009	2,525	107.8 (100.0, 116.2)	0.59 (0.54, 0.66)	55	3.0 (2.3, 3.9)	0.73 (0.49, 1.08)
2010	2,629	108.3 (100.7, 116.6)	0.60 (0.54, 0.66)	32	1.9 (1.3, 2.6)	0.45 (0.29, 0.71)
2011	3,149	125.3 (117.1, 134.0)	0.69 (0.63, 0.76)	16	1.4 (0.9, 2.2)	0.33 (0.19, 0.58)
2012	2,976	113.9 (106.3, 122.0)	0.63 (0.57, 0.69)	14	0.9 (0.5, 1.4)	0.21 (0.12, 0.38)
2013	3,122	116.1 (108.5, 124.2)	0.64 (0.58, 0.71)	14	0.8 (0.5, 1.3)	0.19 (0.11, 0.34)
2014	2,533	91.3 (84.8, 98.4)	0.51 (0.46, 0.56)	13	0.9 (0.5, 1.6)	0.22 (0.12, 0.41)

RR: rate ratio; CI: confidence interval.

† Model-adjusted hospital admission rates for asthma per 100,000 population were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

‡ Rate ratios compared with 2000 (the reference year) are adjusted for age, sex, and nationality.

§ Model-adjusted mortality rates due to asthma per 100,000 population were calculated using Poisson regression while adjusting for sex, nationality, and age group.

Figure Legends

Figure 1. Trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. Asthma hospital admission rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis.

Figure 2. Age-, sex-, and nationality-specific trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. A) Rates among males of Kuwaiti nationality. B) Rates among females of Kuwaiti nationality. C) Rates among males of non-Kuwaiti nationality. D) Rates among females of non-Kuwaiti nationality. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis.

Figure 3. Trends in annual asthma mortality rates per 100,000 population in Kuwait, 2000 to 2014. Asthma mortality rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total

study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis. *PC is given as rate in 2014 vs. rate in 2001.

Figure 4. Rate ratios of hospital admission rates for asthma in females vs. males by age group in Kuwait, 2000 to 2014. Rate ratios comparing females to males in the total population and by nationality are presented according to age groups. Rate ratios in the total population were adjusted for nationality.

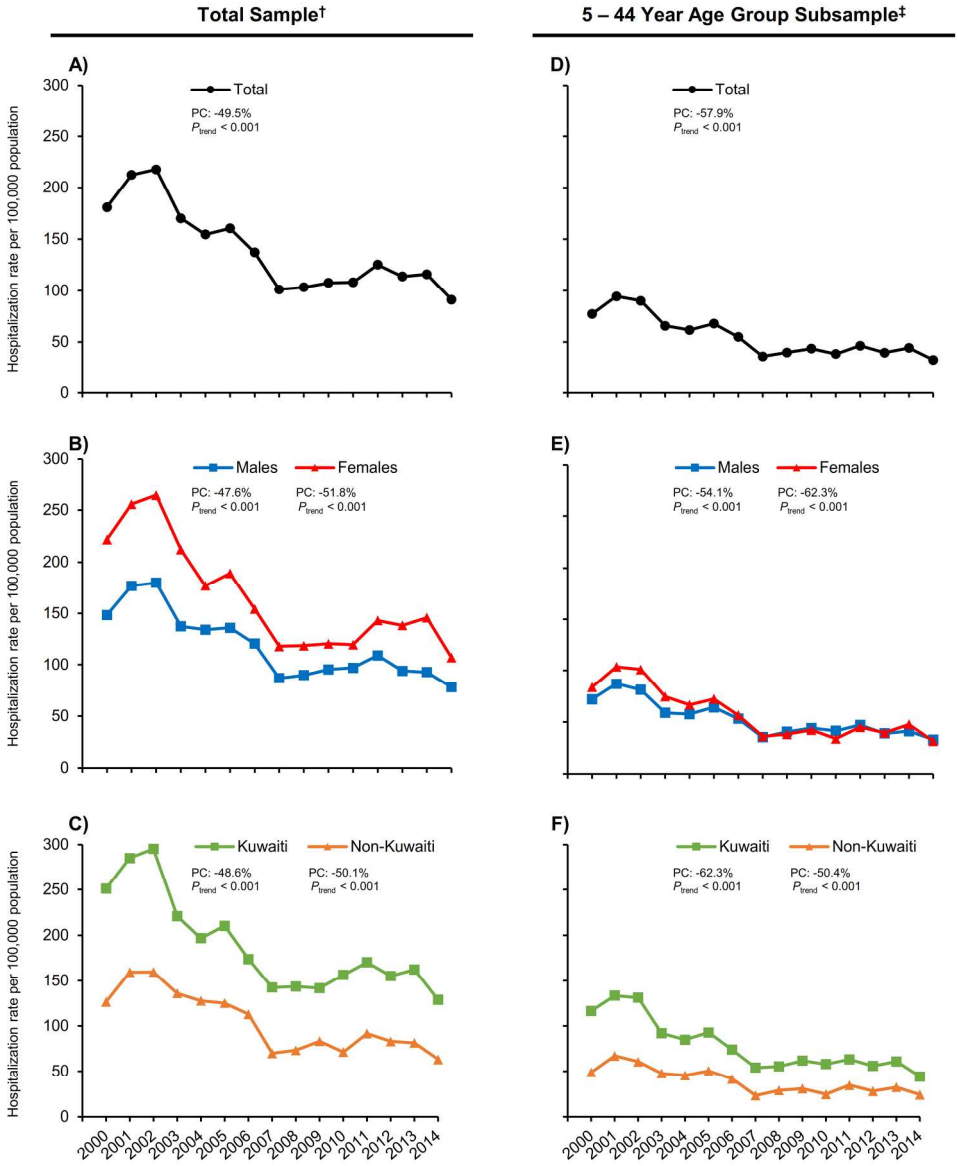


Figure 1. Trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. Asthma hospital admission rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. P-values for linear trend were derived from Poisson regression analysis.

213x252mm (300 x 300 DPI)

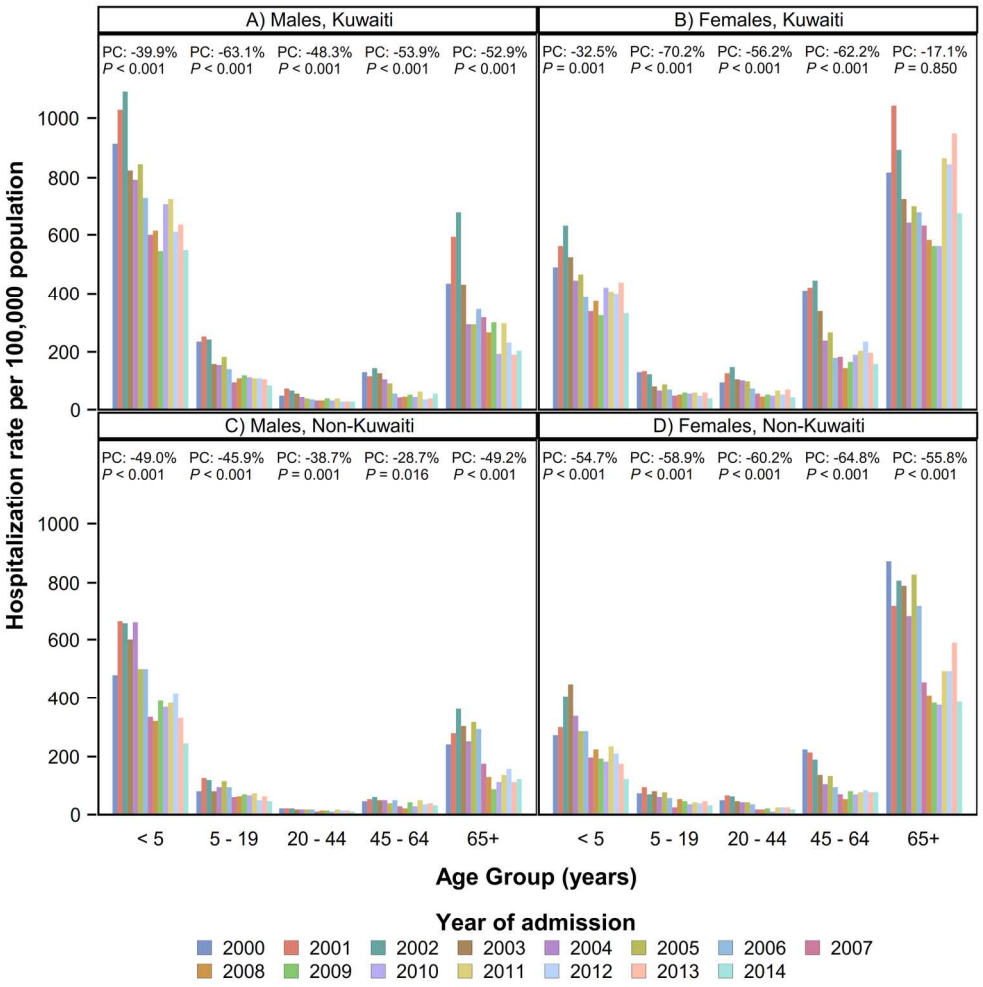


Figure 2. Age-, sex-, and nationality-specific trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. A) Rates among males of Kuwaiti nationality. B) Rates among females of Kuwaiti nationality. C) Rates among males of non-Kuwaiti nationality. D) Rates among females of non-Kuwaiti nationality. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. P-values for linear trend were derived from Poisson regression analysis.

167x167mm (300 x 300 DPI)

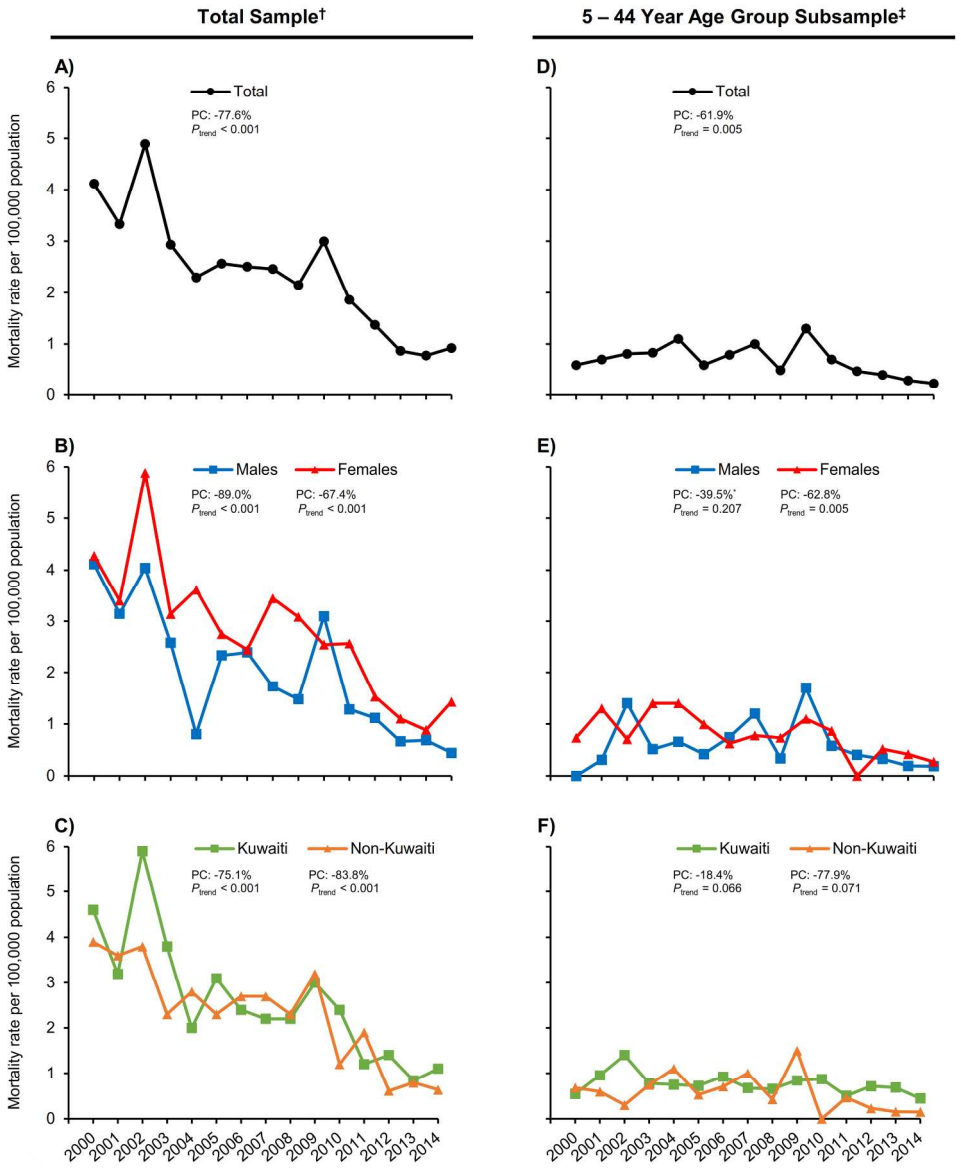


Figure 3. Trends in annual asthma mortality rates per 100,000 population in Kuwait, 2000 to 2014. Asthma mortality rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. P-values for linear trend were derived from Poisson regression analysis. *PC is given as rate in 2014 vs. rate in 2001.

213x252mm (300 x 300 DPI)

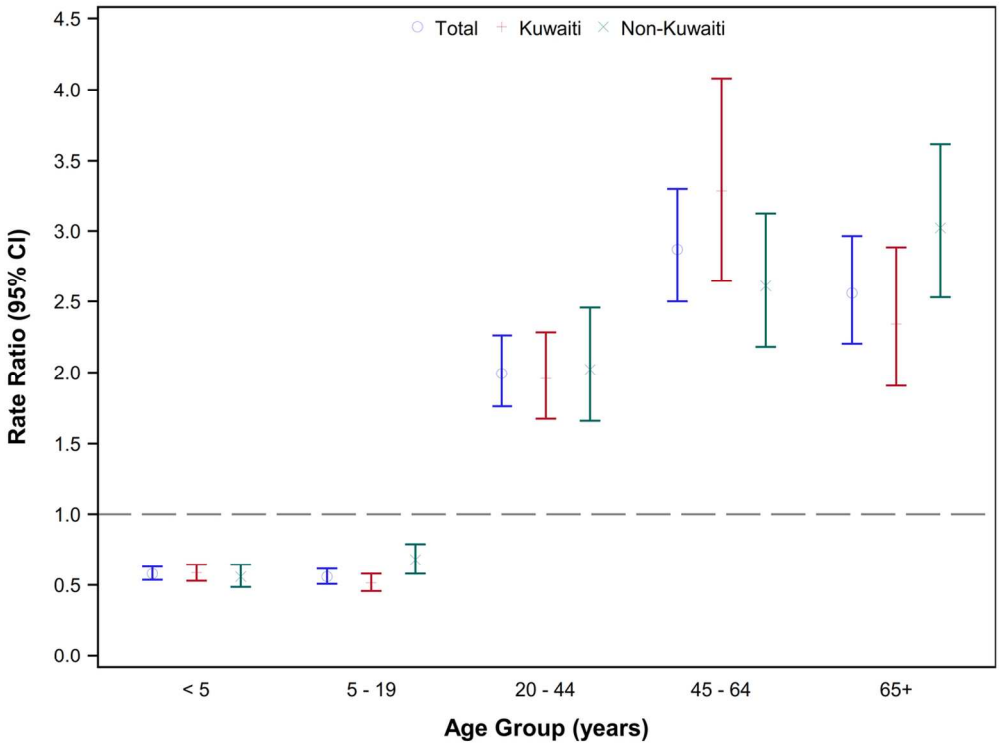


Figure 4. Rate ratios of hospital admission rates for asthma in females vs. males by age group in Kuwait, 2000 to 2014. Rate ratios comparing females to males in the total population and by nationality are presented according to age groups. Rate ratios in the total population were adjusted for nationality.

124x94mm (300 x 300 DPI)

Table S1. Rates and rate ratios of hospital admissions for asthma comparing Kuwaiti and non-Kuwaiti individuals stratified by sex and age group in Kuwait, 2000 to 2014

	Age group (years)	Nationality	Number of hospital admissions for asthma	Average annual rate of hospital admissions per 100,000 population† (95% CI)	RR‡ (95% CI)
Males	< 5	Kuwaiti	8,318	733.5 (690.3, 779.4)	1.67 (1.49, 1.86)
		Non-Kuwaiti	3,502	440.6 (401.4, 483.7)	1.00
	5 – 19	Kuwaiti	4,077	141.5 (131.7, 152.0)	1.80 (1.57, 2.06)
		Non-Kuwaiti	1,535	78.8 (70.1, 88.4)	1.00
	20 – 44	Kuwaiti	1,061	40.0 (35.6, 44.9)	2.62 (2.27, 3.02)
		Non-Kuwaiti	2,127	15.3 (14.0, 16.6)	1.00
	45 – 64	Kuwaiti	559	73.4 (61.4, 87.8)	1.82 (1.48, 2.25)
		Non-Kuwaiti	1,510	40.3 (36.1, 44.9)	1.00
	≥ 65	Kuwaiti	720	319.9 (289.0, 354.0)	1.65 (1.39, 1.96)
		Non-Kuwaiti	375	194.2 (168.9, 223.3)	1.00
	Total	Kuwaiti	14,735	151.7 (143.9, 159.9)	1.81 (1.69, 1.94)
		Non-Kuwaiti	9,049	83.7 (79.2, 88.5)	1.00
Females	< 5	Kuwaiti	4,711	431.5 (400.8, 464.5)	1.75 (1.52, 2.01)
		Non-Kuwaiti	1,874	246.5 (219.3, 277.0)	1.00
	5 – 19	Kuwaiti	2,025	72.3 (66.5, 78.6)	1.36 (1.17, 1.57)
		Non-Kuwaiti	941	53.2 (47.1, 60.1)	1.00
	20 – 44	Kuwaiti	2,202	76.5 (67.4, 86.9)	2.50 (2.08, 3.01)
		Non-Kuwaiti	1,903	30.6 (26.7, 35.0)	1.00
	45 – 64	Kuwaiti	2,363	240.5 (217.1, 266.4)	2.27 (1.90, 2.70)
		Non-Kuwaiti	1,239	106.1 (92.2, 122.2)	1.00
	≥ 65	Kuwaiti	1,923	751.0 (683.1, 825.8)	1.33 (1.11, 1.59)
		Non-Kuwaiti	687	566.5 (483.8, 663.4)	1.00
	Total	Kuwaiti	13,224	213.2 (202.2, 224.9)	1.88 (1.72, 2.06)
		Non-Kuwaiti	6,644	113.4 (105.2, 122.3)	1.00

RR: rate ratio; CI: confidence interval.

† Average annual hospital admission rates for asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models.

‡ Age- and sex- specific rate ratios comparing Kuwaiti to non-Kuwaiti individuals.

Table S2. Rates and rate ratios of asthma mortality comparing females to males according to age group in Kuwait, 2000 to 2014

Age group (years)	Sex	Average annual mortality rate per 100,000 population (95% CI)[†]	RR[‡] (95% CI)
< 5	Female	1.7 (1.6, 1.8)	0.99 (0.89, 1.10)
	Male	1.7 (1.6, 1.8)	1.00
5 – 19	Female	1.0 (0.7, 1.6)	1.51 (0.98, 2.32)
	Male	0.7 (0.5, 1.0)	1.00
20 – 44	Female	0.8 (0.5, 1.1)	1.55 (1.10, 2.40)
	Male	0.5 (0.4, 0.7)	1.00
45 – 64	Female	3.0 (2.2, 4.0)	1.07 (0.73, 1.58)
	Male	2.8 (2.2, 3.5)	1.00
≥ 65	Female	38.0 (29.9, 48.2)	1.50 (1.06, 2.12)
	Male	25.3 (19.5, 32.9)	1.00

RR: rate ratio; CI: confidence interval.
[†] Model-adjusted average annual mortality rates due to asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for nationality.
[‡] Age-specific rate ratios comparing females to males while adjusting for nationality.

Table S3. Sex- and age-standardized rates and rate ratios of asthma hospital admissions in the total population and stratified by nationality in Kuwait, 2000 to 2014

	Sex- and age-standardized asthma hospital admission rate per 100,000 population[†] (95% CI)			
Year	**Total**	**Kuwaiti**	**Non-Kuwaiti**	**RR[‡] (95% CI)**
2000	190.6 (181.6, 199.6)	241.8 (228.8, 254.8)	138.4 (124.5, 152.4)	1.75 (1.56, 1.96)
2001	221.3 (211.8, 230.7)	278.6 (264.8, 292.3)	156.3 (143.0, 169.6)	1.78 (1.62, 1.97)
2002	224.9 (215.7, 234.1)	286.7 (273.1, 300.2)	161.2 (147.8, 174.6)	1.78 (1.62, 1.96)
2003	175.2 (167.3, 183.1)	215.5 (204.0, 226.9)	143.0 (130.5, 155.6)	1.51 (1.36, 1.67)
2004	153.5 (146.5, 160.6)	184.5 (174.3, 194.7)	129.2 (117.9, 140.6)	1.43 (1.29, 1.58)
2005	162.8 (155.6, 169.9)	194.7 (184.6, 204.9)	135.4 (123.9, 146.9)	1.44 (1.30, 1.59)
2006	140.7 (134.1, 147.2)	163.8 (154.5, 173.1)	119.8 (109.4, 130.1)	1.37 (1.23, 1.52)
2007	107.0 (101.3, 112.6)	138.6 (130.1, 147.1)	75.5 (67.7, 83.3)	1.84 (1.63, 2.07)
2008	103.9 (98.6, 109.2)	134.1 (126.1, 142.1)	74.5 (67.2, 81.8)	1.80 (1.61, 2.02)
2009	107.2 (102.0, 112.3)	136.7 (128.7, 144.7)	79.4 (72.5, 86.4)	1.72 (1.55, 1.91)
2010	106.3 (101.3, 111.3)	141.8 (134.0, 149.5)	72.2 (65.6, 78.8)	1.96 (1.77, 2.18)
2011	127.1 (121.6, 132.6)	166.6 (158.0, 175.2)	88.8 (81.6, 95.9)	1.88 (1.71, 2.07)
2012	118.3 (113.1, 123.5)	152.5 (144.5, 160.5)	84.2 (77.3, 91.1)	1.81 (1.64, 2.00)
2013	120.7 (115.6, 125.9)	158.0 (150.1, 166.0)	84.4 (77.4, 91.4)	1.87 (1.70, 2.06)
2014	93.7 (89.3, 98.2)	126.0 (119.0, 133.0)	63.6 (57.8, 69.4)	1.98 (1.78, 2.20)
Average[⁋]	136.3 (134.7, 137.9)	175.3 (172.9, 177.8)	98.8 (96.6, 101.1)	1.77 (1.73, 1.82)

RR: rate ratio; CI: confidence interval.

[†] Asthma hospital admission rates per 100,000 population were sex- and age-standardized to the World Health Organization Standard Population.

[‡] Rate ratios comparing sex- and age-standardized hospital admission rates among Kuwaiti to non-Kuwaiti subjects.

[⁋] Average annual sex- and age-standardized asthma hospital admission rates per 100,000 population per year over the period from 2000 to 2014.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Trends in asthma hospital admissions and mortality in Kuwait, 2000 to 2014: a national retrospective observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021244.R2
Article Type:	Research
Date Submitted by the Author:	08-Mar-2018
Complete List of Authors:	Ziyab, Ali; Kuwait University Faculty of Medicine, Community Medicine Abul, Adnan; Kuwait University Faculty of Medicine, Community Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Respiratory medicine
Keywords:	Epidemiology < THORACIC MEDICINE, Asthma < THORACIC MEDICINE, Asthma Hospitalization, Asthma Mortality

Trends in asthma hospital admissions and mortality in Kuwait, 2000 to 2014: a national retrospective observational study

Authors: Ali H. Ziyab[1], Adnan T. Abul[1,2]

Affiliations:

[1] Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait

[2] Department of Medicine, Faculty of Medicine, Kuwait University, Kuwait

Corresponding author:

Ali H. Ziyab, PhD

Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait.

P. O. Box 24923

Safat 13110, Kuwait

Tel: (+965) 24636545

Fax: (+965) 25338948

Email: aziyab@hsc.edu.kw

Word count: 4,482 words

ABSTRACT

Objectives: To examine trends in asthma hospitalization and mortality rates from 2000 to 2014 in Kuwait according to sex, age, and nationality.

Methods: For this nationwide, retrospective observational study, data from hospital discharge records and death certificates listing asthma as the primary reason for hospitalization or mortality were obtained from the National Center for Health Information database using ICD-10 codes J45 and J46. Trends in sex-, age-, and nationality-adjusted hospitalization and mortality rates were examined. Poisson regression models were applied to test for linear trends overtime and estimate adjusted rate ratios (aRR) and 95% confidence intervals (CI).

Results: During the 15-year study period, a total of 43,652 hospitalizations and 484 deaths due to asthma exacerbations were identified. The average annual adjusted rates of asthma hospitalization and mortality were estimated to be 134.9 (95% CI: 131.8-138.1) and 2.1 (95% CI: 1.8-2.4) per 100,000 population, respectively. Hospitalization rates decreased by 49.5% in the total population (from 180.8 to 91.3 admissions per 100,000 population between 2000 and 2014, $P_{trend}<0.001$) and by 57.9% in the 5-44 year age group (from 77.3 to 32.5 admissions per 100,000 population, $P_{trend}<0.001$). Mortality rates decreased from 4.1 to 0.9 deaths per 100,000 population between 2000 and 2014 in the total population (77.6% decrease, $P_{trend}<0.001$) and from 0.6 to 0.2 deaths per 100,000 population among those aged 5-44 years (61.9% reduction, $P_{trend}=0.005$). Kuwaiti compared to non-Kuwaiti subjects had higher risk of asthma hospitalization and mortality. Among children aged ≤ 19 years, the risk of hospitalization was higher in boys compared to girls; however, among adults, women experienced more hospitalizations than men.

Conclusions: Asthma hospitalization and mortality rates have substantially decreased between 2000 and 2014 in Kuwait, with persisting differences between genders, age groups, and citizens vs. non-citizens. The observed decreasing trends in Kuwait are in agreement with global trends.

Strengths and limitations of this study

- This study provided, at a national level, a comprehensive perspective on trends and disparities in hospitalizations and mortality related to asthma exacerbations in Kuwait over a 15-year period.

- Although data analyzed in the current report were obtained from the National Center for Health Information database using ICD-10 codes J45 and J46, misclassification of asthma-related hospitalizations or deaths is inevitable in epidemiological studies based on routinely collected data, which could either underestimate or overestimate the frequency.

- Lack of information on ethnicity/race of patients is a further limitation to our study.

INTRODUCTION

Asthma is the most common inflammatory chronic disorder of the lungs that affects children and adults. Globally, it was estimated in 2015 that 358 million people suffer from asthma, which reflects a 12.6% increase in asthma prevalence compared to 1990.[1] Whereas, asthma-related mortality, causing 397,000 deaths in 2015, decreased by 26.7% between 1990 and 2015.[1] The International Study of Asthma and Allergies in Childhood (ISAAC) revealed variations in the prevalence of asthma both between and within countries..[2] For instance, among children aged 13 to 14 years old, the 12-month prevalence of asthma symptoms ranged from 3.4% to 31.2%.[3] In Westernized countries, asthma is usually seen in around 10% of the general population.[4] Hence, due to the elevated prevalence, morbidity, and mortality, asthma is considered a global public health problem.

The major pathophysiological hallmarks that contribute to the complex heterogeneity of the clinical manifestations of asthma include recurrent airway inflammation, variable airway obstruction, and bronchial hyper-responsiveness.[5] Asthma exacerbations, defined as "a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome", have been graded in severity from mild to severe and in some instances as life-threatening.[6 7] Exacerbations requiring emergency department visits and hospitalizations are associated with substantial morbidity, medical expenditures, and economic as well as social burden on individuals and families.[6 8] In principle, asthma exacerbations are preventable events in the presence of high quality health care, patient awareness and compliance, and optimal asthma management.

In Kuwait, the burden of asthma is comparable to what is observed in Western nations. For instance, 7.6% and 15.6% of schoolchildren aged 13 to 14 years reported current wheeze and ever doctor-diagnosed asthma, respectively.[9] A recent study showed that 11.9% of university students in Kuwait suffer from asthma.[10] Annually, asthma management and treatment cause a considerable financial burden, costing US$207 million (United States dollar) with hospital admissions accounting for 43% of the total direct costs for asthma treatment in Kuwait.[11] During the period from 1992 to 1994, the annual rate of asthma hospitalization and mortality in Kuwait were estimated to be 205 admissions and 1.59 deaths per 100,000 population, respectively.[12] Given the ongoing improvements in asthma therapeutic and management strategies, we hypothesized that asthma hospitalizations and mortality to have decreased; however, there have been no recent efforts to assess temporal trends in Kuwait. Therefore, this study sought to describe trends in asthma hospital admissions and mortality according to sex, age, and nationality in Kuwait between 2000 and 2014 using national hospital discharge records and death certificates.

METHODS

Study setting

Kuwait, a small country with a total approximate area of 18,000 km^2, is located in the Arabian Peninsula with sandy desert covering its landscape. Generally, the climate in Kuwait is arid with extreme hot temperatures during summer and mild-cool weather in winter and frequent dust storms that occur throughout the year.[13] As of June 2017, the total population was estimated to be around 4.4 million. The population of Kuwait can be divided into two separate communities, namely citizens of Kuwait (Kuwaitis) and labor migrants/expatriates (non-Kuwaitis). Kuwaitis make around 30% (1.3 million) of the population, whereas non-Kuwaitis constitute about 70% (3.1 million) of the population. The majority of the non-Kuwaitis are of Asian ethnicity (1.8 million) and Arab ethnicity (1.2 million). Demographically, the majority of expatriates are males (65%), poorly educated (70% with less than secondary level education), and relatively young (83% aged between 15 and 60 years old).[14] Hence, distorting the demographic distribution of this population towards male and working-age predominance.

Health care services in Kuwait are divided into primary, secondary, and tertiary care. There are six public general hospitals, providing secondary level care, across Kuwait equipped with child and adult emergency departments. Moreover, at a smaller scale, some private hospitals provide emergency care services.

Study design, data sources, and outcomes

In this nationwide, retrospective observational study, we analyzed data from hospital discharge records and death certificates on asthma for the period from January 1, 2000 to December 31,

2014. Public and private hospitals across the state of Kuwait are required to report health and vital statistics data on regular bases to the National Center for Health Information (NCHI) at the Ministry of Health. In this study, data was collected from all hospital discharge records and death certificates listing asthma as the primary reason for admission or death using ICD-10 (International Classification of Diseases, Tenth Revision) codes: J45 (asthma, including predominantly allergic asthma, non-allergic asthma, mixed asthma, asthma unspecified) and J46 (status asthmaticus). In the data extraction process, we included all anonymized asthma-related hospital admission episodes or mortality and collected data on age, sex, and nationality using the NCHI database. If a person has been hospitalized several times for asthma, we counted and considered all admissions per-person as independent events. Annual mid-year population estimates, total and stratified according to sex, age, and nationality, were obtained from the Public Authority for Civil Information, Kuwait. Ethical approval was obtained from the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait.

Statistical analysis

Counts of asthma hospital admissions and deaths resembled the unit of analysis. Five age groups were defined: < 5 years, 5 to 19 years, 20 to 44 years, 45 to 64 years, and ≥ 65 years. Annual and average annual rates of asthma hospital admissions and mortality per 100,000 population were estimated for the 15-year study period (from January 1, 2000 to December 31, 2014) for the total population and stratified according to age group, sex, and nationality. In trend analysis, using calendar year as the exposure variable of interest, annual changes in rates of asthma hospital admissions and mortality were examined. Trend analysis was conducted using the total study sample and a subsample restricted to those aged between 5 and 44 years old. The rationale for

additionally examining trends in those aged 5-44 years old was to minimize the effect of misclassification of asthma hospitalization and mortality among younger and older age groups.[15] Moreover, percent change (PC) in hospitalization and mortality rates comparing the years 2000 and 2014 were calculated as follows: PC = [((rate in 2014 – rate in 2000)/rate in 2000) x 100]. Poisson regression models, with log link function, were used to calculate overall as well as stratified model-adjusted rates and adjusted rate ratios (aRR) and their corresponding 95% confidence intervals (CI) using the GENMOD procedure in SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Regression-based adjustments for age, sex, and nationality were considered when estimating rates and rate ratios. In all regression models, we treated the observed counts of asthma-related hospitalizations/mortality in each year as the outcome variable and the corresponding denominator (i.e., logarithm of mid-year population counts) as an offset term. Additionally, sex- and age-standardized asthma hospital admission rates for the total population and stratified according to nationality were calculated using weights from the World Health Organization (WHO) new World Standard Population.[16] The STDRATE procedure in SAS 9.4 was used to compute directly sex- and age-standardized rates. All statistical analyses were conducted using SAS 9.4. The statistical significance level was set to $\alpha = 0.05$ for all association and trend analyses.

Patient and public involvement

This research did not directly involve patients nor the public since the analysis was based on routinely collected data, i.e. data from hospital discharge records and death certificates.

RESULTS

Characteristics and trends of asthma hospital admissions

During the 15-year study period, a total of 43,652 hospital admissions due to asthma exacerbations were identified from hospital discharge records in Kuwait. Of the total hospital admissions, 23,784 (54.5%) were among males, 27,959 (64.1%) were among Kuwaiti individuals, and 18,405 (42.1%) were among children aged < 5 years old (table 1). The sex, age, and nationality model-adjusted average annual rate of asthma hospital admissions was estimated to be 134.9 (95% CI: 131.8, 138.1) admissions per 100,000 population per year. On average, significantly higher hospitalization rates were observed among females compared to males (159.3 vs. 114.3 admissions per 100,000 population per year, $P < 0.001$) and Kuwaiti nationals compared to non-Kuwaiti subjects (182.5 vs. 99.8 admissions per 100,000 population per year, $P < 0.001$). Average annual hospitalization rates were highest among children aged < 5 years (426.5 admissions per 100,000 population) and in adults aged ≥ 65 years (405.1 admissions per 100,000 population), whereas individuals aged 20 to 44 years had the lowest average annual hospitalization rate of 34.6 admissions per 100,000 population (table 1).

Trend analysis showed that asthma hospitalization rates decreased from 180.8 to 91.3 admissions per 100,000 population between 2000 and 2014 in the total population (a 49.5% decrease [95% CI: 44.2, 54.3], $P_{trend} < 0.001$; figure 1A, table 2). Significantly decreasing trends were observed in both sexes, with reductions in admissions rates between 2000 and 2014 amounting to 51.8% in females (from 221.8 to 106.9 admissions per 100,000 population, $P_{trend} < 0.001$) and 47.6% in males (from 148.5 to 77.9 admissions per 100,000 population, $P_{trend} < 0.001$; figure 1B). Similarly, decreasing trends in asthma hospitalization rates were evident among Kuwaiti and

non-Kuwaiti subjects (figure 1C). Among Kuwaiti subjects, hospitalization rate decreased from 251.0 to 128.9 admissions per 100,000 population between 2000 and 2014; representing a 48.6% reduction. Among non-Kuwaiti subjects, hospitalization rate was estimated to be 126.5 admissions per 100,000 population in 2000, and decreased to 63.2 admissions per 100,000 population in 2014; representing a 50.1% reduction.

Similar to the observed trends in the total study sample, analysis among those aged between 5 and 44 years old (referred to as subsample) showed decreasing trends in asthma hospitalization rates. In the total subsample, hospitalization rate decreased from 77.3 to 32.5 admissions per 100,000 population between 2000 and 2014; representing a 57.9% reduction (figure 1D). Sex-stratified analysis of the subsample showed that hospitalization rates have decreased between 2000 and 2014 in both females (from 83.6 to 31.5 admissions per 100,000 population, $P_{trend} < 0.001$) and males (from 71.9 to 33.0 admissions per 100,000 population, $P_{trend} < 0.001$; figure 1E). Similarly, between 2000 and 2014, decreasing trends in hospitalization rates were observed among Kuwaiti individuals (from 116.6 to 44.0 admissions per 100,000 population, $P_{trend} < 0.001$) and non-Kuwait subjects (from 48.8 to 24.2 admissions per 100,000 population, $P_{trend} < 0.001$; figure 1F).

Moreover, using the total study sample, decreasing trends in hospital admission rates were observed in most subgroups stratified according to sex, nationality, and age group (figure 2). For instance, most pronounced decreases in hospitalization rates between 2000 and 2014 among both Kuwaiti males and females were observed among those aged 5 to 19 years old (decrease of 63.1% in males and 70.2% in females, $P_{trend} < 0.001$) when compared to other age groups.

Whereas, non-Kuwaiti males aged < 5 (49.0% decrease, $P_{trend} < 0.001$) and ≥ 65 (49.2% decrease, $P_{trend} < 0.001$) years experienced the highest decreases in hospitalization rates. Among non-Kuwaiti females, those aged 45 to 64 years had a 64.8% decrease in asthma hospital admissions between 2000 and 2014 ($P_{trend} < 0.001$; figure 2).

Characteristics and trends of asthma mortality

A total of 484 asthma deaths were identified over the 15-year study period in Kuwait (table 1). Of the total deaths, 245 (50.6%) were among males, 248 (51.2%) were among Kuwaiti individuals, and 224 (46.3%) were among individuals aged ≥ 65 years old (table 1). The average annual adjusted asthma mortality rate was estimated to be 2.1 (95% CI: 1.8, 2.4) deaths per 100,000 population per year. On average, significantly higher mortality rates were observed among females compared to males (2.5 vs. 1.8 deaths per 100,000 population per year, $P < 0.001$) and Kuwaiti nationals compared to non-Kuwaiti subjects (2.4 vs. 1.9 deaths per 100,000 population per year, $P = 0.010$). Average annual mortality rate was highest among individuals aged ≥ 65 years (27.7 deaths per 100,000 population) and least among those aged 20-44 years (0.6 deaths per 100,000 population; table 1).

Across the study period, asthma mortality rates decreased from 4.1 to 0.9 deaths per 100,000 population between 2000 and 2014 in the total population; translating to a 77.6% (95% CI: 58.9, 87.8, $P_{trend} < 0.001$) reduction (figure 3A, table 2). Among males, asthma mortality rates decreased from 4.1 to 0.5 deaths per 100,000 population between 2000 and 2014. Whereas, among females, asthma mortality rates reduced from 4.3 to 1.4 deaths per 100,000 population between 2000 and 2014. Hence, the magnitude of reduction in mortality rates was higher among

males (89.0% decrease) compared to females (67.4% decrease; figure 3B). Moreover, decreasing trends between 2000 and 2014 in asthma mortality rates were evident among Kuwaiti subjects (from 4.6 to 1.1 deaths per 100,000 population, $P_{trend} < 0.001$) and non-Kuwaiti individuals (from 3.9 to 0.6 deaths per 100,000 population, $P_{trend} < 0.001$; figure 3C).

Furthermore, trends in asthma mortality were examined in a subsample restricted to those aged between 5 and 44 years old. In the total subsample, asthma mortality rates decreased from 0.6 to 0.2 deaths per 100,000 population between 2000 and 2014; representing a 61.9% reduction ($P_{trend} = 0.005$; figure 3D). Mortality rates among females aged 5-44 years old showed decreasing trends across the study period (from 0.7 to 0.3 deaths per 100,000 population, $P_{trend} = 0.005$; figure 3E). In contrast, mortality rates among males aged 5-44 years old did not demonstrate statistically significant decreasing trends ($P_{trend} = 0.207$; figure 3E). Although the decreasing trends in nationality-stratified mortality rates in the subsample did not gain statistical significance, the magnitude of reduction between 2000 and 2014 was higher among non-Kuwaiti subjects (77.9% decrease, $P_{trend} = 0.071$) compared to Kuwaiti individuals (18.4% decrease, $P_{trend} = 0.066$; figure 3F).

Associations between nationality and asthma hospitalization and mortality rates

In regard to nationality disparity in asthma hospitalization, Kuwaiti nationals compared to non-Kuwaiti subjects had higher risk of asthma hospital admission in the total population (aRR = 1.83, 95% CI: 1.75, 1.92). Moreover, our analysis showed that both males and females of Kuwaiti nationality had higher asthma hospitalization rates compared to non-Kuwaitis across all age groups (see online supplementary table S1). Overall, Kuwaiti males had 1.81 times (95% CI:

1.69, 1.94) the risk of hospitalization compared to non-Kuwaiti males. Similarly, Kuwaiti females had 1.88 times (95% CI: 1.72, 2.06; see online supplementary table S1) the risk of hospitalization compared to non-Kuwaiti females.

In regard to asthma mortality, Kuwaiti individuals compared to non-Kuwaiti subjects had higher mortality rate (aRR = 1.29, 95% CI: 1.06, 1.56). Sex-stratified analysis showed that the risk of asthma mortality is similar between Kuwaiti females and non-Kuwaiti females (aRR = 0.85, 95% CI: 0.67, 1.08). In contrast, Kuwaiti males had 1.99 times (95% CI: 1.48, 2.68) the risk of asthma mortality compared to non-Kuwait males.

Sex differences in asthma hospitalization and mortality rates

Overall, females had higher risk of asthma hospitalization compared to males (aRR = 1.39, 95% CI: 1.33, 1.46). However, the sex ratio of asthma hospitalization varied significantly across age groups (figure 4). Among children aged ≤ 19 years, the risk of hospital admission for asthma was significantly lower in females compared to males (age < 5 years: $RR_{female\ vs.\ male}$ = 0.58, 95% CI: 0.54, 0.63; age 5 to 19 years: $RR_{female\ vs.\ male}$ = 0.56, 95% CI: 0.51, 0.62). On the contrary, among those aged ≥ 20 years, asthma hospitalization risk was significantly higher in females compared to males. For instance, among those aged 20 to 44 years old, females had 1.99 times (95% CI: 1.76, 2.26) the risk of hospitalization compared to males. These sex and age specific associations were similar for Kuwaiti and non-Kuwaiti subjects (figure 4).

In general, the risk of asthma mortality was higher among females compared to males (aRR = 1.41, 95% CI: 1.19, 1.68). In age stratified analysis, mortality rates were higher among females

compared to males among those aged 5-19 years ($aRR_{female\ vs.\ male}$ = 1.51, 95% CI: 0.98, 2.32), 20-44 years ($aRR_{female\ vs.\ male}$ = 1.55, 95% CI: 1.10, 2.40), and ≥ 65 years ($aRR_{female\ vs.\ male}$ = 1.50, 95% CI: 1.06, 2.12; see online supplementary table S2).

DISCUSSION

The purpose of this study was to examine national trends in hospitalization and mortality due to asthma exacerbations in Kuwait using data from hospital discharge records and death certificates. This retrospective analysis of national data showed substantial reductions in asthma hospital admission and mortality rates in Kuwait between 2000 and 2014. Decreases in asthma hospital admissions and mortality rates over the 15-year study period were evident in both sexes, across different age groups, and among Kuwaiti nationals and non-Kuwaiti subjects. On average, females compared to males and Kuwaitis compared to non-Kuwaitis had higher rates of asthma hospitalization and mortality. Children aged < 5 years and adults aged ≥ 65 years had significantly higher hospitalization rates compared to other age groups. Asthma mortality rate among subjects aged ≥ 65 years was pronouncedly elevated in comparison to those aged < 65 years. The observed decreasing trends in hospitalization and mortality rates might be, in part, explained by improved management strategies and treatments and accessibility to high quality health care services.

Up to our knowledge, there have been no recent investigations characterizing trends in asthma hospital admissions and mortality in Kuwait. A previous report estimated asthma hospitalization and mortality rates in Kuwait during two three-year periods: from 1987-to-1989 and 1992-to-1994.[12] In 1994, asthma hospital admission and mortality rates were estimated to be 231.2 admissions and 1.36 deaths per 100,000 population, respectively.[12] In 2014, the latest year in the current analysis, there were 91.3 admissions and 0.9 deaths per 100,000 population due to asthma exacerbations. Hence, this comparison clearly shows substantial reductions, specifically in asthma hospitalization, between 1994 and 2014 in Kuwait.

A main finding in this report is that the estimated asthma hospital admission rate in the total population has reduced markedly from 180.8 admissions per 100,000 population in 2000 to 91.3 admissions per 100,000 population in 2014; translating to a 49.5% decrease. These declining trends were evident in both sexes, different age groups, and Kuwaiti nationals and non-Kuwaiti subjects. Moreover, comparable declining trends were observed in the subsample restricted to those aged 5-44 years old. Similar declining trends have been observed in different global regions.[17] For instance, between 1997 and 2011 in Costa Rica, asthma hospital admission rate decreased by 53%, with reductions observed among males and females as well as children and adults.[18] Similar to our findings, reports from the United States, Spain, Finland, and Norway have shown significant decreasing trends in asthma hospitalization among the pediatric population.[19-22] A report from the United Kingdom, looking at trends in asthma hospitalization over a 50-year period from 1955 to 2004, indicated that asthma hospital admissions increased until late 1980s and have been declining thereafter.[23] Similarly, a comprehensive report investigating trends in pediatric asthma hospital admissions in developed countries, showed a peak in asthma hospitalizations around 1989-1990 and subsequently progressive declining trends.[24]

In regard to trends in asthma mortality, the current report showed that mortality related to asthma exacerbations has decreased by 77.6% between 2000 and 2014 in Kuwait in the total study sample and by 61.9% in the 5-44 year age group. In a global analysis of data from 188 countries, age-standardized asthma mortality rate decreased by 58.8% (95% CI: 39.0, 69.0) between 1990 and 2015.[1] Another study based on data from 46 countries, investigating trends in asthma mortality between 1993 and 2012, showed reductions in asthma deaths between 1993 and 2006,

with no further changes from 2006 to 2012.[15] These international data further support the observed decreases in asthma morality in Kuwait.

To this end, at a global level, the decreasing trends in asthma hospital admission and mortality rates over the past few decades can be explained, at least in part, by important changes in asthma medical care. These include developments in the pharmacological selectivity and delivery of adrenergic and corticosteroid drugs.[23] Specifically, the wide availability and utilization of long-term asthma control medications, such as inhaled corticosteroids. Moreover, the development of international, regional, and local asthma management guidelines have also contributed to reducing asthma exacerbations and burden. The Global Initiative for Asthma (GINA), established in 1993, has continuously been developing evidence-based strategies for managing and preventing asthma that have been serving the international community at large.[25] Collectively, improved therapeutics that are accessible and quality-assured coupled with patient education and accessibility to quality health care services have contributed to the declining trends in asthma hospitalizations and mortality.

Across the 15-year study period, sex-, age-, and nationality-based disparities in asthma hospitalizations and mortality were observed. Overall, hospital admission rates were higher among females compared to males. However, these sex-based differences were found to vary across age-groups. Among subjects aged ≤ 19 years old, males experienced more asthma hospitalizations compared to females; whereas, among adults, this observation is switched, where asthma hospitalizations become more frequent among females compared to males. Such observations have been reported in previous investigations.[26 27] Studies adjusting for the effect of

potential confounders (e.g., obesity, smoking, race) and comorbidities (e.g. chronic obstructive pulmonary diseases), concluded that the age-stratified sex differences in asthma hospitalizations persisted even after adjustments.[28-30] Hormonal factors have been speculated to differentially predispose males and females to disease development.[31] For instance, estrogen and progesterone were shown to alter pulmonary function and modify airway responsiveness.[32] However, the exact mechanisms underlying the age-stratified sex disparity in hospitalizations due to asthma exacerbations are not fully elucidated.

Preschool children aged < 5 years and adults aged ≥ 65 years had, on average, higher asthma hospitalization rates (426.5 and 405.1 admissions per 100,000 population, respectively) over the study period than all other age groups; an observation that has been previously reported.[33 34] However, careful interpretation of these age-specific rates should be exercised since diagnosis of asthma in early childhood is challenging[25] and diagnostic overlap of asthma with acute bronchitis and bronchiolitis may occur,[35] which could contribute to the high hospitalization rates observed among preschool children. Among older adults, diagnostic substitution of chronic obstructive pulmonary disease for asthma may occur, leading to the observed elevated asthma hospital admission rates. Hence, as an attempt to lessen the effect of misclassification in the younger and older age groups, trends, in the current report, were additionally examined in a subsample restricted to individuals aged 5-44 years old.

Geographical as well as racial/ethnic variations in asthma prevalence, hospital admissions, and mortality have been reported.[3 34] For instance, in the United States, African-Americans had higher asthma hospitalization and mortality rates compared to white subjects.[36] In the Scottish

population, South Asians compared to Scottish white subjects had higher rates of asthma hospitalization.[37] The current analysis demonstrated differences in asthma hospitalization rates based on nationality, with Kuwaiti nationals compared to non-Kuwaiti subjects having higher risk of asthma hospitalization. In addition to the different racial/ethnic backgrounds of Kuwaiti and non-Kuwaiti subjects, the different sex and age structure of the two populations (non-Kuwaitis mainly being of male gender and working age) could highly confound the observed nationality-based variation. However, both model adjusted rates (see online supplementary table S1) and sex- and age-standardized rates (see online supplementary table S3) showed that Kuwaiti nationals have higher risk of asthma hospitalization compared to non-Kuwait subjects. Thus, the different sex- and age-structure of the two populations (Kuwaiti and non-Kuwait population) did not explain the observed nationality-based disparity. On the other hand, accessibility to health care, quality of care and treatment, patient education, and social, behavioral, and environmental aspects could be some of the underlying factors for the observed nationality-based differences.[38]

This investigation provided, at a national level, a comprehensive understanding of trends and disparities in hospitalizations and mortality related to asthma exacerbations in Kuwait over a 15-year period. Nonetheless, we acknowledge some limitations, including misclassification of asthma-related hospitalizations or deaths, which is inevitable in epidemiological studies based on routinely collected data, such as data from hospital discharge records and death certificates. Such misclassification could either underestimate or overestimate the frequency of asthma hospitalizations and mortality. However, this is unlikely to fully account for the observed long-term declining trends and the sex-, nationality-, and age-based differences. Moreover, throughout the study period, there were no changes in the ICD disease-coding or coding rules; hence,

avoiding the influence of diagnostic shift or procedural changes. Although governmental and private hospitals are required to report health and vital statistics to the NCHI, private hospitals tend not to fully comply with reporting requirements, which might lead to underestimating the burden of asthma hospitalizations and mortality. However, underreporting, if any, by private hospitals does not directly impact the reported trends since the Ministry of Health has not relaxed the policies and requirements of reporting health and vital statistics. Moreover, to estimate the relative contributions of public and private hospitals to the data, we used the number of beds as a proxy measure due to the lack of information on the reporting hospitals in the analyzed data. In 2014, there were 6962 (86.8%) beds in public hospitals and 1058 (13.2%) beds in private hospitals (Annual Health Report, NCHI, 2014); hence, we expect that the majority of the analyzed data was reported by public hospitals and any underreporting by private hospitals should not majorly impact results and conclusions of the current report. Another limitation is the inability of identifying multiple/repeated hospitalizations for each patient during the same year or over the study period due to the anonymous nature of the analyzed data.

A further limitation is that the analyzed data did not include information on race/ethnicity of patients, which has been shown to be an important factor in asthma hospitalizations and deaths.[37] Rather, information on nationality (Kuwaiti vs. non-Kuwaiti), a variable that could partially account for the race/ethnicity effect, was available and analysis comparing the two population groups showed that Kuwaiti nationals have higher hospitalization and mortality rates compared to non-Kuwaiti subjects. On the other hand, a recent report has concluded that caution should be practiced when interpreting declining trends in mortality rates in countries with high influx of migrant workforce, as the case in Kuwait, since such trends could be, in part, attributed to the

healthy worker/migrant effect.[39] Although our findings are susceptible to such bias, results of stratified analysis showed that the declining trends in asthma hospital admission and mortality rates were similar in Kuwaiti and non-Kuwaiti subjects (see figure 1C and figure 3C). Hence, the healthy worker/migrant effect does not explain the observed decreasing trends.

In conclusion, this study provided a national perspective on trends and burden of hospital admissions and mortality related to asthma exacerbations in Kuwait between 2000 and 2014. Trend analysis indicated that hospitalization and mortality rates have significantly decreased over the 15-year study period. The decreasing trends were evident in both sexes, all age groups, and among Kuwaiti nationals and non-Kuwaiti subjects. Improvements in clinical care and development of targeted interventional strategies could further reduce rates of hospital admissions and mortality related to asthma exacerbations. Nevertheless, sex-, age-, and nationality-based differences in asthma hospitalization and mortality persisted across the study period. Therefore, future etiologic research is needed to address factors underlying such disparities and gaps in knowledge.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Contributors

AHZ: conceived and designed the epidemiologic study, contributed to acquisition of data, analyzed and interpreted the data, and drafted the manuscript. ATA: conceived and designed the epidemiologic study, interpreted the data, and revised the manuscript. All authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by all authors.

Ethics approval

The study was approved by the Standing Committee for Coordination of Health and Medical Research, Ministry of Health, Kuwait.

Patient consent

Not applicable.

Data sharing statement

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request at: aziyab@hsc.edu.kw.

Acknowledgements

We would like to thank staff at the National Center for Health Information, Ministry of Health, Kuwait, for providing the analyzed data in this manuscript. Specifically, we thank Dr. Fahad Al-Khalifa, Dr. Ali Sadek, and Dr. Gamal Makboul for their cooperation and support.

REFERENCES

1. Collaborators GBDCRD. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:691-706.

2. Asher MI, Montefort S, Bjorksten B*, et al.* Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.

3. Lai CK, Beasley R, Crane J*, et al.* Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;64:476-83.

4. Holgate ST, Wenzel S, Postma DS*, et al.* Asthma. *Nat Rev Dis Primers* 2015;1:15025.

5. Martinez FD, Vercelli D. Asthma. *Lancet* 2013;382:1360-72.

6. Fuhlbrigge A, Peden D, Apter AJ*, et al.* Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012;129(Suppl 3):S34-48.

7. Sears MR. Epidemiology of asthma exacerbations. *J Allergy Clin Immunol* 2008;122:662-8; quiz 69-70.

8. Pawankar R, Canonica GW, Holgate ST*, et al.* Allergic diseases and asthma: a major global health concern. *Curr Opin Allergy Clin Immunol* 2012;12:39-41.

9. Owayed A, Behbehani N, Al-Momen J. Changing prevalence of asthma and allergic diseases among Kuwaiti children. An ISAAC Study (Phase III). *Med Princ Pract* 2008;17:284-9.

10. Ziyab AH. Prevalence and Risk Factors of Asthma, Rhinitis, and Eczema and Their Multimorbidity among Young Adults in Kuwait: A Cross-Sectional Study. *BioMed Research International* 2017;2017:10.

11. Khadadah M. The cost of asthma in Kuwait. *Med Princ Pract* 2013;22:87-91.

12. Abul AT, Nair PC, Behbehanei NA*, et al.* Hospital admissions and death rates from asthma in Kuwait during pre- and post-Gulf War periods. *Ann Allergy Asthma Immunol* 2001;86:465-8.

13. Al-Awadhi JM, Alshuaibi AA. Dust fallout in Kuwait city: deposition and characterization. *Sci Total Environ* 2013;461-462:139-48.

14. De Bel-Air F. The demographic and economic framework of migration in Kuwait: Gulf Labour Market and Migration (GLMM) programme of the Migration Policy Center (MPC) and the Gulf Research Center (GRC), 2013.

15. Ebmeier S, Thayabaran D, Braithwaite I*, et al.* Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993-2012). *Lancet* 2017;390:935-45.

16. Ahmad OB, Boschi-Pinto C, Lopez AD, *et al.* Age standardization of rates: a new WHO standard - GPE Discussion Paper Series: 31 EIP/GPE/EBD. *Geneva: World Health Organization* 2001

17. The Global Asthma Report 2014. *Global Asthma Network* 2014; Auckland, New Zealand

18. Soto-Martinez M, Avila L, Soto N, *et al.* Trends in hospitalizations and mortality from asthma in Costa Rica over a 12- to 15-year period. *J Allergy Clin Immunol Pract* 2014;2:85-90.

19. Hasegawa K, Tsugawa Y, Brown DF, *et al.* Childhood asthma hospitalizations in the United States, 2000-2009. *J Pediatr* 2013;163:1127-33 e3.

20. de Miguel-Diez J, Jimenez-Garcia R, Hernandez-Barrera V, *et al.* National trends in hospital admissions for asthma exacerbations among pediatric and young adult population in Spain (2002-2010). *Respir Med* 2014;108:983-91.

21. Saynajakangas O, Valmari P, Tuuponen T, *et al.* Trends in hospitalization for childhood asthma in Finland in 1996-2004. *Acta Paediatr* 2007;96:919-23.

22. Mikalsen IB, Skeiseid L, Tveit LM, *et al.* Decline in admissions for childhood asthma, a 26-year period population-based study. *Pediatr Allergy Immunol* 2015;26:750-5.

23. Anderson HR, Gupta R, Strachan DP, *et al.* 50 years of asthma: UK trends from 1955 to 2004. *Thorax* 2007;62:85-90.

24. Chawla J, Seear M, Zhang T, *et al.* Fifty years of pediatric asthma in developed countries: how reliable are the basic data sources? *Pediatr Pulmonol* 2012;47:211-9.

25. Bateman ED, Hurd SS, Barnes PJ*, et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.

26. Chen Y, Stewart P, Johansen H*, et al.* Sex difference in hospitalization due to asthma in relation to age. *J Clin Epidemiol* 2003;56:180-7.

27. Schatz M, Clark S, Camargo CA, Jr. Sex differences in the presentation and course of asthma hospitalizations. *Chest* 2006;129:50-5.

28. Lin RY, Ji R, Liao W. Age dependent sex disproportion in US asthma hospitalization rates, 2000-2010. *Ann Allergy Asthma Immunol* 2013;111:176-81.

29. Chasm RM, Pei YV, Pallin DJ*, et al.* Sex differences in risk of hospitalization among emergency department patients with acute asthma. *Ann Allergy Asthma Immunol* 2015;115:70-2 e1.

30. Goto T, Tsugawa Y, Camargo CA, Jr.*, et al.* Sex differences in the risk of hospitalization among patients presenting to US emergency departments with asthma exacerbation, 2010-2012. *J Allergy Clin Immunol Pract* 2016;4:149-51 e2.

31. Klein SL. Immune cells have sex and so should journal articles. *Endocrinology* 2012;153:2544-50.

32. Haggerty CL, Ness RB, Kelsey S*, et al.* The impact of estrogen and progesterone on asthma. *Ann Allergy Asthma Immunol* 2003;90:284-91; quiz 91-3, 347.

33. Moorman JE, Akinbami LJ, Bailey CM. National surveillance of asthma: United States, 2001-2010. National Center for Health Statistics. *Vital Health Stat* 2012;3:1-67.

34. Mehal JM, Holman RC, Steiner CA*, et al.* Epidemiology of asthma hospitalizations among American Indian and Alaska Native people and the general United States population. *Chest* 2014;146:624-32.

35. Mansbach JM, Clark S, Teach SJ*, et al.* Children Hospitalized with Rhinovirus Bronchiolitis Have Asthma-Like Characteristics. *J Pediatr* 2016;172:202-04 e1.

36. Gupta RS, Carrion-Carire V, Weiss KB. The widening black/white gap in asthma hospitalizations and mortality. *J Allergy Clin Immunol* 2006;117:351-8.

37. Sheikh A, Steiner MF, Cezard G*, et al.* Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. *BMC Med* 2016;14:3.

38. Shah NM, Shah MA, Behbehani J. Ethnicity, nationality and health care accessibility in Kuwait: a study of hospital emergency room users. *Health Policy Plan* 1996;11:319-28.

39. Chaabna K, Cheema S, Mamtani R. Migrants, healthy worker effect, and mortality trends in the Gulf Cooperation Council countries. *PLoS One* 2017;12:e0179711.

Table 1. Number and average annual rate of asthma hospital admissions and mortality in Kuwait, 2000 to 2014

Characteristic	Number of hospital admissions for asthma (%)	Average annual rate of hospital admissions per 100,000 population[†] (95% CI)	Number of Asthma mortalities (%)	Average annual mortality rate per 100,000 population[‡] (95% CI)
Overall	43,652 (100.0)	134.9 (131.8, 138.1)	484 (100.0)	2.1 (1.8, 2.4)
Sex				
Male	23,784 (54.5)	114.3 (110.4, 118.5)	245 (50.6)	1.8 (1.5, 2.1)
Female	19,868 (45.5)	159.3 (154.6, 164.1)	239 (49.4)	2.5 (2.1, 3.0)
Nationality				
Kuwaiti	27,959 (64.1)	182.5 (177.1, 188.1)	248 (51.2)	2.4 (2.0, 2.8)
Non-Kuwaiti	15,693 (35.9)	99.8 (96.3, 103.5)	236 (48.8)	1.9 (1.6, 2.2)
Age group (years)				
< 5	18,405 (42.1)	426.5 (413.3, 440.1)	16 (3.3)	1.4 (0.9, 2.3)
5 – 19	8,578 (19.7)	81.1 (77.5, 84.9)	21 (4.3)	0.7 (0.5, 1.1)
20 – 44	7,293 (16.7)	34.6 (33.0, 36.1)	99 (20.5)	0.6 (0.5, 0.7)
45 – 64	5,671 (13.0)	92.4 (87.4, 97.7)	124 (25.6)	2.6 (2.2, 3.1)
≥ 65	3,705 (8.5)	405.1 (377.1, 435.1)	224 (46.3)	27.7 (24.2, 31.8)

CI: confidence interval.

[†] Model-adjusted average annual hospital admission rates for asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

[‡] Model-adjusted average annual mortality rates due to asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

Table 2. Annual rates and rate ratios of asthma hospital admissions and mortality in Kuwait, 2000 to 2014

Year	Number of hospital admissions for asthma	Hospital admission rate per 100,000 population† (95% CI)	Adjusted hospital admission RR‡ (95% CI)	Number of asthma mortalities	Mortality rate per 100,000 population§ (95% CI)	Adjusted mortality RR‡ (95% CI)
2000	3,004	180.8 (168.7, 193.8)	1.00 (Reference)	39	4.1 (3.0, 5.6)	1.00 (Reference)
2001	3,557	212.4 (199.3, 226.4)	1.18 (1.07, 1.29)	37	3.3 (2.4, 4.6)	0.81 (0.52, 1.25)
2002	3,755	217.7 (204.6, 231.7)	1.20 (1.10, 1.32)	51	4.9 (3.6, 6.6)	1.19 (0.79, 1.78)
2003	3,022	170.1 (158.8, 182.2)	0.94 (0.86, 1.04)	34	2.9 (2.1, 4.1)	0.71 (0.46, 1.11)
2004	2,860	154.5 (144.0, 165.9)	0.86 (0.78, 0.94)	21	2.3 (1.5, 3.5)	0.56 (0.34, 0.93)
2005	3,133	160.4 (149.9, 171.6)	0.89 (0.81, 0.97)	37	2.6 (1.8, 3.6)	0.62 (0.41, 0.96)
2006	2,819	137.2 (127.7, 147.2)	0.76 (0.69, 0.84)	43	2.5 (1.9, 3.4)	0.61 (0.40, 0.92)
2007	2,215	101.3 (93.6, 109.8)	0.56 (0.51, 0.62)	40	2.5 (1.8, 3.6)	0.60 (0.39, 0.92)
2008	2,353	103.5 (95.8, 111.8)	0.57 (0.52, 0.63)	38	2.2 (1.6, 3.0)	0.52 (0.34, 0.81)
2009	2,525	107.8 (100.0, 116.2)	0.59 (0.54, 0.66)	55	3.0 (2.3, 3.9)	0.73 (0.49, 1.08)
2010	2,629	108.3 (100.7, 116.6)	0.60 (0.54, 0.66)	32	1.9 (1.3, 2.6)	0.45 (0.29, 0.71)
2011	3,149	125.3 (117.1, 134.0)	0.69 (0.63, 0.76)	16	1.4 (0.9, 2.2)	0.33 (0.19, 0.58)
2012	2,976	113.9 (106.3, 122.0)	0.63 (0.57, 0.69)	14	0.9 (0.5, 1.4)	0.21 (0.12, 0.38)
2013	3,122	116.1 (108.5, 124.2)	0.64 (0.58, 0.71)	14	0.8 (0.5, 1.3)	0.19 (0.11, 0.34)
2014	2,533	91.3 (84.8, 98.4)	0.51 (0.46, 0.56)	13	0.9 (0.5, 1.6)	0.22 (0.12, 0.41)

RR: rate ratio; CI: confidence interval.

† Model-adjusted hospital admission rates for asthma per 100,000 population were calculated using Poisson regression models while adjusting for sex, nationality, and age group.

‡ Rate ratios compared with 2000 (the reference year) are adjusted for age, sex, and nationality.

§ Model-adjusted mortality rates due to asthma per 100,000 population were calculated using Poisson regression while adjusting for sex, nationality, and age group.

Figure Legends

Figure 1. Trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. Asthma hospital admission rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis.

Figure 2. Age-, sex-, and nationality-specific trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. A) Rates among males of Kuwaiti nationality. B) Rates among females of Kuwaiti nationality. C) Rates among males of non-Kuwaiti nationality. D) Rates among females of non-Kuwaiti nationality. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis.

Figure 3. Trends in annual asthma mortality rates per 100,000 population in Kuwait, 2000 to 2014. Asthma mortality rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total

study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. *P*-values for linear trend were derived from Poisson regression analysis. *PC is given as rate in 2014 vs. rate in 2001.

Figure 4. Rate ratios of hospital admission rates for asthma in females vs. males by age group in Kuwait, 2000 to 2014. Rate ratios comparing females to males in the total population and by nationality are presented according to age groups. Rate ratios in the total population were adjusted for nationality.

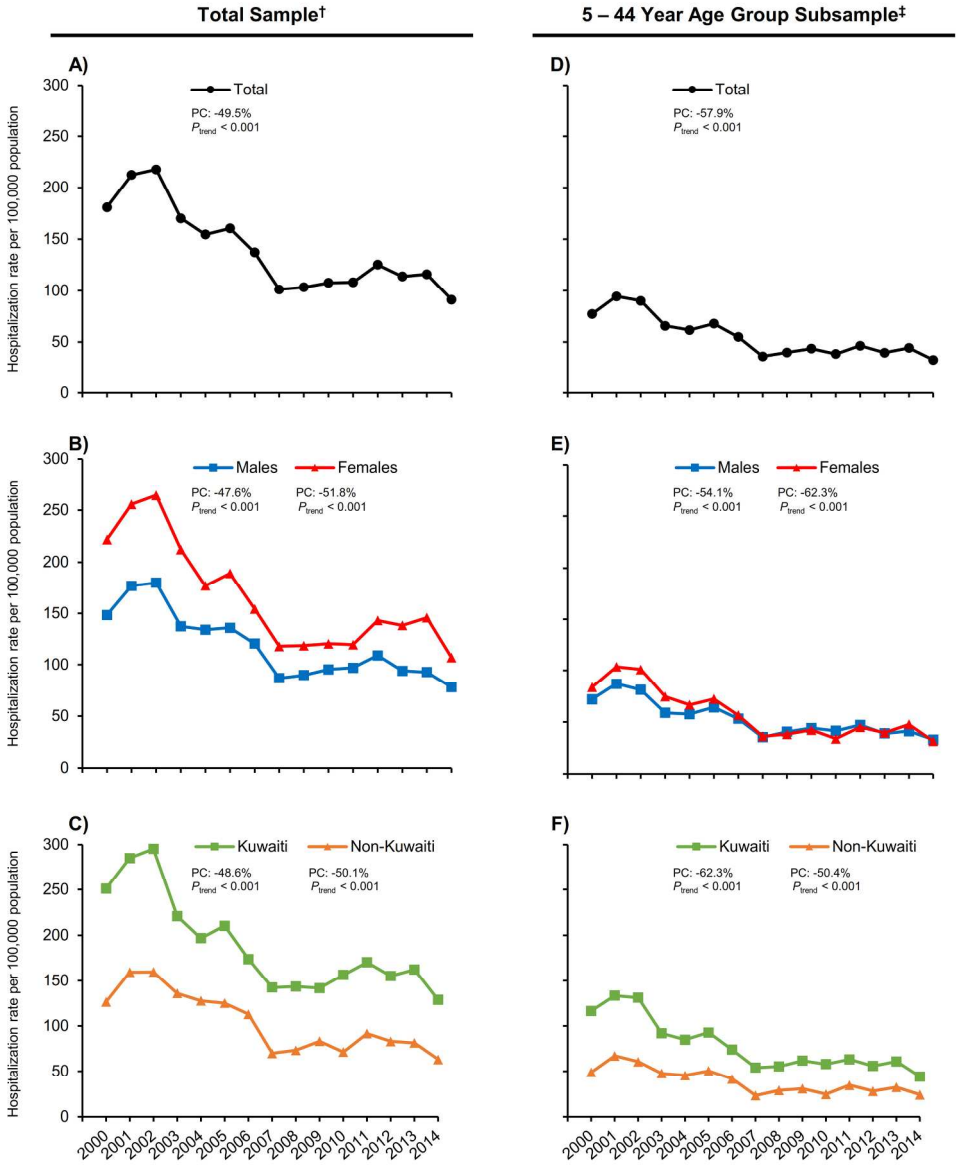


Figure 1. Trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. Asthma hospital admission rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. P-values for linear trend were derived from Poisson regression analysis.

213x252mm (300 x 300 DPI)

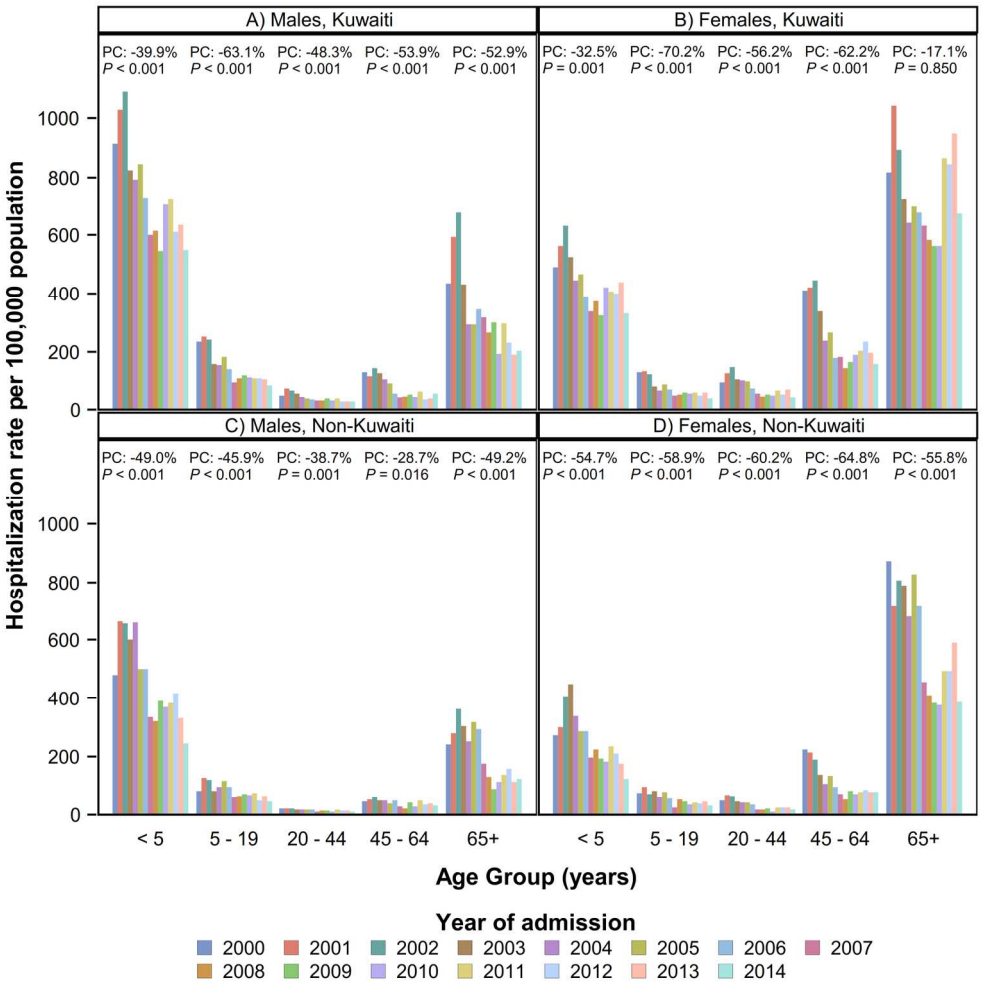


Figure 2. Age-, sex-, and nationality-specific trends in annual hospital admission rates for asthma per 100,000 population in Kuwait, 2000 to 2014. A) Rates among males of Kuwaiti nationality. B) Rates among females of Kuwaiti nationality. C) Rates among males of non-Kuwaiti nationality. D) Rates among females of non-Kuwaiti nationality. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. P-values for linear trend were derived from Poisson regression analysis.

167x167mm (300 x 300 DPI)

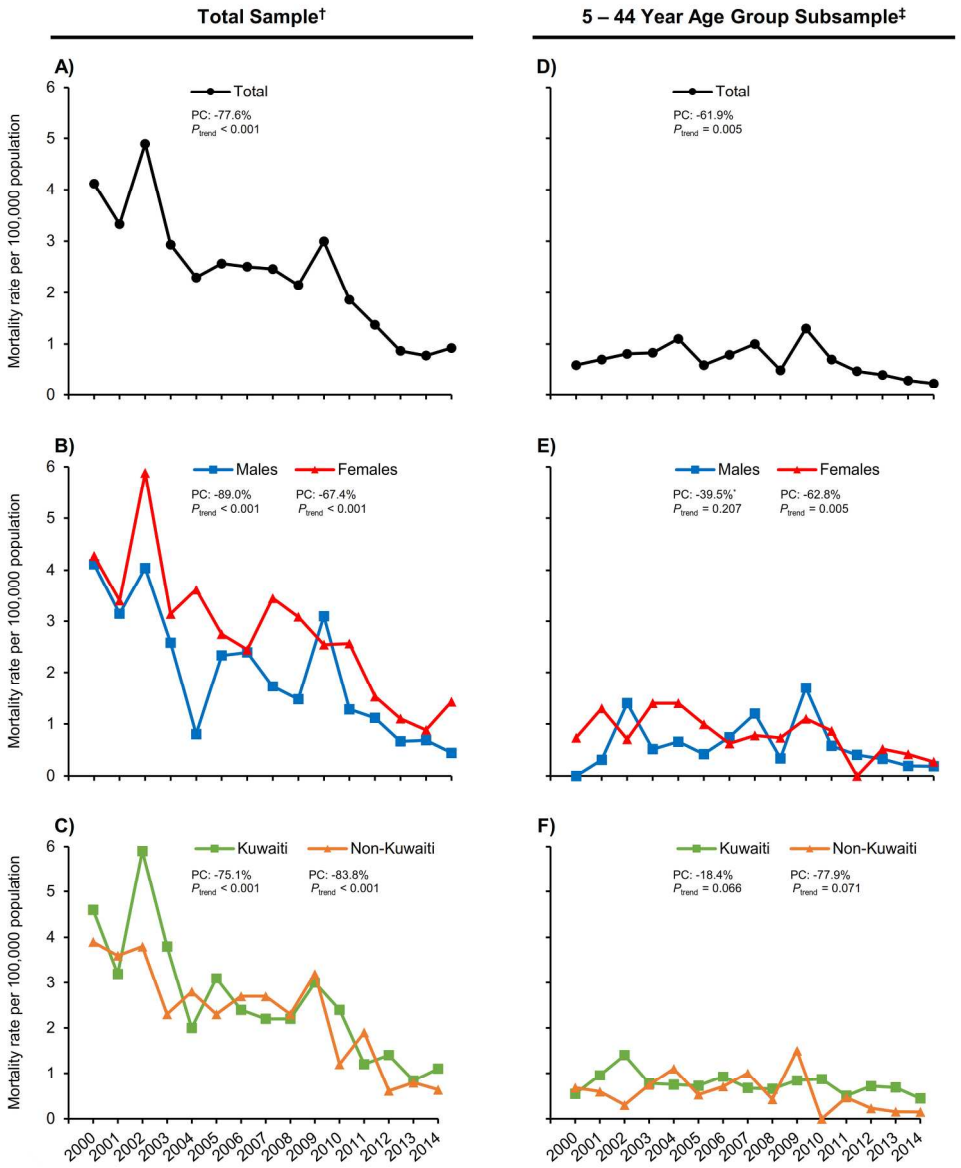


Figure 3. Trends in annual asthma mortality rates per 100,000 population in Kuwait, 2000 to 2014. Asthma mortality rates in the †total study sample (panels A, B, and C) and in a ‡subsample restricted to those aged 5-44 years old (panels D, E, and F) are presented. A) Trends in the total study sample. B) Sex-stratified trends in the total study sample. C) Nationality-stratified trends in the total study sample. D) Trends in the total subsample. E) Sex-stratified trends in the subsample. F) Nationality-stratified trends in the subsample. Rates for the total population (panels A and D) are sex, age, and nationality model-adjusted. The sex-stratified rates (panels B and E) are age and nationality model-adjusted. Nationality-stratified rates (panels C and F) are age and sex model-adjusted. Percent change (PC) given as rate in 2014 vs. rate in 2000. A negative percent change value represent decrease between 2000 and 2014. P-values for linear trend were derived from Poisson regression analysis. *PC is given as rate in 2014 vs. rate in 2001.

213x252mm (300 x 300 DPI)

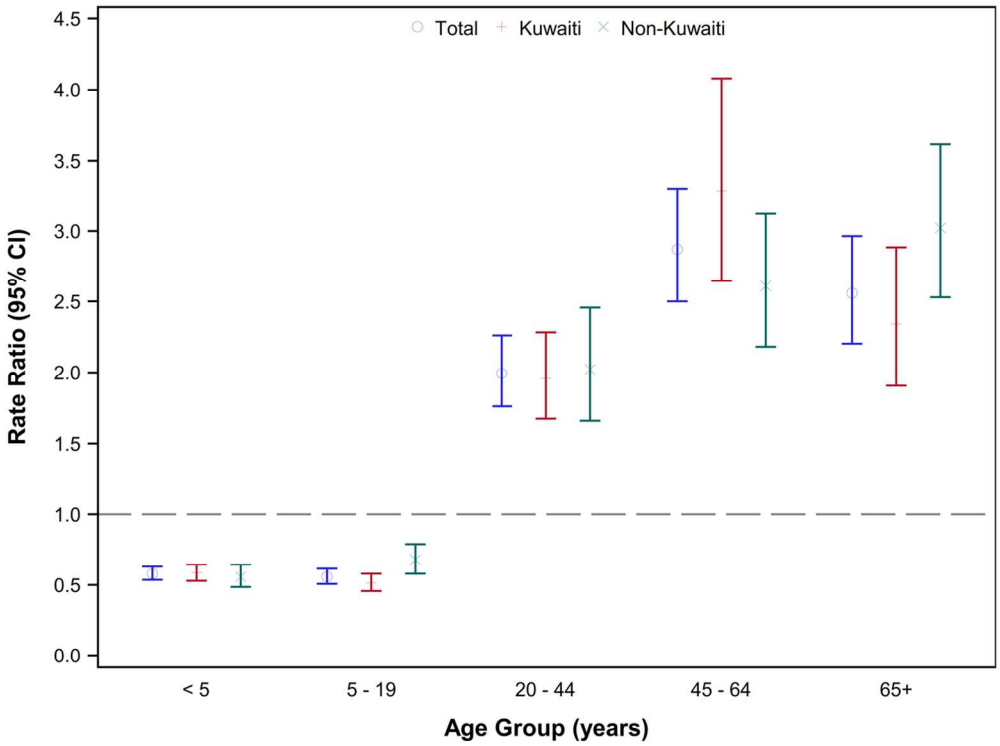


Figure 4. Rate ratios of hospital admission rates for asthma in females vs. males by age group in Kuwait, 2000 to 2014. Rate ratios comparing females to males in the total population and by nationality are presented according to age groups. Rate ratios in the total population were adjusted for nationality.

124x94mm (300 x 300 DPI)

Table S1. Rates and rate ratios of hospital admissions for asthma comparing Kuwaiti and non-Kuwaiti individuals stratified by sex and age group in Kuwait, 2000 to 2014

	Age group (years)	Nationality	Number of hospital admissions for asthma	Average annual rate of hospital admissions per 100,000 population† (95% CI)	RR‡ (95% CI)
Males	< 5	Kuwaiti	8,318	733.5 (690.3, 779.4)	1.67 (1.49, 1.86)
		Non-Kuwaiti	3,502	440.6 (401.4, 483.7)	1.00
	5 – 19	Kuwaiti	4,077	141.5 (131.7, 152.0)	1.80 (1.57, 2.06)
		Non-Kuwaiti	1,535	78.8 (70.1, 88.4)	1.00
	20 – 44	Kuwaiti	1,061	40.0 (35.6, 44.9)	2.62 (2.27, 3.02)
		Non-Kuwaiti	2,127	15.3 (14.0, 16.6)	1.00
	45 – 64	Kuwaiti	559	73.4 (61.4, 87.8)	1.82 (1.48, 2.25)
		Non-Kuwaiti	1,510	40.3 (36.1, 44.9)	1.00
	≥ 65	Kuwaiti	720	319.9 (289.0, 354.0)	1.65 (1.39, 1.96)
		Non-Kuwaiti	375	194.2 (168.9, 223.3)	1.00
	Total	Kuwaiti	14,735	151.7 (143.9, 159.9)	1.81 (1.69, 1.94)
		Non-Kuwaiti	9,049	83.7 (79.2, 88.5)	1.00
Females	< 5	Kuwaiti	4,711	431.5 (400.8, 464.5)	1.75 (1.52, 2.01)
		Non-Kuwaiti	1,874	246.5 (219.3, 277.0)	1.00
	5 – 19	Kuwaiti	2,025	72.3 (66.5, 78.6)	1.36 (1.17, 1.57)
		Non-Kuwaiti	941	53.2 (47.1, 60.1)	1.00
	20 – 44	Kuwaiti	2,202	76.5 (67.4, 86.9)	2.50 (2.08, 3.01)
		Non-Kuwaiti	1,903	30.6 (26.7, 35.0)	1.00
	45 – 64	Kuwaiti	2,363	240.5 (217.1, 266.4)	2.27 (1.90, 2.70)
		Non-Kuwaiti	1,239	106.1 (92.2, 122.2)	1.00
	≥ 65	Kuwaiti	1,923	751.0 (683.1, 825.8)	1.33 (1.11, 1.59)
		Non-Kuwaiti	687	566.5 (483.8, 663.4)	1.00
	Total	Kuwaiti	13,224	213.2 (202.2, 224.9)	1.88 (1.72, 2.06)
		Non-Kuwaiti	6,644	113.4 (105.2, 122.3)	1.00

RR: rate ratio; CI: confidence interval.

† Average annual hospital admission rates for asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models.

‡ Age- and sex- specific rate ratios comparing Kuwaiti to non-Kuwaiti individuals.

Table S2. Rates and rate ratios of asthma mortality comparing females to males according to age group in Kuwait, 2000 to 2014

Age group (years)	Sex	Average annual mortality rate per 100,000 population (95% CI)[†]	RR[‡] (95% CI)
< 5	Female	1.7 (1.6, 1.8)	0.99 (0.89, 1.10)
	Male	1.7 (1.6, 1.8)	1.00
5 – 19	Female	1.0 (0.7, 1.6)	1.51 (0.98, 2.32)
	Male	0.7 (0.5, 1.0)	1.00
20 – 44	Female	0.8 (0.5, 1.1)	1.55 (1.10, 2.40)
	Male	0.5 (0.4, 0.7)	1.00
45 – 64	Female	3.0 (2.2, 4.0)	1.07 (0.73, 1.58)
	Male	2.8 (2.2, 3.5)	1.00
≥ 65	Female	38.0 (29.9, 48.2)	1.50 (1.06, 2.12)
	Male	25.3 (19.5, 32.9)	1.00

RR: rate ratio; CI: confidence interval.
[†] Model-adjusted average annual mortality rates due to asthma per 100,000 population per year over the period from 2000 to 2014 were calculated using Poisson regression models while adjusting for nationality.
[‡] Age-specific rate ratios comparing females to males while adjusting for nationality.

Table S3. Sex- and age-standardized rates and rate ratios of asthma hospital admissions in the total population and stratified by nationality in Kuwait, 2000 to 2014

	Sex- and age-standardized asthma hospital admission rate per 100,000 population[†] (95% CI)			
Year	**Total**	**Kuwaiti**	**Non-Kuwaiti**	**RR[‡] (95% CI)**
2000	190.6 (181.6, 199.6)	241.8 (228.8, 254.8)	138.4 (124.5, 152.4)	1.75 (1.56, 1.96)
2001	221.3 (211.8, 230.7)	278.6 (264.8, 292.3)	156.3 (143.0, 169.6)	1.78 (1.62, 1.97)
2002	224.9 (215.7, 234.1)	286.7 (273.1, 300.2)	161.2 (147.8, 174.6)	1.78 (1.62, 1.96)
2003	175.2 (167.3, 183.1)	215.5 (204.0, 226.9)	143.0 (130.5, 155.6)	1.51 (1.36, 1.67)
2004	153.5 (146.5, 160.6)	184.5 (174.3, 194.7)	129.2 (117.9, 140.6)	1.43 (1.29, 1.58)
2005	162.8 (155.6, 169.9)	194.7 (184.6, 204.9)	135.4 (123.9, 146.9)	1.44 (1.30, 1.59)
2006	140.7 (134.1, 147.2)	163.8 (154.5, 173.1)	119.8 (109.4, 130.1)	1.37 (1.23, 1.52)
2007	107.0 (101.3, 112.6)	138.6 (130.1, 147.1)	75.5 (67.7, 83.3)	1.84 (1.63, 2.07)
2008	103.9 (98.6, 109.2)	134.1 (126.1, 142.1)	74.5 (67.2, 81.8)	1.80 (1.61, 2.02)
2009	107.2 (102.0, 112.3)	136.7 (128.7, 144.7)	79.4 (72.5, 86.4)	1.72 (1.55, 1.91)
2010	106.3 (101.3, 111.3)	141.8 (134.0, 149.5)	72.2 (65.6, 78.8)	1.96 (1.77, 2.18)
2011	127.1 (121.6, 132.6)	166.6 (158.0, 175.2)	88.8 (81.6, 95.9)	1.88 (1.71, 2.07)
2012	118.3 (113.1, 123.5)	152.5 (144.5, 160.5)	84.2 (77.3, 91.1)	1.81 (1.64, 2.00)
2013	120.7 (115.6, 125.9)	158.0 (150.1, 166.0)	84.4 (77.4, 91.4)	1.87 (1.70, 2.06)
2014	93.7 (89.3, 98.2)	126.0 (119.0, 133.0)	63.6 (57.8, 69.4)	1.98 (1.78, 2.20)
Average[⁋]	136.3 (134.7, 137.9)	175.3 (172.9, 177.8)	98.8 (96.6, 101.1)	1.77 (1.73, 1.82)

RR: rate ratio; CI: confidence interval.

[†] Asthma hospital admission rates per 100,000 population were sex- and age-standardized to the World Health Organization Standard Population.

[‡] Rate ratios comparing sex- and age-standardized hospital admission rates among Kuwaiti to non-Kuwaiti subjects.

[⁋] Average annual sex- and age-standardized asthma hospital admission rates per 100,000 population per year over the period from 2000 to 2014.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-13
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-13
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	10-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.