

Sex Differences in Asthma and Gastroesophageal Reflux Disease Incidence Among the World Trade Center Health Program General Responder Cohort

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Background Asthma and gastroesophageal reflux disease (GERD) are two common conditions among the responders to the WTC attacks. This study examined whether the cumulative incidence rates of asthma and GERD differed by sex among 24,022 and 23,557 WTC responders, respectively.

Methods Cox proportional hazards regression was used to examine the sex difference in the rate of onset of physician-diagnosed asthma or GERD, from 9/12/2001 through 12/31/2015.

Results The cumulative incidence of asthma reached 23% for women and 17% for men by the end of 2015, and the cumulative incidence of GERD reached 45% for women and 38% for men. Comparing women to men, the hazard ratio was 1.48 (95% confidence interval (CI): 1.27, 1.74) for asthma, and 1.25 (95% CI: 1.13, 1.38) for GERD.

Conclusions WTC general responders have a substantial burden of asthma and GERD, with higher incidence in women. *Am. J. Ind. Med.* 59:815–822, 2016.

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KEY WORDS: asthma; GERD; 9/11; World Trade Center

INTRODUCTION

Asthma is a common disease, affecting more than 22 million adults in the United States [Centers for Disease

Control and Prevention, 2013] and 330 million people worldwide [The Global Asthma Report, 2014]. Epidemiological studies of asthma indicate a distinct difference in asthma prevalence by sex [Skobeloff et al., 1992; Postma, 2007; Almqvist et al., 2008; McCallister and Mastronarde, 2008; Kynnyk et al., 2011]. The National Health and Nutrition Examination Survey yielded asthma prevalence in the United States of 9.6% for women and 5.8% for men from 2001 to 2014.

Gastroesophageal reflux disease (GERD) involves the presence of symptoms and signs of esophageal damage caused by the reflux of stomach contents in the esophagus [Lin et al., 2004; Kahrilas, 2008]. It has been estimated that the prevalence of GERD in the US in 2014 was 20–30% (60–90 million cases) [El-Serag et al., 2014]. GERD affects both sexes, with women tending to report more severe symptoms than men, potentially contributing to earlier

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recognition of disease, however, the prevalence was similar in men and women [Lin et al., 2004]. Population-based studies of the incidence of GERD are rare in the United State [El-Serag et al., 2014]. One study reported on the incidence of GERD, using Medicaid claims, making generalizability difficult [Kotzan et al., 2001].

Asthma and GERD often coexist. Compared to the prevalence in the general population, GERD prevalence tends to be higher in asthma sufferers, ranging from 25% to 80%, depending on the definition of GERD used [McCallister et al., 2011; Mastrorade, 2012]. These two conditions have been noted to have a sex-specific difference [Skobeloff et al., 1992; Lin et al., 2004; Postma, 2007; Almqvist et al., 2008; McCallister and Mastrorade, 2008; Kynnyk et al., 2011] which may require different prevention and/or treatment approaches in men and women. Among the General Responder Cohort (GRC) of the World Trade Center Health Program (WTCHP), asthma and GERD are two commonly existing comorbid conditions [Wisnivesky et al., 2011; Dasaro et al., 2015]. In this investigation we assess the cumulative incidence rates of asthma and GERD over the 14 years since the WTC attacks, and investigate whether the incidence rates differ by sex.

METHOD

Study Population

The WTCHP GRC is a prospective cohort consisting of workers and volunteers who participated in the rescue and recovery work after the September 11, 2001 (hereafter 9/11) attacks on the World Trade Center. A detailed description of the cohort has been presented elsewhere [Dasaro et al., 2015]. In brief, the cohort began to be established within a month of 9/11, and more formal establishment resulted from National Institute for Occupational Safety and Health funding in 2003, and subsequently continues under the auspices of the James Zadroga 9/11 Health and Compensation Act of 2010. Eligible WTC responders were those who (i) worked or volunteered for 4 hr or more from September 11 to September 14, 2001; or 24 hr or more in September, 2001; or 80 hr or more from September 11 to December 31, 2001 (expanded to July, 2002 with the advent of the Zadroga Act); or (ii) processed relevant human remains; or (iii) spent 24 hr or more in cleaning the Port Authority Trans Hudson tunnels between February 2002 and July 2002. Of the 52,492 persons seeking enrollment in WTCHP as of 12/31/2015, 36,767 (70.0%) met the above-mentioned eligibility criteria and completed a first visit; 35,534 (67.7%) consented to have their data aggregated. For this investigation, responders with pre-9/11/2001 reported asthma (8,362 [23.5% of 35,534]) or GERD (6,588 [18.5% of 35,534]) were excluded from

analyses. The World Trade Center Health Programs were initially approved by the Institutional Review Board of The Mount Sinai School of Medicine, and subsequently by both the IRB of the Icahn School of Medicine at Mount Sinai and IRBs of the clinical sites listed in the author affiliations. The Health Programs obtained the signed consent of all participants.

Outcome Assessment

The WTCHP uses standard clinical practice guidelines for diagnosis of asthma [American Thoracic Society, 1987; Chung et al., 2014] and GERD [DeVault and Castell, 2005]. These conditions are certified for free treatment via the Program through an attestation from a medical professional that conditions were contributed to or aggravated by WTC exposure (e.g., airborne toxins, heavy lifting or repetitive strains on muscles, and joints during WTC clean-up work) [Dasaro et al., 2015]. Certified asthma or GERD were the health outcomes for this analysis. As of December 31, 2015, 5.3% (N = 1,868) of the cohort was certified for asthma only; 16.8% (N = 5,974) was certified for GERD only; and 12.1% (N = 4,288) was certified for both asthma and GERD. Diagnosis dates were self-reported for both conditions. For the current analyses, those who self-reported asthma or GERD but were not certified by the program (N = 2,615 [9.6%] for asthma; N = 4,302 [14.9%] for GERD) were excluded. Those who were certified but did not have a self-reported diagnosis date (N = 535 [2.0%] for asthma; N = 1,087 [3.8%] for GERD) were also excluded. The final analytic sample sizes were 24,022 for asthma and 23,557 for GERD.

Exposure Assessment and Demographic Information

Details of the exposure assessment can be found elsewhere [Wisnivesky et al., 2011; Solan et al., 2013]. In brief, four exposure groups were created: very high, high, intermediate, and low, based on total time spent working on the WTC effort, exposure to the dust cloud, and work on the pile of debris [Wisnivesky et al., 2011]. Data for age on 9/11, sex, race/ethnicity, educational levels, and occupation were collected via interviewer-administered and self-administered medical questionnaires at the time of enrollment or the first monitoring visit (visit 1). Smoking history was collected at each monitoring visit and was categorized into current, former, and never smoker. Height and weight were obtained via physical examination by a physician at each monitoring visit, and Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Smoking history and BMI from visit 1 only were used for this study.

TABLE I. Demographic and Exposure Characteristics of the Entire World Trade Center Health Program General Responder Cohort Who Consented to Have Their Data Aggregated, by Sex, Including Those Who Might Have Reported Asthma or GERD Before 9/11

Characteristics	Men	Women	P-value
	N = 30,488	N = 5,046	
Age at 9/11/2001 (mean ± SD, years)	38.8 ± 8.8	38.2 ± 8.9	<0.001
Smoking status at visit 1 (N,%)			
Never	17,474 (57.3)	3,128 (62.0)	<0.001
Former	7,472 (24.5)	1,070 (21.2)	
Current	4,397 (14.4)	655 (13.0)	
Missing	1,145 (3.8)	193 (3.8)	
Body mass index at visit 1 (mean ± SD, kg/m ²)*	30.1 ± 5.0	28.1 ± 5.9	<0.001
Occupation (N,%)			
Construction	6,616 (21.7)	361 (7.2)	<0.001
Protective	14,964 (49.1)	2,534 (50.2)	
CM&IRG ^a	2,672 (8.8)	553 (10.9)	
Other	5,585 (18.3)	1,481 (29.4)	
Missing	651 (2.1)	117 (2.3)	
Exposure level (N,%) ^b			
Low	4,363 (14.3)	958 (18.9)	<0.001
Intermediate	18,494 (60.7)	2,923 (57.9)	
High	5,256 (17.2)	815 (16.2)	
Very high	1,019 (3.3)	90 (1.8)	
Missing	1,356 (4.5)	260 (5.2)	
Marital status			
Single	3,084 (10.1)	1,280 (25.4)	<0.001
Married	22,576 (74.0)	2,299 (45.6)	
Separated, divorced, or widowed	4,428 (14.5)	1,383 (27.4)	
Missing	400 (1.3)	84 (1.7)	
Educational level			
<High school graduate	2,168 (7.1)	430 (8.5)	<0.001
High school graduate	6,881 (22.6)	673 (13.3)	
Some college	12,228 (40.1)	1,767 (35.0)	
College graduate	8,006 (26.3)	1,937 (38.4)	
Missing	1,205 (3.9)	239 (4.8)	
Race/ethnicity			
Black	3,074 (10.1)	1,051 (20.8)	<0.001
White non-Hispanic	20,609 (67.6)	2,039 (40.4)	
Hispanic not black	5,514 (18.1)	1,722 (34.1)	
Asian non-Hispanic	493 (1.6)	59 (1.2)	
Other non-Hispanic	504 (1.6)	101 (2.0)	
Missing	294 (1.0)	74 (1.5)	
Entry year (N,%)			
2002–2005	12,205 (40.0)	1,872 (37.1)	<0.001
2006–2008	8,629 (28.3)	1,713 (33.9)	
>2008	9,654 (31.7)	1,461 (29.0)	

GERD, gastroesophageal reflux disease; WTC, World Trade Center.

P values via ANOVA for categorical variables, and via generalized linear regression for continuous variables.

*N = 29,699 for men and N = 4,882 for women, due to missing data.

^aCM&IRG, buildings and grounds cleaning and maintenance and electrical, telecommunications and other installation and repair groups.

^bExposure level assignment was based on the total time spent working at the WTC effort; exposure to the cloud of debris from the collapse of the WTC buildings; and work on the pile of debris.

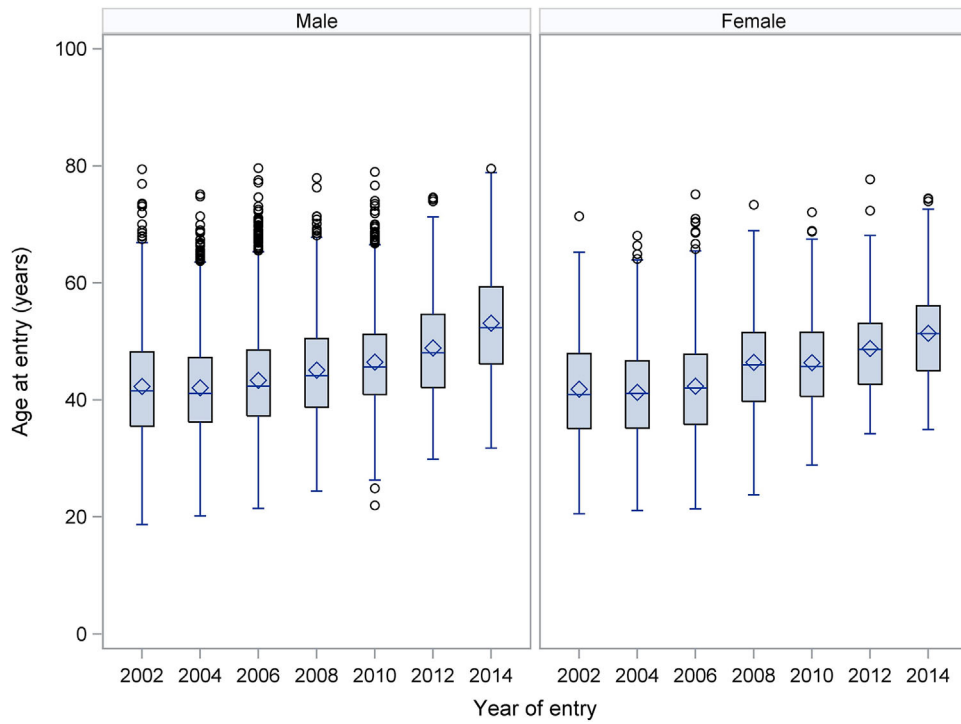


FIGURE 1. Distribution of age at entry into World Trade Center Health Program General Responder Cohort by year of entry, stratified by sex, including those who reported asthma or Gastroesophageal Reflux Disease before 9/11.

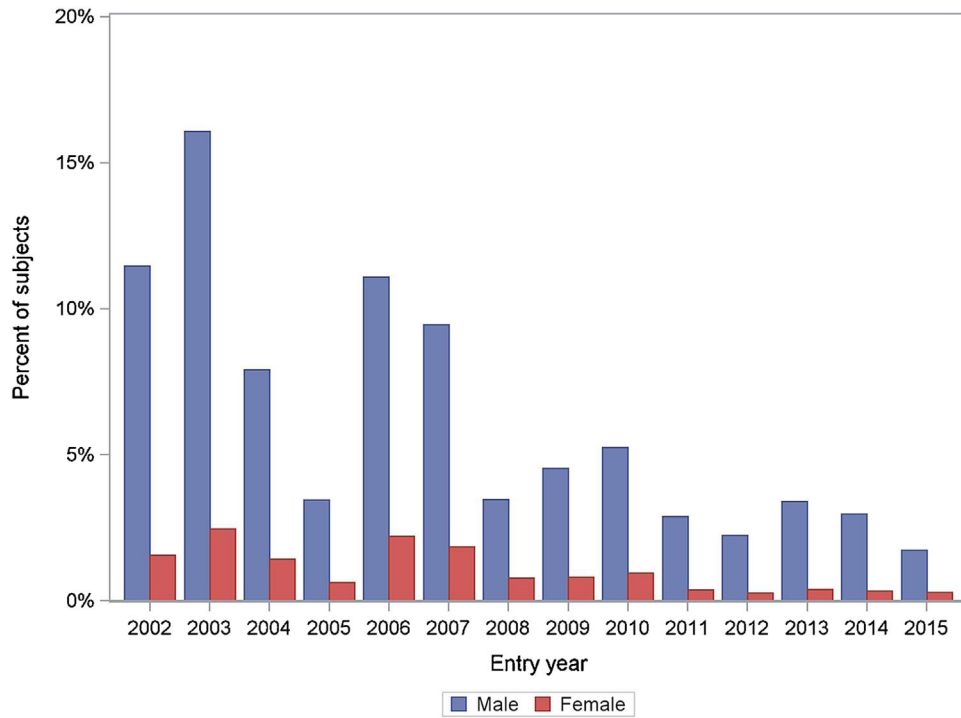


FIGURE 2. Percentage of the responders who entered the World Trade Center Health Program General Responder Cohort and who consented to have their data aggregated, by year and sex.

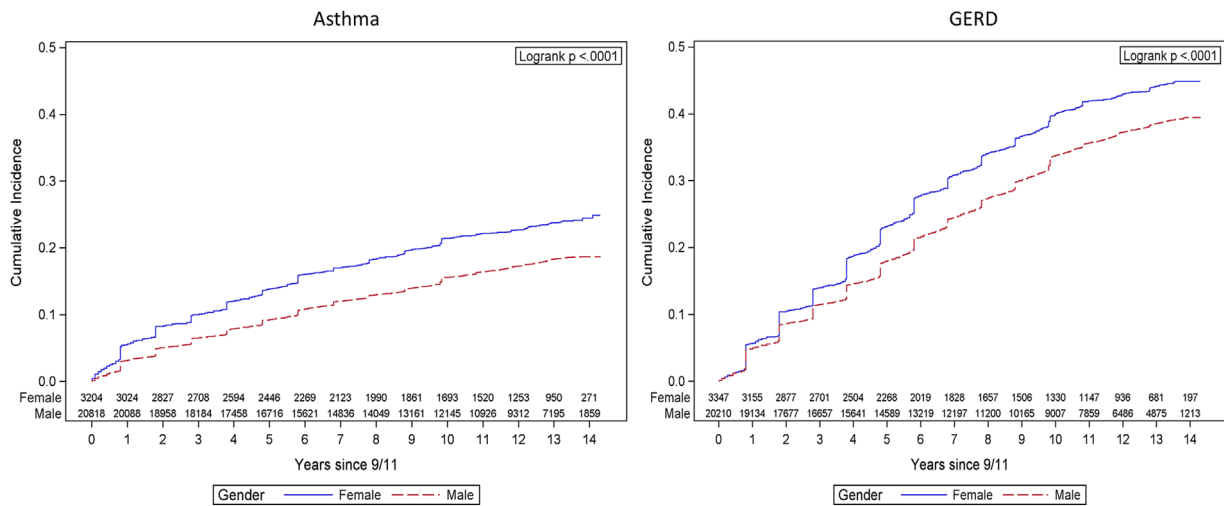


FIGURE 3. Cumulative incidence of asthma or Gastroesophageal Reflux Disease (GERD) in the World Trade Center Health Program General Responder Cohort, for those consented to have their data aggregated.

Statistical Analysis

Descriptive analyses to compare sex differences in demographics, exposure levels, and entry year into the WTCHP were conducted first. In order to minimize the impact of entry year on sex differences, we compared both (i) age at entry versus year of entry, stratified by sex; and (ii) the percentage of the analysis group who entered the WTCHP each year, stratified by sex. Kaplan–Meier estimates were then employed to obtain the cumulative incidence and number of individuals at risk for asthma or GERD, by sex. Person-years were calculated from 9/11/2001 to the first date that the responder reported a physician

TABLE II. Association Between Sex and Certified Asthma or GERD Among the World Trade Center Health Program General Responder Cohort Who Consented to Have Their Data Aggregated, 2002–2015

Hazard ratios for sex	Outcome	
	Asthma	GERD
N at risk	24,022	23,557
Person-years	230,084	197,345
No. of events	3,886	7,744
HR1 (95% CI) women vs men ^a	1.69 (1.55,1.86)	1.41 (1.32,1.51)
HR2 (95% CI) women vs men ^b	1.48 (1.27,1.74)	1.25 (1.13,1.38)

Note: Members with available information on certification and self-reported date of diagnose asthma or GERD were included.

CI, confidence interval; HR, hazard ratio; GERD, gastroesophageal reflux disease; BMI, body mass index.

^aControlled for exposure level, age at 9/11, occupation, race/ethnicity, education level, smoking status at visit 1, BMI at visit 1, and entry period.

^bControlled for model 1 covariates plus certified GERD when outcome is certified asthma and certified asthma when outcome is certified GERD.

diagnosis of asthma or GERD, or at the date of the last follow-up visit until 12/31/2015. Hazard ratios for asthma or GERD associated with sex were obtained via Cox proportional-hazard regression modeling, adjusting for exposure level, age on 9/11, race/ethnicity, educational level, occupation, smoking status, BMI, and entry period (2002–2005, 2006–2008, after 2008). As asthma and GERD often coexist, we also adjusted for GERD that was diagnosed before the onset of asthma when assessing the association between sex and asthma. Similarly, we adjusted for asthma diagnosed before the onset of GERD when assessing the association between sex and GERD. Furthermore, three levels of comparison were conducted, using responders with no asthma or GERD as the reference group, to examine whether the impact of sex on asthma or GERD differed by the coexistence of GERD or asthma, respectively. For subjects with both asthma and GERD, person years were calculated based on the date a condition was reported, whichever came first. Interaction terms were added to examine whether associations between sex and asthma or GERD differed across three BMI categories (normal: 18.5–24.9; overweight: 25.0–29.9; obese: ≥30.0) [Centers for Disease Control and Prevention, 2012]. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc. Cary, NC). All statistical tests of significance were conducted two sided and $P < 0.05$ was considered “significant.”

RESULTS

Compared to women, male WTC responders were more likely to be slightly older and more frequently White non-Hispanic; married; current smokers; construction workers; have a higher BMI; and have lower educational levels and have higher levels of WTC dust exposure (Table I). No sex

TABLE III. Association Between Sex and Three Outcomes: Certified for Asthma Only, Certified for GERD Only, and Certified for Both Asthma and GERD, Among the World Trade Center Health Program General Responder Cohort Who Consented to Have Their Data Aggregated, 2002–2015

Hazard ratios for sex	Outcomes		
	Asthma only	GERD only	Asthma and GERD
N at risk	12,569	14,583	14,481
Person-years	118,889	130,375	124,479
No. of events	509	2,523	2,421
Hazard ratio (95% CI) women <i>cf.</i> men ^a	1.52 (1.16, 1.98)	1.26 (1.11, 1.42)	1.85 (1.65, 2.07)

Note: Only subjects with available information on certification and self-reported date for both conditions were included.

CI, confidence interval; GERD, gastroesophageal reflux disease; BMI, body mass index.

^aThe reference group for comparison is responders without asthma or GERD. The model was controlled for exposure level, age on 9/11/2001, occupation, smoking status at visit 1, race/ethnicity, education level, BMI at visit 1, and entry period.

differences in age at entry versus year of entry, or annual percent entry were observed (Figs. 1 and 2).

At the end of the follow-up, the cumulative incidence of asthma reached 23% for women and 17% for men and the cumulative incidence of GERD reached 45% for women and 38% for men (Fig. 3). The cumulative incidence of asthma was 27%, 20%, and 13% for entry period 2002–2005, 2006–2008, and >2008, respectively; the cumulative incidence of GERD was 49%, 44%, and 29% for each entry period. The hazard ratio (HR) for certified asthma was 1.69 (95% confidence interval [CI]: 1.55, 1.86) for women compared to men, and adjustment for GERD attenuated the HR 12% to 1.48 (95% CI: 1.27, 1.74). Likewise, the HR for certified GERD was 1.41 (95% CI: 1.32, 1.51) for women compared to men, and decreased 11% to 1.25 (95% CI: 1.13, 1.38) after adjusting for asthma (Table II). Comparing the three outcome groups (asthma only, GERD only, and both asthma and GERD) to responders without either asthma or GERD, the HRs for asthma without GERD, GERD without asthma and both asthma and GERD (ignoring condition diagnosis sequence) were, respectively, 1.52 (95% CI: 1.16, 1.98), 1.26 (95% CI: 1.11, 1.42), and 1.85 (95% CI: 1.65, 2.07), for women compared to men (Table III). Sex effects on asthma or GERD were similar across three BMI categories (data not shown). The interactions between sex and BMI on either asthma or GERD were not statistically significant.

DISCUSSION

Our analysis indicates that 14 years after the 9/11 attacks, WTCHP responders have a substantial burden of asthma and GERD and the cumulative incidence rate for each condition differs by sex.

Our finding of sex-related differences in asthma among WTCHP responders is larger but consistent with data from the general population showing that asthma is more common

in women [Skobeloff et al., 1992; Postma, 2007; Almqvist et al., 2008; McCallister and Mastronarde, 2008; Kynnyk et al., 2011]. The lifetime likelihood of asthma development was approximately 11% greater in women than men [American Lung Association, 2010]. A recent study in a Swiss cohort of approximately 5,000 participants reported a 20-year cumulative incidence of asthma of 7.5% in women and 5.1% in men, and an odds ratio that was twice as high in women [Hansen et al., 2015]. Among the WTCHP responders, we found that the cumulative incidence of asthma was even higher in women than men (23% for women and 17% for men, respectively).

GERD is generally not considered to be sex-related in the general population, [Lin et al., 2004; Nilsson et al., 2004; El-Serag et al., 2014] but women tend to experience more severe symptoms [Lin et al., 2004]. In this subset of the WTCHP GRC, women were 41% more likely to have certified GERD than men, over the period from 9/11 until the end of 2015. It is not clear what reasons account for this difference, however, surveillance bias could exist within the WTCHP monitoring program. Men with less severe symptoms may not be diagnosed although they may have GERD, while more severe symptoms in women may result in diagnoses of GERD. In addition, the coexistence of asthma with GERD might also account for the significant sex difference of GERD in the WTCHP GRC.

The coexistence of asthma and GERD has been reported in the general population as well as in the WTCHP GRC [McCallister et al., 2011; Wisnivesky et al., 2011; Mastronarde, 2012; Dasaro et al., 2015]: women are 85% more likely to develop both conditions than men. In our analysis, the hazard ratio of asthma or GERD in women was reduced by 12% and 11%, respectively when each condition was additionally adjusted for the other. These results indicate that sex plays a role in asthma or GERD onset, irrespective of comorbidities of both conditions, for these GRC members.

This investigation has several strengths and limitations. One strength is that the presence of asthma or GERD was

established via certification, eliminating the bias that can accompany self-reported conditions. Another strength is the comprehensive set of covariates that allow adjustment for confounders. Finally, the large sample size for our analysis enables us to calculate cumulative incidence rate of both conditions by sex. In contrast, it is possible that the group analyzed is not completely representative of the entire population of WTC responders because WTCHP participation is voluntary, and self-selection of responders into the program might be based on WTC-related exposures or the presence of disease, which might reduce the generalizability of our findings to the entire WTC responder cohort.

Although, women are a minority in the GRC, based on the findings of this investigation, they are more likely than men to develop both asthma and GERD.

AUTHORS' CONTRIBUTIONS

JJ, MAC, and SLT provided input on study conception and design. JJ, NI, LP, MS, ACT, and SLT contributed to data acquisition, analysis, and interpretation. JJ, ACT, and SLT contributed to the drafting of manuscript. NI, MAC, CRD, JRK, RGL, BJL, JMM, IGU, and ACT contributed to the critical revision of intellectual content. All authors provided final manuscript approval and agree to be accountable for all aspects of the work in order to ensure that all questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

The authors are grateful to the responders; all past and present staff at the World Trade Center Health Programs; the work force, community and volunteer organization program stakeholders; and the philanthropic sources that funded treatment from 2003 to 2006.

FUNDING

This publication was supported via contracts and grants 200-2002-00384, U10-OH008216/23/25/32/39/75 and 200-2011-39356/61/77/84/85/88 from the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC/NIOSH.

ETHICS APPROVAL AND INFORMED CONSENT

The World Trade Center Health Programs were initially approved by the Institutional Review Board of The Mount

Sinai School of Medicine, and subsequently by both the IRB of the Icahn School of Medicine at Mount Sinai and IRBs of the clinical sites listed in the author affiliations. The Health Programs obtained the signed consent of all participants. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

DISCLOSURE (AUTHORS)

The authors declare no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

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