

Asthma, the sex difference

Jessica A. Kynnyk, John G. Mastronarde and Jennifer W. McCallister

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University Medical Center, Columbus, Ohio, USA

Correspondence to Jennifer W. McCallister, MD, Assistant Professor of Internal Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University, 201 Davis Heart & Lung Research Institute, 473 West 12th Avenue, Columbus, OH 43210, USA
Tel: +1 614 293 4925;
e-mail: Jennifer.McCallister@osumc.edu

Current Opinion in Pulmonary Medicine 2011, 17:6–11

Purpose of review

Asthma is a common chronic disease with significant clinical impact worldwide. Sex-related disparities in asthma epidemiology and morbidity exist but debate continues regarding the mechanisms for these differences. There is a need to review the recent findings for asthma care providers and to highlight areas in need of additional research.

Recent findings

Recent data illustrate striking sex-related differences in asthma epidemiology and disease expression. Studies show an increased incidence of asthma in women. Data demonstrate that asthmatic women have a poorer quality of life and increased utilization of healthcare compared to their male counterparts despite similar medical treatment and baseline pulmonary function. Research continues to explore hypotheses for these differences including the potential influences of the female sex hormones, altered perception of airflow obstruction, increased bronchial hyper-responsiveness, and medication compliance and technique. However, no single explanation has been able to fully explain the disparities.

Summary

Women are more likely to be diagnosed with asthma and suffer greater morbidity than men. The physiologic mechanisms for these differences are not well understood. Understanding sex-related differences in asthma and providing patients with education geared toward these disparities are important in establishing effective, individualized asthma management strategies for all patients.

Keywords

asthma, differences, sex-related, treatment

Curr Opin Pulm Med 17:6–11
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1070-5287

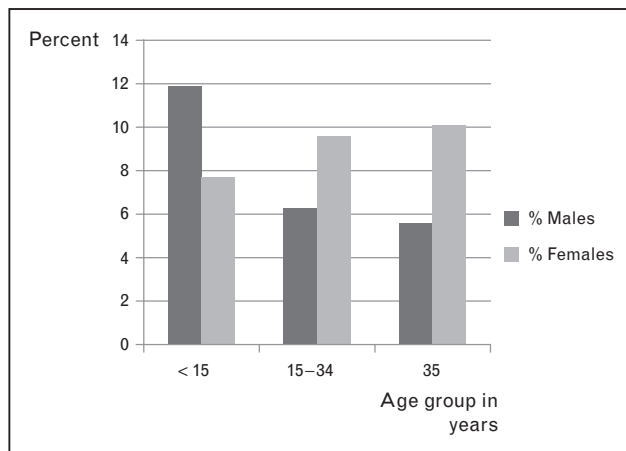
Introduction

Asthma is a common disease affecting more than 23 million adults in the United States [1] and 300 million people worldwide. The prevalence of asthma has increased, and an estimated 250 000 deaths globally are related to asthma each year [2]. Considerable differences in asthma prevalence, morbidity, and healthcare utilization have been identified between men and women although the exact mechanisms underlying these disease disparities remain uncertain. The major sex-related differences in asthma related disease manifestations and some of the hypotheses that have been developed to explain these are reviewed here.

Prevalence of asthma

Epidemiologic studies of asthma show a striking difference in asthma prevalence and severity closely related to sex and age, which interestingly seem to follow key transition points in the reproductive cycle of women. In general, the lifetime likelihood of developing asthma

is about 10.5% greater in women than men [3•]. When examined at specific time points, asthma is more common and more severe in prepubertal boys, with boys less than 18 years of age having a 54% higher rate of asthma than girls of the same age [3•]. However, the prevalence of asthma and its severity increases significantly in women after puberty, with asthma becoming more common in women by age 20 in the United States [4]. As an example, 2009 estimates from the National Health Interview Survey in the United States demonstrate a prevalence of asthma in those less than 15 years of age of 11.9% in boys and 7.7% in girls [5•]. In young adults aged 15–34 years, the pattern shifts, with a prevalence of 6.3% in men and 9.6% in women. The difference continues to widen in adults older than 35 years with a prevalence of 5.6 versus 10.1% in men and women, respectively (refer to Fig. 1). European studies evaluating the prevalence of asthma by age yield similar results [6]. However, more recent studies suggest a narrowing of the gap in asthma prevalence during childhood [7]. After menopause, the difference in asthma prevalence between men and women seems to narrow but does not disappear [8,9].

Figure 1 Prevalence of asthma by age and sex

Prevalence of current asthma in the United States in 2009 by age group [5].

Mortality

Sex-related differences in asthma mortality also exist but the patterns are difficult to predict based on prevalence data alone. In 2006, asthma accounted for 3613 deaths in the United States [3]. Women comprised 64% of these, with an age-adjusted death rate that was 44% higher than men [3]. Data collected by the National Vital Statistics System in the United States from 2001 to 2003 revealed that women had a higher at-risk-based death rate from asthma than men (2.3 versus 1.8, respectively) [10]. However, the observed sex-related differences in asthma mortality appeared to be closely related to age. Closer review of data collected over this 3-year period found that women had a higher mortality rate only at age at least 65 years [10]. Review of data from the National Hospital Discharge Survey Database in the United States from 1995 to 2001 found a similar trend, with the highest mortality from asthma in men 35 or less years of age [11]. Ethnicity contributes further to the observed mortality differences between men and women, with black women experiencing the highest age-adjusted mortality from asthma in the United States [3].

Hospitalizations and exacerbations

Age-related sex differences in hospitalized asthma patients have been well described. Patients hospitalized for asthma more than 15 years old are up to three times more likely to be female, whereas those hospitalized for asthma exacerbations at less than 15 years of age are up to two times more likely to be male [12–22]. Although the established differences in asthma prevalence between men and women likely contribute to these observations, it has been suggested that other factors such as altered perception of airflow obstruction or perhaps sex-related

disparities in asthma treatment should also be considered [17]. Women presenting to the emergency department (ED) with acute exacerbations of asthma are more likely to be admitted to the hospital than men despite presenting with better pulmonary function [23,24], less hypoxia [17], and less hypercapnia [25]. However, in currently available series [17,24], the differences in rates of hospitalizations have not been shown to be related to differences in use of controller medications prior to presentation, delays in healthcare evaluation, or disparities in treatment in the ED or during hospitalization, supporting the notion that perhaps there is something inherently different about adult women with asthma that also contributes.

There is conflicting data on whether length of hospital stay differs between men [19,25,26] and women but it appears that African American women suffer more severe exacerbations requiring intensive care unit (ICU) admissions than either men or white women [25]. It is difficult to discern potential mechanisms for these findings as available studies include diverse patient populations with many different asthma phenotypes. Future studies that devote more attention to matching clinical and biomarker profiles among men and women with asthma will be required to verify these findings and to identify underlying mechanisms.

Perception of symptoms and quality of life

Current data have highlighted the fact that adult men and women experience asthma symptoms differently. Studies using standardized questionnaires have shown that women report more asthma symptoms and a poorer quality of life when compared to men despite having similar pulmonary function at baseline [27–29]. In addition, women with asthma report a greater number of unscheduled physician visits [28,30,31], more frequent use of oral corticosteroids [31] and a greater use of short acting beta-agonists for rescue [28,30,32] than men.

Similar disparities in asthma symptoms have been seen in patients presenting to the ED with acute exacerbations. Although no significant differences have been shown in duration of symptoms or treatments attempted prior to ED presentation for acute asthma exacerbations, women are more likely to describe their symptoms as severe compared to men [24,29] despite having less severe airflow obstruction on peak expiratory flow evaluation [24]. Additionally, after hospitalizations, women are 50% more likely than men to continue to report persistent dyspnea [24].

It has been hypothesized that women may actually perceive airflow obstruction differently than men, leading to their reported worse asthma-related quality of life and greater discomfort with symptoms [28,32]. Studies have

shown that asthmatic women more commonly perceive airflow obstruction as dyspnea and have a higher incidence of anxiety than men, resulting in increased impairment on quality of life [28,33^{••},34]. Other possible contributing factors that have been suggested include improper metered-dose inhaler technique [35] and reduced inspiratory muscle strength in women [34].

Bronchial hyperresponsiveness

A clinical hallmark of asthma is bronchial hyperresponsiveness (BHR) to nonspecific stimuli such as methacholine or histamine. Many population-based studies have revealed a greater prevalence of BHR in women [36–41] than men. Some authors have suggested that the observed increased BHR in women may not actually reflect excess BHR but may simply be a result of the smaller caliber of airways found in women when compared to men [36,37,42]. Accordingly, a lower forced expiratory volume in 1 second (FEV1)% predicted has also been associated with increased BHR [37,43–44]. In a study of the utility of eucapnic voluntary hyperventilation testing to diagnose exercise-induced bronchospasm, women were 2.38 times less likely than men to achieve a threshold minute ventilation of 60% maximum voluntary ventilation (MVV) per minute [45^{••}]. Despite that, 33% of patients who did not achieve threshold MVV were still noted to be positive for exercise-induced bronchospasm defined as at least 10% decline in FEV1 and 16 of 17 of these patients were women. Again, this may reflect increased BHR to hyperventilation as a result of smaller airway caliber in women or it may reflect an inherently different sensitivity to the stimulus. Collectively, these findings suggest that the increased dyspnea and other asthma symptoms in women compared to men may be due to exaggerated responses to asthma triggers or increased BHR, despite having similar baseline lung function.

Other authors have proposed that the increased rate of BHR in women may be related to the increased susceptibility to tobacco smoke, which has been documented in women, even during childhood [38,46]. Girls exposed to second-hand smoke have been shown to have a stronger response to methacholine inhalation than boys even after adjusting for caliber of airway [46]. Similar results have been found in larger population-based studies, in which BHR has been shown to be more common in women and more closely associated with tobacco exposure than in men [38,47]. Other studies have continued to document increased BHR in women compared to men but the sex-related association to tobacco exposure has not always been replicated [48,49]. These sex-related differences in BHR related to tobacco exposure follow similar trends noted in other aspects of pulmonary function in women, where female smokers simply appear to be more suscepti-

ble to the effects of tobacco smoke than men [50–54]. During childhood, girls exposed to tobacco smoke have a greater reduction in rate of growth in FEV1 than boys [50,52], and in adulthood, women smokers have a greater decline in FEV1 than men for similar tobacco exposure [51,54]. Tobacco cessation counseling remains an important piece of asthma care for all patients who smoke but education of female smokers with asthma should highlight this increased susceptibility and its potential long-term implications.

Menstrual-linked asthma

As previously discussed, there are trends in asthma prevalence and severity, which seem to coincide with key transition points in a woman's reproductive life. Accordingly, it has been hypothesized that the female sex hormones influence the development of asthma and its severity. A subset of women with asthma experience exacerbations that seem to be linked to their menstrual cycle [55–60], but data are inconclusive in determining the point in the menstrual cycle at which time they are at greatest risk [60–63]. Of women of reproductive age with asthma, 20–40% report worsening of asthma symptoms or a decrease in pulmonary function during the premenstrual or menstrual period [55–59]. In some series, clinically significant changes in pulmonary function and asthma control related to these self-reported changes in symptoms are infrequent [57,58], but in others, menstrual-related changes in asthma symptoms are associated with increased healthcare utilization [55,56,61,62] and near-fatal asthma episodes [7,56,61]. Studies evaluating the effectiveness of oral contraceptives in blunting premenstrual worsening of asthma have been inconclusive [57,64].

Attempts to correlate menstrual-related asthma symptoms with physiologic and inflammatory changes have proven problematic [65^{••},66–68]. A few small studies have shown that markers of inflammation such as exhaled nitric oxide, sputum eosinophils, and serum leukotriene C₄ concentrations are elevated in women with menstrual-related asthma symptoms [69–71], raising the possibility that some women with asthma may have an exaggerated inflammatory response to asthma triggers coinciding with naturally occurring fluctuations in sex hormones. It is interesting to consider that if this enhanced inflammatory response related to hormonal changes is a true phenomenon, then it may also be related to the exaggerated BHR seen in some women with asthma.

With this information, it is clear that some, but not all, women with asthma may become symptomatic during the premenstrual or menstrual phase with an unclear influence of exogenous hormone therapy on these symptoms. For clinicians, it is important to directly query

about this phenomenon, as many women will not associate their worsened asthma control with their menstrual cycle and this sex-specific pattern of disease worsening may be missed with potential implications for treatment. Several small series using leukotriene receptor antagonists [70], intramuscular progesterone [72], or premenstrual long-acting β_2 -agonists [73] have shown some beneficial effects of treatment but there is a lack of solid clinical data on treatment options for menstrual-related symptoms. For now, treatment according to currently published guidelines with attention to identifying potential sex-related triggers and emphasis on patient education regarding identification of potential asthma triggers seems the most prudent approach.

Menopause and hormone replacement therapy

Differences in asthma incidence at the time of menopause lend further support to the idea that at least some of the sex-related differences that have been described may be influenced by alterations in levels of the female sex hormones. The overall incidence of asthma in women decreases after menopause [8,9,74]. However, in two large prospective studies, the use of postmenopausal hormone replacement was associated with an increased rate of newly diagnosed asthma in menopausal women [74,75]. In data published from the Nurses' Health Study, any use of postmenopausal hormone replacement therapy (HRT) was associated with approximately twice the risk of asthma when compared to postmenopausal women without exogenous hormone exposure [74], and HRT was associated with an increased risk of newly diagnosed asthma with a relative risk of 2.30 in current estrogen users [75], with lean women with a BMI 25 kg/m² or less most affected. These data again highlight the importance of questioning women about changes in reproductive health, which may potentially impact the control of underlying asthma, or may contribute to a new diagnosis later in life.

Asthma management and compliance

Although sex differences exist in the perception of asthma symptoms and associated asthma morbidity, it seems unlikely that differences in asthma management between men and women contribute significantly. Women with asthma are more likely to have a primary care physician than men [17], and studies suggest that they are also more likely to recognize asthma symptoms, seek medical care [76–78], and be prescribed systemic corticosteroids for acute symptoms despite being prescribed inhaled corticosteroids for asthma control at a similar rate [78].

Evaluation of adherence to current asthma guidelines has shown that current clinical practices may actually slightly

favor female patients. Analysis of data from two large managed care organizations has shown that women were more likely to use peak flow meters regularly [77], have a written asthma action plan [76,77] and have regularly scheduled clinic visits for asthma care [77]. However, in these populations, men were more likely to use inhaled corticosteroids on a daily basis despite similar prescribing rates for men and women [76,77]. Several other studies have examined the role of sex on adherence to prescription medication use in asthma with conflicting results [33^{••},79,80].

One study has shown that asthma management based on an understanding of potential social differences between men and women with asthma can result in improved asthma outcomes [81^{••}]. In a study of 808 women with asthma, the use of sex-specific asthma education in addition to guideline-based asthma care resulted in improved asthma care as measured by improved use of peak flow meters, reduction in use of short acting beta-agonists, improved quality of life, and increased self-confidence in asthma management when compared to standard guideline-based care alone [81^{••}]. In this thought-provoking study, the authors used telephone counseling to identify potential sex-related factors that might contribute to poor asthma control including premenstrual- or menstrual-related asthma symptoms, use of oral contraceptives or estrogen replacement therapy, symptoms related to housework, exposures through childcare, or symptoms associated with sexual activity and then directed educational efforts accordingly. While limited to a single population of patients, these findings highlight the importance of identifying those asthma triggers in women that may be related to sex-specific factors so that appropriate self-management strategies can be implemented. This study is also of interest as aside from the focus on potential hormonally mediated asthma triggers, some of the measures touted as 'sex specific' for women may no longer be the domain of women in westernized countries where many men now have assumed a primary role in household and childcare duties. It remains to be seen if men who have assumed these responsibilities will have an increase in asthma symptoms and respond differently to occupational-based asthma treatment plans or if female hormonal changes are the main modulator of previously identified differences.

Conclusion

Knowledge of sex-related differences in asthma prevalence and expression is critical in the evaluation and management of all patients with asthma and should be the focus of ongoing research efforts. Treatment of patients with asthma should follow currently available guidelines with efforts to identify those aspects of the disease that may be sex specific, allowing asthma care

providers to develop individualized asthma care plans with these potential disparities in mind. Awareness of the aspects of the disease that are unique to women should stimulate continued research to determine the underlying mechanisms and further aid our understanding of this common disease.

Acknowledgement

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 50).

- 1 Centers for Disease Control and Prevention. 2008 adult asthma data: prevalence tables and maps [database on the Internet]. 2008. <http://www.cdc.gov/asthma/brfss/08/lifetime/tableL1.htm>.
- 2 World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach [database on the Internet]. 2007. http://www.who.int/gard/publications/GARD_Manual/en/index.html.
- 3 American Lung Association. Trends in asthma morbidity and mortality [database on the Internet]. 2010. <http://www.lungusa.org/finding-cures/our-research/trend-reports/asthma-trend-report.pdf>.
- This database summarizes the current sex differences in asthma prevalence and morbidity and mortality.
- 4 Centers for Disease Control and Prevention. Adult self-reported current asthma prevalence rate by sex and state or territory: BRFSS 2008 [database on the Internet]. 2008. <http://www.cdc.gov/asthma/brfss/08/current/tableC21.htm>.
- 5 Barnes PM, Heyman KM, Freeman G, *et al.* Early release of selected estimates based on data from the 2009 National Health Interview Survey. Hyattsville, MD: National Center for Health Statistics; 2010. <http://www.cdc.gov/nchs/nhis.htm>.
- This survey documents the most recent differences in asthma prevalence by sex and age in the United States.
- 6 De Marco R, Locatelli F, Sunyer J, *et al.* Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000; 162:68–74.
- 7 Osman M, Tagiyeva N, Wassall HJ, *et al.* Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. *Pediatr Pulmonol* 2007; 42:60–65.
- 8 Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999; 54:1119–1138.
- 9 Zannolli R, Morgese G. Does puberty interfere with asthma? *Med Hypotheses* 1997; 48:27–32.
- 10 Moorman JE, Rudd RA, Johnson CA, *et al.* National surveillance for asthma: United States, 1980–2004. *MMWR Surveill Summ* 2007; 56:1–54.
- 11 Getahun D, Demissie K, Rhoads GG. Recent trends in asthma hospitalization and mortality in the United States. *J Asthma* 2005; 42:373–378.
- 12 Bloomberg GR, Trinkaus KM, Fisher EB Jr, *et al.* Hospital readmissions for childhood asthma: a 10-year metropolitan study. *Am J Respir Crit Care Med* 2003; 167:1068–1076.
- 13 Chen Y, Stewart P, Johansen H, *et al.* Sex difference in hospitalization due to asthma in relation to age. *J Clin Epidemiol* 2003; 56:180–187.
- 14 Hyndman SJ, Williams DR, Merrill SL, *et al.* Rates of admission to hospital for asthma. *BMJ* 1994; 308:1596–1600.
- 15 Joseph CL, Havstad SL, Ownby DR, *et al.* Racial differences in emergency department use persist despite allergist visits and prescriptions filled for anti-inflammatory medications. *J Allergy Clin Immunol* 1998; 101 (4 Pt 1): 484–490.
- 16 Kao CC, See LC, Yan DC, *et al.* Time trends and seasonal variations in hospital admissions for childhood asthma in Taiwan from 1990 to 1998. *Asian Pac J Allergy Immunol* 2001; 19:63–68.
- 17 Schatz M, Clark S, Camargo CA Jr. Sex differences in the presentation and course of asthma hospitalizations. *Chest* 2006; 129:50–55.
- 18 Schaubel D, Johansen H, Mao Y, *et al.* Risk of preschool asthma: incidence, hospitalization, recurrence, and readmission probability. *J Asthma* 1996; 33:97–103.
- 19 Skobeloff EM, Spivey WH, St Clair SS, *et al.* The influence of age and sex on asthma admissions. *JAMA* 1992; 268:3437–3440.
- 20 To T, Dick P, Feldman W, *et al.* A cohort study on childhood asthma admissions and readmissions. *Pediatrics* 1996; 98 (2 Pt 1):191–195.
- 21 Von Behren J, Kreutzer R, Smith D. Asthma hospitalization trends in California, 1983–1996. *J Asthma* 1999; 36:575–582.
- 22 Wilkins K, Mao Y. Trends in rates of admission to hospital and death from asthma among children and young adults in Canada during the 1980s. *CMAJ* 1993; 148:185–190.
- 23 Awadh N, Chu S, Grunfeld A, *et al.* Comparison of males and females presenting with acute asthma to the emergency department. *Respir Med* 1996; 90:485–489.
- 24 Singh AK, Cydulka RK, Stahmer SA, *et al.* Sex differences among adults presenting to the emergency department with acute asthma. Multicenter Asthma Research Collaboration Investigators. *Arch Intern Med* 1999; 159:1237–1243.
- 25 Trawick DR, Holm C, Wirth J. Influence of gender on rates of hospitalization, hospital course, and hypercapnea in high-risk patients admitted for asthma: a 10-year retrospective study at Yale-New Haven Hospital. *Chest* 2001; 119:115–119.
- 26 Gehlbach B, Kress JP, Kahn J, *et al.* Correlates of prolonged hospitalization in inner-city ICU patients receiving noninvasive and invasive positive pressure ventilation for status asthmaticus. *Chest* 2002; 122:1709–1714.
- 27 Ostrom NK. Women with asthma: a review of potential variables and preferred medical management. *Ann Allergy Asthma Immunol* 2006; 96:655–665.
- 28 Osborne ML, Vollmer WM, Linton KL, *et al.* Characteristics of patients with asthma within a large HMO: a comparison by age and gender. *Am J Respir Crit Care Med* 1998; 157:123–128.
- 29 Cydulka RK, Emerman CL, Rowe BH, *et al.* Differences between men and women in reporting of symptoms during an asthma exacerbation. *Ann Emerg Med* 2001; 38:123–128.
- 30 Sinclair AH, Tolsma DD. Gender differences in asthma experience and disease care in a managed care organization. *J Asthma* 2006; 43:363–367.
- 31 Lee JH, Haselkorn T, Chipps BE, *et al.* Gender differences in IgE-mediated allergic asthma in the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study. *J Asthma* 2006; 43:179–184.
- 32 Wijnhoven HA, Kriegsman DM, Snoek FJ, *et al.* Gender differences in health-related quality of life among asthma patients. *J Asthma* 2003; 40:189–199.
- 33 Sundberg R, Toren K, Franklin KA, *et al.* Asthma in men and women: treatment adherence, anxiety, and quality of sleep. *Respir Med* 2010; 104:337–344.
- This study found an increase in anxiety in asthmatic women as well as sex differences in self-reported medication compliance.
- 34 Weiner P, Magadle R, Massarwa F, *et al.* Influence of gender and inspiratory muscle training on the perception of dyspnea in patients with asthma. *Chest* 2002; 122:197–201.
- 35 Goodman DE, Israel E, Rosenberg M, *et al.* The influence of age, diagnosis, and gender on proper use of metered-dose inhalers. *Am J Respir Crit Care Med* 1994; 150 (5 Pt 1):1256–1261.
- 36 Bakke PS, Baste V, Gulsvik A. Bronchial responsiveness in a Norwegian community. *Am Rev Respir Dis* 1991; 143:317–322.
- 37 Britton J, Pavord I, Richards K, *et al.* Factors influencing the occurrence of airway hyperreactivity in the general population: the importance of atopy and airway calibre. *Eur Respir J* 1994; 7:881–887.
- 38 Leynaert B, Bousquet J, Henry C, *et al.* Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. *Am J Respir Crit Care Med* 1997; 156:1413–1420.
- 39 Manfreda J, Sears MR, Becklake MR, *et al.* Geographic and gender variability in the prevalence of bronchial responsiveness in Canada. *Chest* 2004; 125:1657–1664.
- 40 Norrman E, Plaschke P, Björnsson E, *et al.* Prevalence of bronchial hyperresponsiveness in the southern, central and northern parts of Sweden. *Respir Med* 1998; 92:480–487.
- 41 PausJenssen ES, Cockcroft DW. Sex differences in asthma, atopy, and airway hyperresponsiveness in a university population. *Ann Allergy Asthma Immunol* 2003; 91:34–37.
- 42 Kanner RE, Connett JE, Altose MD, *et al.* Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. *Am J Respir Crit Care Med* 1994; 150:956–961.

- 43 Rijcken B, Schouten JP, Mensinga TT, *et al.* Factors associated with bronchial responsiveness to histamine in a population sample of adults. *Am Rev Respir Dis* 1993; 147 (6 Pt 1):1447–1453.
- 44 Sparrow D, O'Connor G, Colton T, *et al.* The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. The Normative Aging Study. *Am Rev Respir Dis* 1987; 135:1255–1260.
- 45 Brummel NE, Mastrorade JG, Rittinger D, *et al.* The clinical utility of eucapnic
•• voluntary hyperventilation testing for the diagnosis of exercise-induced bronchospasm. *J Asthma* 2009; 46:683–686.
This study evaluated exercise-induced bronchospasm and noted that although women were less likely to reach maximal voluntary ventilation per minute they still had evidence of exercise-induced bronchospasm.
- 46 Forastiere F, Agabiti N, Corbo GM, *et al.* Passive smoking as a determinant of bronchial responsiveness in children. *Am J Respir Crit Care Med* 1994; 149 (2 Pt 1):365–370.
- 47 Paoletti P, Carrozzi L, Viegi G, *et al.* Distribution of bronchial responsiveness in a general population: effect of sex, age, smoking, and level of pulmonary function. *Am J Respir Crit Care Med* 1995; 151:1770–1777.
- 48 Chinn S, Jarvis D, Luczynska CM, *et al.* An increase in bronchial responsiveness is associated with continuing or restarting smoking. *Am J Respir Crit Care Med* 2005; 172:956–961.
- 49 Tashkin DP, Altose MD, Bleecker ER, *et al.* The Lung Health Study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. The Lung Health Study Research Group. *Am Rev Respir Dis* 1992; 145 (2 Pt 1):301–310.
- 50 Chen Y, Rennie DC, Lockinger LA, *et al.* Gender, environmental tobacco smoke, and pulmonary function in rural children and adolescents: the Humboldt study. *J Agric Saf Health* 2005; 11:167–173.
- 51 Dransfield MT, Davis JJ, Gerald LB, *et al.* Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. *Respir Med* 2006; 100:1110–1116.
- 52 Gold DR, Wang X, Wypij D, *et al.* Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med* 1996; 335:931–937.
- 53 Prescott E, Bjerg AM, Andersen PK, *et al.* Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997; 10:822–827.
- 54 Xu X, Weiss ST, Rijcken B, *et al.* Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. *Eur Respir J* 1994; 7:1056–1061.
- 55 Agarwal AK, Shah A. Menstrual-linked asthma. *J Asthma* 1997; 34:539–545.
- 56 Eliasson O, Scherzer HH, DeGraff AC Jr. Morbidity in asthma in relation to the menstrual cycle. *J Allergy Clin Immunol* 1986; 77 (1 Pt 1):87–94.
- 57 Gibbs CJ, Coutts II, Lock R, *et al.* Premenstrual exacerbation of asthma. *Thorax* 1984; 39:833–836.
- 58 Hanley SP. Asthma variation with menstruation. *Br J Dis Chest* 1981; 75:306–308.
- 59 Shames RS, Heilbron DC, Janson SL, *et al.* Clinical differences among women with and without self-reported perimenstrual asthma. *Ann Allergy Asthma Immunol* 1998; 81:65–72.
- 60 Brenner BE, Holmes TM, Mazal B, *et al.* Relation between phase of the menstrual cycle and asthma presentations in the emergency department. *Thorax* 2005; 60:806–809.
- 61 Martinez-Moragon E, Plaza V, Serrano J, *et al.* Near-fatal asthma related to menstruation. *J Allergy Clin Immunol* 2004; 113:242–244.
- 62 Skobeloff EM, Spivey WH, Silverman R, *et al.* The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Intern Med* 1996; 156:1837–1840.
- 63 Zimmerman JL, Woodruff PG, Clark S, *et al.* Relation between phase of menstrual cycle and emergency department visits for acute asthma. *Am J Respir Crit Care Med* 2000; 162 (2 Pt 1):512–515.
- 64 Murphy VE, Gibson PG. Premenstrual asthma: prevalence, cycle-to-cycle variability and relationship to oral contraceptive use and menstrual symptoms. *J Asthma* 2008; 45:696–704.
- 65 Farha S, Asosingh K, Laskowski D, *et al.* Effects of the menstrual cycle on lung
•• function variables in women with asthma. *Am J Respir Crit Care Med* 2009; 180:304–310.
This article demonstrates cyclic changes in airflow and diffusion capacity in asthmatic women throughout their menstrual cycle.
- 66 Juniper EF, Kline PA, Roberts RS, *et al.* Airway responsiveness to methacholine during the natural menstrual cycle and the effect of oral contraceptives. *Am Rev Respir Dis* 1987; 135:1039–1042.
- 67 Pauli BD, Reid RL, Munt PW, *et al.* Influence of the menstrual cycle on airway function in asthmatic and normal subjects. *Am Rev Respir Dis* 1989; 140:358–362.
- 68 Weinmann GG, Zacur H, Fish JE. Absence of changes in airway responsiveness during the menstrual cycle. *J Allergy Clin Immunol* 1987; 79:634–638.
- 69 Jeziorska M, Salamonsen LA, Woolley DE. Mast cell and eosinophil distribution and activation in human endometrium throughout the menstrual cycle. *Biol Reprod* 1995; 53:312–320.
- 70 Nakasato H, Ohru T, Sekizawa K, *et al.* Prevention of severe premenstrual asthma attacks by leukotriene receptor antagonist. *J Allergy Clin Immunol* 1999; 104 (3 Pt 1):585–588.
- 71 Oguzulgen IK, Turkas H, Erbas D. Airway inflammation in premenstrual asthma. *J Asthma* 2002; 39:517–522.
- 72 Beynon HL, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. *Lancet* 1988; 2:370–372.
- 73 Magadle R, Berar-Yanay N, Weiner P. Long-acting bronchodilators in premenstrual exacerbation of asthma. *Respir Med* 2001; 95:740–743.
- 74 Troisi RJ, Speizer FE, Willett WC, *et al.* Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Crit Care Med* 1995; 152 (4 Pt 1):1183–1188.
- 75 Barr RG, Wentowski CC, Grodstein F, *et al.* Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Arch Intern Med* 2004; 164:379–386.
- 76 Krishnan JA, Diette GB, Skinner EA, *et al.* Race and sex differences in consistency of care with national asthma guidelines in managed care organizations. *Arch Intern Med* 2001; 161:1660–1668.
- 77 Naleway AL, Vollmer WM, Frazier EA, *et al.* Gender differences in asthma management and quality of life. *J Asthma* 2006; 43:549–552.
- 78 Sexton M, Althuis MD, Santanello N, *et al.* Sex differences in the use of asthma drugs: cross sectional study. *BMJ* 1998; 317:1434–1437.
- 79 Williams LK, Joseph CL, Peterson EL, *et al.* Race-ethnicity, crime, and other factors associated with adherence to inhaled corticosteroids. *J Allergy Clin Immunol* 2007; 119:168–175.
- 80 Lindberg M, Ekstrom T, Moller M, *et al.* Asthma care and factors affecting medication compliance: the patient's point of view. *Int J Qual Healthcare* 2001; 13:375–383.
- 81 Clark NM, Gong ZM, Wang SJ, *et al.* From the female perspective: long-term
•• effects on quality of life of a program for women with asthma. *Gend Med* 2010; 7:125–136.
This study found improvement in quality of life in asthmatic women who received sex-specific asthma education.