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Gender and asthma

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The preponderance of epidemiologic evidence demonstrates disparities in asthma burden when comparing females and males. Males develop asthma at a younger age than do females [1], and the incidence of asthma generally is reported to be higher in boys throughout preadolescence, resulting in a 2:1 male predominance in childhood [2,3]. The increased risk for asthma and wheeze among boys reverses at puberty, however, after which the incidence rate of asthma in girls increases, resulting in a 2:1 female predominance among adults [4–6]. These findings are demonstrated by De Marco and colleagues in a retrospective analysis of data from the European Respiratory Health Survey (Fig. 1). In infancy, girls have a lower risk for developing asthma than do boys, with a rate ratio (RR) for girls compared with boys ranging from 0.74 to 0.56 among children 10 years old or younger. At the time of puberty, the risk equalizes in both sexes (RR, 0.84; 95% confidence interval [CI], 0.66–1.12), and after puberty the risk is significantly higher in women than in men, ranging from 1.38 to 5.91 [7]. Among adults aged 25 to 74, being female has been shown to be the strongest predictor of incident cases of asthma [8]. There is evidence for a disparate increase in the prevalence of asthma between men and women. Between 1982 and 1992, the prevalence among US women increased 82% (from 2.9% to 5.4%) compared with an increase of 29% among men (4.0% to 5.1%) [9]. Other investigators suggest that the reversal in the prevalence rates of asthma among young adults is caused by a higher remission rate among boys and a higher incidence rate among girls [10–14].

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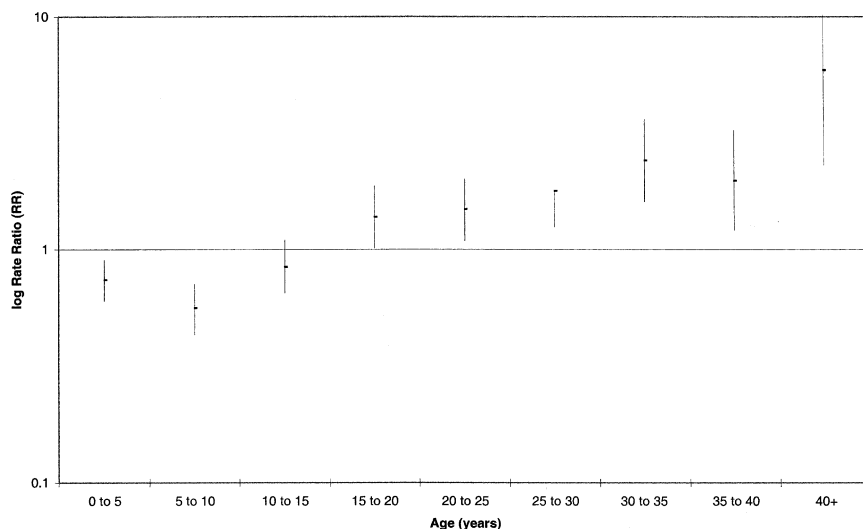


Fig. 1. Age-specific RR for asthma in girls and women versus boys and men, adjusted by age at interview. (From de Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women: a retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000;162:68–74; with permission.)

Differences between females and males in asthma severity, morbidity, and mortality have been observed. Using data from the Healthcare Cost and Utilization Project, Meurer and co-workers observed that among children hospitalized with asthma, boys were more likely than girls to be classified as having high-severity asthma [15]. Some evidence suggests that girls with asthma have poorer lung function [16], experience more frequent relapses after an emergency department (ED) visit for asthma [17], and have a poorer prognosis than do boys with asthma [18]. Among adults, women disproportionately account for the rise in healthcare use for asthma [19]. Of adults who presented to the ED with an acute exacerbation of asthma, women were twice as common as men, and women were more likely to be admitted from the ED after presentation [20]. The female-to-male ratio in the rate of urgent healthcare use seems to follow the same general pattern that is seen with asthma prevalence; during childhood, boys are admitted twice as often as girls and during adulthood, women have consistently higher admission rates than do men [21]. When considering all age groups, asthma mortality rates are higher among women [22], although in the younger age groups a higher death rate has been reported among boys [23,24].

To explore potential causes of the observed disproportionate asthma burden among the sexes, it is helpful to consider how sex may influence health in general and to frame hypotheses within the current asthma paradigm. The term sex has been used to refer to biologic processes related to sexual dimorphism. Theoretically, however, many processes that are associated with females or males are described as more precisely gender. Extensive scholarship has delineated com-

ponents of gender [25,26]. In simplified form, gender can be defined as processes that fundamentally are shaped by environmental or sociocultural distinctions that arise from biologic sex. These distinctions can include: social roles that females or males may occupy but that generally are associated with one gender or another (eg, primary caregiver as female, coal miner as male); sets of beliefs and expectations about the self and others (eg, deferent female, confident male); and behaviors that are associated with femininity or masculinity (eg, housecleaning, playing football). In practice, the line between sex and gender is not distinct, because there is a bidirectional influence between biologic processes and the environmental and sociocultural factors that produce asthma [27]. To acknowledge the inextricable ties between biologic and environmental and sociocultural factors, the term gender is used to encompass both sets of processes.

Whether the term sex or gender is used, both terms often have been used mistakenly to refer solely to attributes of girls or women. Boys and men, as well as girls and women, have and are influenced by sex and gender. When possible, the authors discuss the impact of being male on asthma alongside the impact of being female. Although most asthma research has been done on males, few studies explore how the attributes of males (from genetics to masculinity to male roles) manifest in increased asthma morbidity and mortality. Most of the gender-specific literature on asthma reviewed in this article is about females.

To understand the influence of gender on asthma, the interaction of gender with the natural history of asthma should be examined; topics include factors that influence the biologic susceptibility to disease (diathesis), exacerbation of existing disease (triggers), or the diagnosis and treatment of asthma (management). Gregerson proposed the use of multifactorial systems models to analyze research methods in asthma [28]. Using this framework, many of the factors that influence asthma development can be represented. Individual factors can be thought of as internal or external to the individual person with asthma, with psychosocial factors forming a bridge between and impacting the internal and external influences. The authors examine how selected factors influence the biologic susceptibility to disease, triggering of preexisting asthma, and the management of disease. Examination of the factors that are known to influence asthma leads to the conclusion that gender can influence most of these relationships and can help clarify and expand the existing knowledge of the natural history of disease.

Maternal–fetal interactions

Asthma begins in childhood [29,30], with most disease occurring before age 6 years [31]. Remission and subsequent recurrence are common [30], and studies have shown that up to 80% of asthmatic children become asymptomatic during puberty [32,33]. The British national childhood development study documented that only 5% of children who reported wheeze at age 7 years reported persistent wheeze at subsequent time points (age 11, 16, 23, and 33). More than half of

children who reported wheeze before age 7 years later reported periods of remission during a 7-year interval (age, 16–23) but subsequent relapse at age 33 [34].

Between 80% to 90% of asthma cases start in early childhood, which suggests that the environmental exposures of the neonate and infant are important. A maternal history of asthma and allergy confers a higher risk for allergy than does a paternal history of atopy, particularly among children who develop asthma early in life [35,36]. Gender may influence asthma risk through maternal–fetal interactions. Reasons for the greater importance of maternal inheritance are not well understood. It has been postulated that in addition to genetic inheritance, mechanisms for conferring increased risk may include transplacental transfer of maternal antibodies or antigens, dietary factors, and inflammatory products [37–39].

Recognition of asthma as an inflammatory disease raises the possibility that the genetic and environmental factors that affect maturation of the immune system during childhood set the stage for the inflammatory processes and altered reactivity to stimuli that are characteristic of chronic asthma [40]. Among children who become allergic or asthmatic, the polarization of the immune system into an atopic phenotype occurs in the first years of life and likely begins before birth [41,42]. T helper cell 1 (T_H1) immunity may be detrimental to the fetus [43,44], and an increase in T_H2 immunity and a shift away from T_H1 responses occurs during pregnancy, resulting in the T_H2 skewed response seen in newborns [45,46]. This finding is confirmed in studies in which the newborn period is dominated by T_H2 reactivity in response to allergens [47,48].

Immune maturation

Normal immune maturation that occurs during the first year of life involves suppression of T_H2 responses and deviation toward T_H1 immunity, influenced by regulatory mechanisms that may be driven by environmental factors and exposure to specific allergens. Such exposures cause up-regulation of the T_H1 immune response to allow development of balanced T_H1 and T_H2 responses [49,50]. Compared with newborns who do not develop atopy in childhood, newborns who do develop atopy have relatively immature T_H1 immunity (ie, a reduced capacity to produce interferon γ [IFN- γ]) and an age-dependent increase in the T_H2 response [51–53]. The T_H2 cytokine phenotype promotes IgE production with subsequent recruitment of inflammatory cells, which may initiate or potentiate allergic inflammation and asthma [50,54].

Early sensitization can be seen as a marker of defective immune maturation [50,55]. Early-life exposure to particular aeroallergens may influence polarization of the immune system toward the atopic phenotype [56] and predispose to wheeze expression in the first year of life [57]. Evidence from experimental and epidemiologic studies suggests that microbial exposure is an important stimulus for normal postnatal maturation of T_H1 -associated immune development [58,59]. Theories suggest that widespread use of antibiotics during early life may lead to changes in the intestinal flora of young infants, influencing immune maturation [60].

The relationship between asthma and hypersensitivity to aeroallergens has been documented in cross-sectional [61] and prospective studies [62,63]. T-cell reactivity to specific antigenic stimulation has been studied in cross-sectional studies of several differently aged cohorts from atopic familial backgrounds [64]. The response to the food allergen ovalbumin was most frequent in cord blood, declining throughout childhood. Whereas responses to house dust mite were present in at least 25% of cord blood samples, responses to this aeroallergen increased with age, were present in 30% to 60% of samples from the cohorts from age 6 months to 2 years, and were highest (about 75%) in the adult cohort [65]. Proliferation to specific antigen stimulation is likely to be a specific recognition of that antigen. If these T-cell responses are specific, dietary and inhalant allergen responses may be initiated frequently in utero or during early infancy. The production of cytokines by the stimulated lymphocytes of infants and children, who are in the process of lymphocyte maturation, is beginning to be understood. Evidence in the authors' laboratory demonstrates that early-life allergen exposure at age 3 months predicts antigen-specific T-cell proliferative responses at age 2 years [56]. Genetic factors, in utero and postnatal environmental factors, and the timing of these factors affect the differentiation of the immune response.

Gestational exposure to maternal stress has been shown in offspring to alter the development of humoral immunocompetence and the hormonal and immunologic responses to postnatal stress [66–68]. Evidence in rhesus monkeys indicates that stress experienced during pregnancy impacts the infant monkeys' response to antigens at birth [67]. Some investigators speculate that stress triggers hormones in early life, which in turn influences T_H2 predominance, perhaps through the direct effect of stress hormones on cytokine production through modulation of the direction of differentiation [69]. Maternal stress may continue to influence immune maturation into childhood, setting the stage for the inflammatory processes and altered reactivity to stimuli characteristic of airway obstruction and recurrent wheeze.

A substantial amount of literature has demonstrated the influence of psychologic stress on cell trafficking, T-cell function, and lymphocyte production of cytokines [70]. Stress can modulate immune response through pathways that connect the autonomic nervous system, endocrine regulation, and immune system by triggering the release of hormones and neuropeptides that interact with immune cells [71,72]. This phenomenon includes stress-elicited changes of cytokine production [73,74].

Prenatal maternal stress also may influence childhood wheeze through its documented relationship to low birth weight [75]. A growing number of studies that link birth weight to disease risk in childhood and later life have focused on the prenatal environment. Over the past decade, associations have been shown between size at birth and risk for adult chronic diseases, including type 2 diabetes, cardiovascular disease, and breast cancer [76–78]. Studies have shown a relationship between childhood asthma and lower birth weight [79,80], preterm births [81,82], and full-term births [79] (discussed later).

Hormonal influences

In addition to their influence through the maternal–fetal environment, gender-related hormonal differences affect immune function after pregnancy. A task force that examined the understanding of gender effects on autoimmune disease has reported its findings. As summarized by Whitacre and colleagues [83], the task force concluded that the basis for sex differences in autoimmune disease is most likely multifactorial, with contributions from hormones, genetics, immune bias, and the environment [84].

Sex hormones have been documented to affect a wide array of immune processes. Immune responses in women with higher immunoglobulin levels (immunoglobulin G [IgG], IgM) generally are more robust than responses in men [85]. Women have elevated levels of CD4 lymphocytes [86], resulting in a higher CD4:CD8 T-cell ratio in their peripheral blood than that seen in men [87]. There also are documented effects of sex hormones on several aspects of the immune response, including humoral immunity [88], cellular immunity [89,90], chemokine levels [85,91], and antigen presentation and regulation, including apoptosis [92,93]. Sex steroids also have been shown to affect the expression of endothelial adhesion molecules [94,95] and lymphocyte homing [96]. Eosinophil recruitment [97] and deregulation [98] also have been affected. It has been proposed that hormones can affect the T_H1 – T_H2 balance, in which estrogen tends to push the immune phenotype toward a T_H2 cytokine profile, and androgens favor a T_H1 profile [85,98].

The importance of hormonal influences is supported by the observation that autoimmune diseases are more prevalent among women than men and are related to hormonal changes; these diseases often begin after menarche, become quiescent after menopause, and are influenced by exogenous hormonal therapy. The effects of sex steroids on asthma can be seen in the hormonal changes that are seen throughout the life cycle in women (ie, menarche, pregnancy, menopause). The influence of hormones is illustrated by the reversal in the gender ratio of asthma prevalence and incidence during adolescence. The increase in the incidence rate among girls correlates well with the hormonal changes that occur with the onset of puberty.

Pregnancy

Women can alter their usual immunologic status during pregnancy. The clinical course of asthma has been shown to vary with pregnancy. About one third of pregnant women experience a deterioration of their asthma during pregnancy, mostly during weeks 29 to 36 (peak progesterone); another one third experience an improvement that is more marked in the final 4 weeks of gestation (when free cortisol is at its greatest level); and approximately one third have no change in their clinical course [99]. Similar patterns have been reported for other inflammatory conditions. The improvement of a mother's rheumatoid arthritis during pregnancy has been well documented, with improvement in symptoms in

about three quarters of pregnancies during the first trimester. The rheumatoid arthritis invariably recurs within 3 to 4 months of delivery [100].

Menstrual cycle

The changes seen during the menstrual cycle offers insight into the influence of hormonal changes on airway inflammation, airway size, function of airway smooth muscles, and immune function. Similar to what is seen in pregnancy, menstruation is associated with exacerbation of many medical conditions including rheumatoid arthritis [101], systemic lupus erythematosus, and asthma [102]. Premenstrual worsening of asthma occurs in the late luteal phase of the menstrual cycle; up to 40% of women report exacerbation of their symptoms [103–107] and increased use of rescue bronchodilators during this time [108]. This phenomenon may be an exaggeration of the cyclic decrease in peak expiratory flow (PEF) during the menstrual cycle that has been seen in normal women. Among women with asthma who previously were not aware of their premenstrual asthma, a worsening of asthma symptoms and decrease in PEF rates around the perimenstrual period has been documented [109].

The rate of healthcare use is influenced by the menstrual cycle. Skobleoff et al documented a four-fold variation in the frequency of asthma exacerbation between the postovulatory and perimenstrual intervals, with the perimenstrual time (day 26 to day 4 of the cycle) as the most common time (46%) for ED visits related to asthma [110]. Other investigators have confirmed variations in exacerbations with the menstrual cycle, although Zimmerman and colleagues reported that more women had exacerbations in the preovulatory period instead of the perimenstrual period, as reported by Skobeloff [111].

There is an observable relationship between the cyclic changes in other measures of asthma morbidity and the hormonal fluctuations of the menstrual cycle. Daily peak flow measurements demonstrate a positive correlation between levels of serum progesterone and estrogen [112]. The use of intramuscular progesterone has been shown to eliminate premenstrual dips in peak flow and reduce the requirement for prednisolone in asthmatic patients, suggesting that a rapid decrease in serum progesterone may have an important role in the pathogenesis of premenstrual asthma [113,114]. Based on this evidence, a correlation between markers of inflammation and the hormonal changes seen throughout the menstrual cycle would be expected. IL-6 is produced in the uterus [115]. Variation in the concentration of serum IL-6 [116] and expression of T_H2 cytokines in endometrial samples are influenced by secretion of sex hormones and vary with the menstrual cycle [117]. Kharitonov et al demonstrated that nitric oxide production (endothelium-derived relaxing factor activity) is influenced by cyclic hormonal changes in women; concentrations at midcycle were more than 100% higher than during menstruation [118].

A contributing mechanism for the increase in asthma morbidity that is associated with hormonal fluctuations may be secondary to abnormal regulation of the β_2 -adrenergic receptor (AR). In normal women, function of the lympho-

cyte β_2 -AR is under the cyclic influence of ovarian sex steroids; higher β_2 -AR density is seen during the luteal phase than during the follicular phase. The increase in density mirrors an increase in the concentrations of estradiol and progesterone exhibited between phases of the menstrual cycle, suggesting that hormonal alterations may be responsible [119,120]. In contrast, in asthmatic women, this cyclical pattern of β_2 -AR regulation is absent, and there is no luteal-phase increase in β_2 -AR despite an appropriate postovulatory hormone response [121]. Because female hormones potentiate the bronchorelaxant and vasorelaxant effects of catecholamines [122,123], a blunted β_2 -AR response may fuel the mechanisms underlying premenstrual asthma.

Alternatively, perimenstrual changes in the balance of T_H1 and T_H2 cytokines may be involved. Data suggest that healthy women have a shift in the balance of T_H1 and T_H2 cytokines toward a T_H2 response during a normal menstrual cycle [124,125]. During the perimenstrual interval, peripheral blood mononuclear cells produce less IFN- γ and more IL-10, resulting in a decreased IFN- γ :IL-10 ratio compared with the ratio in the midcycle interval.

Hormonal therapy

Oral contraceptive pills (OCPs) and hormone replacement therapy (HRT) are gender-specific therapies, but reports of the impact of these therapies on asthma prevalence and morbidity vary. In premenopausal women, some studies suggest that the prevalence of self-reported asthma, wheeze, use of asthma medication, and cough at exertion are not related significantly to use of OCPs [126,127]. Other case reports suggest that asthma exacerbations are related to OCPs and that exogenous sex hormones or OCPs may exacerbate asthma in some premenopausal women, contrary to expectation [128]. The effects of OCPs are complex, which may explain some of these conflicting reports. As stated earlier, healthy women have a perimenstrual shift in the balance of T_H1 and T_H2 cytokines toward a T_H2 response; however, despite the less dramatic cyclic change in this balance in women taking OCPs, there is a shift in the overall balance toward a T_H2 response throughout the menstrual cycles of these women [124]. Consistent with this blunting of the immune response, women taking OCPs have less cyclical change in airway reactivity than do women with natural menstrual cycles [129].

Hormone replacement therapy has been shown to have a favorable influence on the course of asthma, with reported reductions in daily use of glucocorticosteroids [130] and frequency of asthma exacerbations [131]. In the Cardiovascular Health Study, HRT was associated with a significantly higher forced expiratory volume in 1 second (FEV₁) and lower levels of obstruction [132]. In contrast, Troisi and colleagues observed that HRT was associated with a significantly increased relative risk for incident asthma in women (RR=1.49; for ever using HRT versus never using HRT). Among current users of conjugated estrogens, there was a positive dose-response relationship between daily dose and asthma risk (P for trend = 0.007) [133]. In the Copenhagen City Heart Study, a weak but consistent

association was observed between HRT and both self-reported asthma cough at exertion and use of asthma medication [126]. Though the reasons for these conflicting results have not been elucidated, the effects of estrogen on the immune system may be related to dose. Low levels of estrogen enhance specific immune activities, but high levels (as seen during pregnancy) can inhibit these activities, explaining some of the contradictory findings in the literature [83]. There also may be differential effects on incident compared with the effects of prevalent disease, or the effects of exogenous hormones may be different in premenopausal and postmenopausal women.

Risk factors associated with asthma and gender

Lung physiology

Whereas gender may influence the biologic susceptibility to disease through hormonal and immune-mediated effects, additional effects of gender may manifest through differences in physiology and airway function. Becklake and Kauffmann made detailed examinations of the gender differences in lung growth and development in childhood through adulthood [27,134]. They found that the development of the female lung is different from that of the male lung. Female lungs result from a growth of the airway in proportion to that of the parenchyma; male lungs exhibit dysanapsis, the disproportionate growth between the airways and the air spaces; thus, boys have proportionately smaller airways than girls relative to lung size [135]. Although the lungs of girls and women are smaller and weigh less than those of boys and men of the same height, the force expiratory flow rates and ratios of FEV₁ and forced vital capacity (FVC) are higher in girls and women [136,137]. This apparent mechanical disadvantage in boys decreases at the time of puberty and may help to explain the reversal in male-to-female ratio of asthma prevalence reported around this time.

Growth and decline of lung function

To further examine the influence of gender on growth and development of the lung, a model of the growth and decline of pulmonary function can be used that was developed from the results of multiple cross-sectional and longitudinal studies [138]. FEV₁ reaches a maximal level during early adulthood with girls, who have an earlier growth spurt and reach their plateau earlier than boys do [139]. After a plateau phase of variable length, FEV₁ gradually decreases throughout adulthood [140,141].

Development of symptomatic airflow obstruction in adults is influenced by factors that alter the maximal level of lung function that is attained or the rate of decline in adulthood. Asthma has been shown to adversely affect lung growth. This effect may be modified by gender, but the evidence has not been consistent.

Weiss and co-workers documented that a girl who develops asthma at age 7 years could expect a 5% reduction in FEV₁ by age 10 and a 7% reduction by age 15. Boys with asthma did not experience a significant deficit in FEV₁, but they did have reductions in FVC and forced expiratory flow (FEF₂₅₋₇₅) rate compared with boys without asthma [16]. In contrast, among a cohort of children in New Zealand, reports of wheeze at any time during childhood were associated with slower growth of FEV₁ and FVC, but this effect was seen only in boys. The criteria used for selection of study populations may explain some of the difference. Weiss et al evaluated subjects with a diagnosis of asthma, whereas the study population of Sherrill et al included children with report of wheeze, and a diagnosis of asthma was not required [142]. Asthma is known to accelerate the rate of decline of pulmonary function among adults. Patients with asthma have a significantly greater decline in FEV₁ than do those without asthma—a phenomenon seen in both genders [143]. This effect in part may be caused by airway remodeling in which chronic airway inflammation leads to a thickening of the airway walls [49].

In addition to factors related to airway size and function, factors associated with airway inflammation or airway smooth muscle function are associated closely with the development of asthma. The prevalence of asthma and bronchial hyperresponsiveness (BHR) is related strongly to measures of atopy (serum IgE levels and skin test reactivity), suggesting that atopy is an important risk factor for asthma [144,145]. Consistent with this finding is the fact that atopy has been associated with an accelerated decline in lung function, more so in girls than in boys [146]. The degree of hyperresponsiveness in childhood is a significant predictor of adult asthma. Roorda and colleagues found that the main predictor of adult asthma was childhood histamine responsiveness. They also observed that the degree of bronchial responsiveness in adults was predicted significantly by gender, and women were more responsive in adulthood than were men [147].

Gender, psychosocial factors, and asthma

To understand more fully the influence of gender on asthma, psychosocial factors must be considered [28]. Psychosocial factors can initiate, amplify, suppress, or change the course of the genetic, biologic, and behavioral processes that contribute to asthma. Five major psychosocial factors that are associated with gender and asthma are highlighted: (1) life stressors and perceived stress, (2) cognitive appraisals, (3) emotion, (4) coping, and (5) identity. Gender influences each of these factors; in turn, each factor influences at least one etiologic phase of asthma, whether it is the diathesis, trigger, development, diagnosis, or treatment. To simplify this discussion, the authors focus on a unidirectional pathway: how gender influences psychosocial factors, which in turn influence asthma. For each psychosocial factor, literature is reviewed that links the factor to asthma, and literature is explored that links the factor to gender.

Life stressors and perceived stress

Psychosocial stressors are defined functionally: They result in stress. A psychosocial stressor does not have to be valenced negatively to result in stress; threats (negative) and challenges (positive) can be perceived as stressful. In addition to the role that stress has in pregnancy outcomes, it is also possible that life stress may influence health beliefs and behaviors (eg, cigarette smoking) that subsequently may impact asthma risk.

Females and males experience recurrent stressors, such as family responsibilities, peer relations, school or employment concerns, and racial discrimination. Similarly, females and males of all ages experience less frequent but potent stressors, such as the death of a loved one, moving, or divorce [148]. The stress experienced by a key person—such as primary caregiver—can be a stressor to other persons in close proximity with this individual [149]. Growing evidence links caregiver stress to the stress response in their female and male offspring. Animal and human studies support the idea that caregiver stress may influence the stress response of the child and modify infant neuroendocrine function during early development [150]. Gender remains important in this regard because most primary caregivers are female. Research on paternal influences on asthma are warranted, because little is known about paternal influences on the development of asthma and psychologic functioning [151,152].

In one study, the perceived stress of the caregiver remained significant after controlling for factors that potentially are associated with stress and wheeze (parental asthma, socioeconomic status, race or ethnicity) and for potential mediators through which stress might influence wheeze (smoking, breast-feeding, birth weight, lower respiratory infections) [153]. Stressors that are common to females and males can be experienced differently, however. Among people in poverty, gender differences exist in the influences that socioeconomic inequalities have on physical health [154].

There are stressors that are unique to females and to males. Many women deal with stressors related to being pregnant. Women generally juggle the primary responsibility of multiple social roles, such as parent, worker, housekeeper, and caregiver to aging parents, more often than men do [155]. Many men deal with stressors related to being overworked, the responsibility for financial security of the family, social isolation, being socialized to aggression and violence, and the lack of support for healthy emotional expression [156–160].

One notable psychosocial stressor is more important for girls and women than for boys and men (and could exacerbate asthma) is self-objectification [161,162]. Self-objectification is the adoption of an observer's perspective as the primary perspective of one's own body. Girls and women have been shown to self-objectify more than boys and men do, leading to increases in anxiety [163]. Adopting an observer's perspective on one's body is a logical survival response to a culture that uses female attractiveness as currency in exchange for financial security or other material resources [164]. Self-objectification leads to anxiety because of constant body monitoring. Stressors like self-objectification that encourage self-monitoring

could exacerbate existing asthma, because they lead to hypervigilance and anxiety, which have been associated with recurrent asthma attacks [165].

A possible role for stress in the inception of wheeze and asthma has been mentioned [166]. In the next sections, the psychosocial factors are reviewed that—along with biologic and behavioral reactivity to stress—may modify the stress–illness link. These factors are cognitive appraisals, emotion, coping, and identity.

Cognitive appraisals

There is growing evidence that cognitive appraisals influence health and illness generally [167] and lung functioning specifically [168]. In a short-term, prospective, longitudinal study, Jackson and colleagues found that among college students, optimistic explanatory style buffered the effect of stress on mild physical illnesses, but pessimistic explanatory style exacerbated the stress–illness link. Kubzansky et al, in a prospective, longitudinal study of older men, found that men with more optimism showed less pulmonary decline than did men with more pessimism. Whether optimism has a buffering effect in the development of asthma and whether there are gender differences in this process have not been studied. Optimistic explanatory style may help ward off an asthma attack by allaying anxiety.

Cognitive appraisals have shown a linkage to gender [169]. Compared with females, males tend to show a greater sense of mastery over their environments. Bunce and Peterson found that females tended to make more pessimistic attributions than males in the domains of sociability and socialization. Accurate self-perception of asthma symptoms is crucial for proper management of the syndrome. In a sample of older adults, it was demonstrated that men had lower mean bronchoconstriction perception scores than did women [170]. Research is needed that simultaneously studies how gender influences cognitive styles and how cognitive styles support the development or exacerbation of asthma.

Emotion

The most familiar link between asthma and psychosocial factors is the trigger of emotion, especially anxiety, for an asthma attack [171]. Asthma first was explained as a consequence of repressed emotion [27,28,166]. Emotions have been shown to contribute to the onset and progression of numerous health outcomes, including heart disease, cancer, AIDS, and the common cold [172,173], but asthma as an outcome of emotions remains less studied. A review by Thoren and Petermann examined the anxiety–asthma relationship but focused on how asthma can trigger and prolong the course of an anxiety attack [165].

Depression and anxiety have been shown to be more frequent in females than males [174,175]. Depressive symptoms limit the lives of people, especially girls and women, across all economic levels and cultural backgrounds [176,177]. From adolescence onward, females are about twice as likely as males to experience depressive symptoms [178,179]. Brody argues “when gender differences in

emotional expression do occur, they can be traced to social processes such as dissimilar gender roles, status and power imbalances, and differing socialization histories of males and females ” [180, p. 369].

Although there are robust findings linking emotion to asthma, and gender to emotion, scant attention has been paid to bringing these findings together. A retrospective study by Hindi-Alexander and colleagues showed that among patients diagnosed with asthma, females were prescribed central nervous system depressants three times as often as were males [181]. Females may be prescribed more depressants because of higher rates of depression, but this also may contribute to increased death rates for asthma among females. Gender differences in asthma at different ages over the lifespan follow a similar trajectory to those of depression, lagged by several years, suggesting that the development of asthma may be associated with depression [182]. Understanding that gender influences both depression and asthma over the lifespan suggests one possible causal mechanism—depression contributing to asthma—that might not otherwise be apparent [166,173].

Studies have noted gender differences in the role of psychologic factors, such as mood states, in the reporting of physical symptoms and symptom perception [183]. Affleck and colleagues examined the within-person relations between transitory changes in mood, asthma symptoms, and PEF rates in adult asthmatics. Mood changes with an arousal component were related significantly to changes in PEF rates, and mood changes with a pleasantness component were related to changes in the reporting of asthma symptoms [184].

Coping

Stressful experiences, cognitive appraisals, resulting emotions, and how people cope with these factors probably have an important explanatory role in the onset and course of asthma [185]. One important coping strategy that was found to prolong emotional distress was ruminative coping [186]. Ruminative coping is the passive focus on the causes, consequences, and symptoms of one's distress. Part of asthma monitoring is noticing the causes and symptoms of one's asthma. It is reasonable to hypothesize that excessive monitoring could lead to ruminative coping, though this relationship has not been tested.

Many laboratory and naturalistic studies have shown that women ruminate more than men do, and this rumination exacerbates depression and accounts for the gender difference in depression [169]. Because ruminative coping leads to depression, another possible area of inquiry is whether ruminative coping indirectly contributes to the development of asthma through depressive symptoms.

Another important psychosocial coping mechanism with implications for asthma is social support (ie, ties to family, friends, and social groups that buffer the association between stress and physical and psychologic morbidity) [187]. Social isolation has been linked to many adverse health outcomes [188] and physiologic effects, such as altered immunologic functioning [189]. Greater diversity in one's social network has been related to lesser anxiety, depression, and psychologic distress [190]. Social support may reduce or buffer the effects of

stress by altering the perception of a situation [191]. There is also evidence that social networks influence the immune system and have a role in susceptibility to infection [192]. Social support may influence health behaviors, such as cigarette smoking [193]. Ptacek et al found that women tend to engage in social support more than men do, and men tend to engage in problem solving more than women do. Social ties can come with costs, however, and women may not necessarily benefit from having more people to whom they feel connected [194].

Gender identity

All females and males have components of both femininity and masculinity that come together to comprise the self, known as gender identity [195]. Gender identity is an important concept because it influences each of the important psychosocial factors discussed above: psychosocial stressors, cognitive appraisals, emotion, and coping. Previous research has shown that gender identity has an important impact on asthma [196]. Understanding gender identity is critical to understanding the motivations for behaviors that impact asthma, such as heightened anxiety among girls [197] or lower compliance with treatment among boys [196].

In the study by Williams, teenage boys diagnosed with asthma, who saw themselves as masculine, tended to think of asthma as separate from who they were. This strategy probably kept anxiety about asthma at a minimum—because asthma was not seen as a fundamental part of who they were, they did not need to pay much attention to it—but also had important health consequences, especially for those with more extreme cases of asthma. For example, these boys would ignore their symptoms or did not follow their treatment regimen as well as they should have to maintain optimal health. However, for those boys who saw themselves as less masculine but more feminine, being diagnosed with asthma and the inability to be masculine in culturally prescribed ways—such as being in control of one's life—caused notable distress. In contrast, teenage girls diagnosed with asthma, who saw themselves as feminine, identified their disease status as an integral part of who they were. As such, having asthma was more salient for them than it tended to be for the boys, and the girls worried more about their asthma (compare with the discussion on ruminative coping). This might have contributed to more frequent recurrences of asthma for the girls, because as mentioned above, asthma is linked with anxiety. Girls also tended to lower their expectations about their ability to engage in health-enhancing activities, like exercise. However, this vigilance also meant that the girls were more conscientious about their treatment regimens. Thus, masculinity added to the boys' quality of life (QOL) but at the expense of increased mortality risks. For the girls, femininity detracted from quality of life but resulted in decreased mortality risks.

Environmental determinants

Many of the psychosocial factors discussed earlier help link the internal (genetic and biologic) and external (environmental and behavioral) processes that

can modify the course of asthma. Tobacco use is an environmental exposure with well-documented effects on pulmonary function and the development of airflow obstruction. Among persons with asthma, tobacco use has effects on several measures of disease activity. Effects have been noted in health care use and health-related QOL. In a cohort of asthmatic patients, those who were exposed to tobacco smoke (ie, current smokers or patients exposed to environmental tobacco smoke [ETS]) reported significantly worse QOL and an increased rate of hospital-based care than did patients who were not exposed to tobacco smoke [198,199]. Smoking is associated with markers of airway inflammation in persons with asthma. In patients with asthma who smoke, induced sputum samples showed higher counts of total sputum cells and increased levels of relative and absolute neutrophilia and IL-8 than did nonsmoking, asthmatic patients [200]. An association between smoking and decreased efficacy of inhaled corticosteroids has been observed [201].

Although early studies did not suggest a gender effect of tobacco on respiratory illness, differences in smoking behavior between men and women were not controlled for adequately in these early analyses. More recent studies suggest that women are more susceptible to the deleterious effects of smoking. In a reanalysis of two Danish populations, women were found to have a higher rate of decrease in lung function than did men [202]. The risk for respiratory disease associated with smoking was higher in women than in men, and there was a suggestion of a higher mortality rate among women smokers. In another analysis of smokers, although men started smoking at a younger age, the total and cause-specific relative mortality was similar in men and women [203].

Studies of adolescents suggest that gender differences on the effects of tobacco are evident at a young age. Gold et al reported that cigarette smoking slowed the growth of lung function in adolescents but that girls were more vulnerable than boys. Smoking five or more cigarettes per day, compared with never smoking, was associated with a decrease in the yearly growth of FEV₁ in girls but not boys. Lung function plateaued in girls aged 17 to 18 years who did not smoke, whereas girls in this age group who were active smokers demonstrated declines in FEV₁ and maximum midexpiratory flow (MMEF). A dose-response relation between smoking and lower FEV₁, FVC, and MMEF was observed [204].

In addition to the observed differential effects of tobacco exposure between men and women, the influence of gender on smoking behavior must be considered. There have been large changes in smoking prevalence during the last 50 years. In the last 2 to 3 decades, Western countries have seen a significant decrease in the number of male smokers and an overall rise in the number of female smokers. The mean age of smoking initiation has remained constant for men, whereas this age has declined progressively for women [205].

Similar gender differences in smoking habits are observed in children. A higher prevalence of smoking has been reported among girls than among boys (13.7% versus 9.5%, respectively) [206]. Boys and girls are susceptible to the advertising campaigns for cigarettes that are directed at them [207]. Differences in the motivation for engaging in tobacco use have been observed among boys

and girls. In young men, peer pressure and an increase in risk-taking behavior can lead to the initiation of smoking. Once they have initiated tobacco use, boys have a higher risk for transitioning from experimental use to regular smoking. In girls, adolescence is a time of difficulties with body image, and smoking may be a way of controlling weight [208].

Large-scale promotions have been aimed at smoking cessation, but the overall success rate remains low, and the risk for relapse is high. It seems that women have more difficulty than do men in achieving and maintaining abstinence from smoking [209,210]. Among women, concern about weight gain is one factor that has been associated with a higher likelihood of relapse [211] and has been reported as an important reason for continued smoking [212]; however, weight gain after cessation is an important consideration for women and men. Borrelli and co-workers confirmed that although women were more likely to relapse than were men, there was an important interaction between gender and weight: For every kilogram increase in weight, the risk for subsequent relapse increased by 17% for men, compared with a 2% increased risk for women [213].

Passive smoking

Exposure to passive smoke has well-documented effects on respiratory health. Among children, a consistent relationship between exposure to passive smoke and risk for respiratory illnesses and asthma symptoms has been observed, the OR usually being higher for preschool children than for school-aged children [214]. Among children with established asthma, parental smoking is associated with more severe disease [215]. Effects on pulmonary function have been noted. Maternal smoking seems to carry greater risk than paternal smoking with in utero exposure a potential source of the differential effect [216]. In addition, a small increase in bronchial hyperresponsiveness (BHR) and greater variation in peak expiratory flow has been observed in children of smoking parents [217]. Susceptibility may vary among individuals, with an increased risk in boys. Among a population of children in New Zealand, ETS exposure was associated with decrement in the FEV₁:FVC ratio in boys but not girls; however, among a subpopulation of children with wheeze or asthma, ETS exposure was associated with progressive decline in the FEV₁:FVC ratio in both sexes [218]. In a Tucson, Arizona, cohort, FEV₁ increased more slowly between ages 13 to 16 years, and the rate of decline of the FEV₁:FVC ratio increased only in boys [219]. Among adults, the effects of ETS exposure are less pronounced but are associated with small deficits in lung function. No effect of gender has been reported [220].

Home environment

The home environment has an independent effect on respiratory symptoms and increases the risk for asthma in women. Early work by Melia et al triggered interest in the effects of gas appliances [221]. Inhalation of high levels of NO₂ has been associated with enhanced BHR and induced late-phase asthmatic response to

inhaled allergen [222,223]. A consistent picture of the association between gas appliances and nitric oxide and respiratory health has not been found [224–238]. To address the concern that low statistical power was responsible for the lack of consistent findings, Hasselblad and colleagues performed a meta-analysis in 1992 [229]. Subsequent work by Jarvis et al added evidence to the association between domestic gas appliances and respiratory health. The use of gas for cooking was associated with an increased risk for respiratory symptoms and poorer lung function. Their results also suggested effect modification of the association of gas appliances and respiratory symptoms by gender and atopic status. Among women exposed to gas cooking, there was a trend toward increased respiratory symptoms in atopic women than in nonatopic women [230]—a finding confirmed in other studies [231–233]. Two explanations for the gender differences in environmental exposures have been offered. The effect modification by gender may be constitutional and caused by hormonal differences. Animal and human studies show that other environmental exposures can affect men and women differently. Exposure of rats to cigarette smoke led to a greater increase in the number of mucus-producing tracheal goblet cells in female rats than in male rats [234,235]; these differences were related to the estrous cycle [236]. Differences in time activity patterns can be used to explain the differences in the levels of exposure. Assessment of health risk caused by environmental exposures requires information on the distribution of the individual's time in various microenvironments. Traditionally, women and girls have higher indoor allergen exposures, secondary to more time spent indoors and more time doing household chores and cleaning. On the other hand, men generally have more exposure to other exposures in the workplace, secondary to differences in the type of employment sought by men and women. Given that the prevalence of asthma and BHR is related strongly to measures of atopy (serum IgE levels and skin test reactivity) [144,145,237], it is reasonable to assume that, among sensitized subjects, higher levels of exposure can lead to more symptoms, more airway inflammation, and persistence of disease. It can be postulated that differences in the effects for other environmental exposures may follow a similar paradigm, in which modification by gender occurs because of differences in exposure level.

Obesity and body fat

Diet has been identified as a risk factor or a modifier for the effect of other environmental exposures on the inception of asthma [238]. Maternal diet may influence birth weight [239], and birthweight has effects on body mass index (BMI) during adulthood. Low-birth-weight babies tend to have a more truncal or abdominal distribution of fat as adults (independent of overall fatness), suggesting that perturbations of central endocrine regulatory systems that are established in early gestation may contribute to the development of abdominal obesity in later life [240]. Impaired fetal growth and subsequent adult fatness have been identified as risk factors for adult asthma. The prevalence of asthma among young adults is

inversely related to birth weight [241]. This finding was confirmed in an analysis of National Health and Examination Survey III data [242].

The Barker hypothesis states that the relationship between maternal malnutrition, low birth weight, and asthma arises from adaptations that the fetus makes when it is undernourished during a critical period of early life, resulting in long-term changes in physiology or metabolism [243]. This relationship between maternal nutrition, birth weight, and adult BMI is dependent on the time of exposure and is well illustrated by observations of a population of pregnant women who lived during the Dutch winter famine of 1944 to 1945. Women with severe malnutrition during early and mid-pregnancy had low-birth-weight infants who subsequently exhibited higher rates of obesity in adult life [244,245]. If malnutrition occurred during the last trimester of pregnancy, the infants had lower rates of obesity in adulthood [246]. Subsequent work demonstrated that the risk for obstructive airway disease in infants who were exposed to famine follows a pattern similar to that seen with birth weight; there is an increased risk for obstruction if the infant is exposed in early and mid-gestation, but not in late gestation [247]. This effect is seen predominantly among women and girls; maternal malnutrition during early gestation has been associated with higher BMI and waist circumference in 50-year-old women but not in men of similar age [248].

Independent of the relationship between birth weight and adult BMI, obesity and asthma have been linked in many cross-sectional studies [249,250]. Tantisira and Weiss reviewed some of the complex interactions that are believed to underlie this relationship [251]; evidence is highlighted that suggests that gender has an important role. Epidemiologically, the relationship between obesity and asthma is seen predominantly in girls and is strong in postpubertal girls and adult women [241,252–254]. Increases in BMI have been associated with incident wheezing, peak flow variability, and bronchodilator response in school-aged girls, but not in boys. The effect seems to become stronger in girls during puberty. In one study, girls that became obese between age 6 to 11 years were 7 times more likely to develop new asthma symptoms at age 11 to 13 [255]. In a study of 16,862 children aged 9 to 14, although BMI correlated with the prevalence of asthma in both boys and girls, asthma risk was associated with the stage of sexual development; negatively related to Tanner stage in boys (RR of 0.3 for stage V compared with stage I); but was positively related to Tanner stage in girls (RR of 1.6 for stage V compared with stage I) [256]. The association between asthma and BMI has not been found exclusively in women, however. Carey et al observed that changes in weight, body mass, and waist circumference were associated with changes in FEV₁ ($P < 0.001$), with stronger effects seen in men. The effect in men increased with average weight. This phenomenon was not seen in women, possibly because of gender differences in weight distribution in later adult life [257].

Regulation of airway tone may be responsible for some of the observed differences, as suggested by the higher prevalence of PEF variability and increased responsiveness to bronchodilators seen in girls who become obese, despite similar height-adjusted prebronchodilator FEV₁. In cross-sectional study of 7109 adults

from families of patients with asthma in the province of Anhui, China, physiologic studies suggest that extremes of body mass are associated with increases in methacholine airway responsiveness [258]. At least one study found an association between BMI and atopy. In a cross-sectional, population-based study of teenagers in Taiwan, Huang and colleagues noted decreased prevalence of airway hyperresponsiveness in teenage girls with the lowest BMI and increased atopy in girls with the highest BMI [253]. These findings were not noted in boys. However, the relationship between obesity, atopy, and BHR has not been noted uniformly [241,259], suggesting that the effects of increased BMI may be mediated through factors other than the induction of allergic eosinophilic inflammation of the airway epithelium [260,261].

The biologic activity of adipose tissue has been postulated as a potential mechanism for the association between obesity and asthma. There are several lines of evidence that indicate that obesity is a proinflammatory state. IL-6, a proinflammatory cytokine that is produced in adipose tissue, is estimated to account for up to 25% of the IL-6 released into circulation [262,263]. C-reactive protein (CRP) is an acute-phase reactant that is a marker for underlying systemic inflammation. Elevated plasma concentrations of CRP have been associated with increased risk for coronary heart disease [264–267] and peripheral vascular disease [268]. BMI correlates with levels of CRP [269], and adiposity has been reported to be the major determinant of CRP levels in children. [270]. Leptin levels are highly related to obesity [271]. Leptin has been shown to up-regulate production of proinflammatory cytokines, including TNF- α and IL-6, and to increase phagocytosis by macrophages [272].

A potential reason for the gender difference noted in asthma is the influence of obesity on estrogen levels. As discussed previously, estrogen levels have been associated with asthma morbidity [107], which may be mediated through effects on immune function [93,98]. In obesity, peripheral aromatization of androstenedione to estrone and testosterone to estrogen occurs within the stroma of adipose tissue. Decreased sex-hormone-binding globulin is found in obesity; thus, obesity may amplify the effects of estrogen [273].

In addition to the increased peripheral availability of estrone, production of leptin by adipose tissue may contribute to the association between BMI and asthma [271]. Differences in leptin levels have been noted between males and females. Although serum levels of leptin are not associated consistently with gender before puberty, they are associated negatively with testosterone and related positively to estrogen [274,275]. Among adults, leptin levels are higher in women than in men and may indicate an enhanced inflammatory state [276–278]. Although the mechanism of this interaction is not clear, evidence indicates that leptin is associated with an increase in T_H1 levels and suppression of T_H2 cytokine production in mice [279].

The relationship between obesity and asthma is illuminated further by intervention trials that documented the effect of weight loss on asthma morbidity. In an open, randomized, parallel-group design, obese women were enrolled in an 8-week dietary program. Participants in the treatment group lost a mean of 14.5% of their

pretreatment weight and maintained an 11.5% loss over the subsequent 1-year period; controls lost 0.3% in 8 weeks and gained 2.2% of their weight over the year. There were significant improvements in FEV₁, FVC, dyspnea, use of rescue bronchodilators, and the median number of asthma exacerbations in the treatment group compared with the control group [280]. In a second trial, decreased BMI was associated with improved diurnal PEF variation, increased FEV₁ and FVC, and decreased obstruction (FEF₂₅₋₇₅/FVC) [281]. Both trials had small numbers of patients, and no stratification by gender was performed.

The relationship between obesity and asthma is complex and involves interactions between obesity, inflammation, and gender. Although these effects may be mediated partially through hormonal differences, the contribution of gender may be amplified or changed through complex interactions with psychosocial factors, such as stress, which may affect airway inflammation and reactivity through immunologic and neural pathways.

Perception, reporting, and interpretation of symptoms

Misclassification of diagnosis and treatment

The perception, reporting, and interpretation of asthma symptoms can lead to differences in the applied diagnosis and management of disease. Significant epidemiologic evidence shows that women seek medical attention more frequently than do men. Women are hospitalized more frequently across all diseases [282], make more office visits, receive a greater number of medical tests, and use prescription and nonprescription medications more frequently than do men [283–285]. An increase in healthcare use is well documented among women who are diagnosed with asthma [286–289]. Hospitalization rates exhibit the same age-by-gender interaction that is seen with the prevalence of disease. Admission rates among boys are almost two times that of young girls, but later in life, the admission rate increases in women and surpasses that of men. The average length of stay for women is also higher compared with that for men [290,291]. In two studies, women were more likely to present to the ED with a moderate-to-severe exacerbation (PEF rate <80%) [292,293] and were more likely to be admitted. Although a report suggests that men are more likely to present with a life-threatening attack [293], other reports suggest that among adults presenting to the ED, women are more likely than men to describe their symptoms and activity limitation as severe [292], have higher rates of intubation, and have higher mortality rates from asthma (2.3 versus 1.3 per 100,000 population, respectively) [22,294].

Overall, differences in use of asthma care tend to favor women, except in reports that examine use of inhaled corticosteroids and use of specialist care [295]. Evidence of gender differences in the use of asthma medication is inconsistent, with some studies finding no overall difference and others finding increased use of inhaled steroids among women [296–298]. In a retrospective review of patients

with an acute attack of asthma who were treated in an ED, logistic regression analysis showed that women were more likely to be using inhaled or inhaled and oral corticosteroids at the index visit [299]. Sexton and co-workers studied adults from six general practices in East Anglia and found an increase in the rate of prescriptions for oral steroids among female asthmatics. Although they observed no differences in the overall rates of reported use of β -agonists or inhaled steroids, women were five times more likely to report oral steroid use than were men. The degree of asthma symptoms did not predict oral steroid use, but a dose-response effect was seen with the number of visits to the doctor for asthma in the previous 6 months. This finding suggests that the more frequent consultation with a doctor by women results in more requests for oral steroids or that doctors preferentially may prescribe oral steroids to women [300]. Pethica et al also found an higher rate of prescriptions for oral steroids and a higher rate of repeated prescriptions for oral steroid in asthmatic women compared with men. The magnitude of effect was less, however, and they found no difference in the number of asthma consultations between men and women [301].

Among children with asthma, gender differences in asthma medication have been seen. Adams et al evaluated the dispensing patterns from three large, managed care organizations and found significantly lower dispensing of any controller medication in girls compared with boys. This effect was seen for any dispensing and for repeated controller dispensing (> 5) [302]. Several reasons can be postulated for these differences. Among children, asthma symptoms are more common than the diagnostic label of asthma, suggesting that an underdiagnosis of asthma seems to be most prominent in girls. This effect may be secondary to the greater prevalence of wheezing reported in boys, whereas girls present more often with nonspecific symptoms [303]. Dysanaptic growth of airways and lung parenchyma may show sex differences, leading boys to have smaller airways for the same lung volume and more frequent airway obstruction than girls [304]. Symptoms of wheezing are more likely to be treated as asthma than are symptoms such as persistent nocturnal cough.

The relationship between symptoms, diagnostic labeling, and gender is more complex. Kühni and Sennhauser, in their study of Swiss children, found that for all asthma symptoms except wheeze, approximately twice as many boys as girls received bronchodilator treatment. This finding suggests that differences in the frequency with which girls and boys present with wheezing does not account wholly for the differences in the rate of prescription for bronchodilator therapy. Even when the analysis is restricted to children who present with less typical asthma symptoms, gender may influence the diagnostic label and the subsequent treatment received [305]. Consistent with this finding are reports that boys are more likely than girls to receive medication, independent of the frequency of wheezing [306]. The large gender difference for repeat controller use among preschool-aged children who were dispensed at least six β -agonists, as reported by Adams and colleagues, suggests a role for psychosocial factors. The high level of β -agonist use among this group of children suggests that symptoms are likely to be a significant problem and would attract the attention of parents and

physicians [302]. Physicians, parents, and children may have different perceptions of symptoms and different attitudes toward treatment of girls and boys. Exercise limitation in boys may be perceived as a problem that requires treatment more often than it does in girls. Although there is no evidence that gender has an independent effect on adherence to treatment [307], among adolescents there is some evidence that boys may be more likely than girls to deny their asthma symptoms [308].

It is also possible that gender has a role in the proper administration of medication. Metered-dose inhalers (MDIs) are a common route of administration for asthma medication, but coordination of the inspiratory maneuver is difficult for many individuals, and improper technique can result in poor medication delivery. Goodman et al demonstrated that women have poorer MDI technique than do men. They suggested the MDI may be “more unwieldy for a typically smaller female hand.” It commonly is believed, however, that proper MDI technique can be achieved after receiving detailed and repeated instruction [309]. This finding suggests that differences in the received education may account for differences in technique between men and women. In support of this theory, Osborne and colleagues observed that women exhibited marginally better use of MDIs than did men [310].

Observed differences in asthma morbidity between men and women may be related to a difference in the response to disease rather than a difference in the disease itself. Differences in the perception of symptoms between men and women have been observed. Women may experience more discomfort for the same level of airflow obstruction and more frequently seek medical attention. Perception of bronchospasm may be related to gender, because women have reported more shortness of breath than men did during methacholine challenge [311]. Women with asthma reported lower health-related QOL [312], increased use of asthma medication, and more bothersome asthma symptoms than did asthmatic men, despite similar objective measures of lung function [310]. This finding suggests that women perceive the same level of obstruction differently than men [311].

Differences in diagnostic bias may contribute to reports of differences in asthma morbidity although the mechanism of bias may be different in children and adults. Children who are diagnosed asthma are more likely to receive bronchodilator therapy than are children without an asthma diagnosis. As discussed, the propensity to diagnose asthma in girls may be based on differences in the pattern of asthma symptoms in girls compared with boys [305]. In adults, it has been suggested that diagnostic exchange exists secondary to gender bias among physicians in the diagnosis of COPD and asthma. COPD is diagnosed less commonly in women than in men, whereas women present with doctor-diagnosed asthma more often than men. Chapman et al observed that the diagnosis of obstructive lung disease (regardless of subtype) is similar between the sexes, and the larger percentage of men (58%) than women (42%) given the diagnosis of COPD mirrors the preponderance of women in studies of emergency or ambulatory care that is attributable to asthma [313]. Similarly, Dodge and co-workers reported that, given similar presenting symptoms and controlling for smoking,

women were more likely to be diagnosed with asthma, and men were more likely to be diagnosed with COPD [314].

Similarly, there is evidence of diagnostic bias in the management of coronary artery disease, in which women who present with chest pain are less likely to be evaluated with invasive testing, such as cardiac catheterization, compared with men [315]. Even when correctly labeled, differences in the aggressiveness of the management of coronary artery disease between the sexes have been documented. Women who were admitted to the coronary care unit with a coronary diagnosis were less likely to undergo coronary arteriography [316], and women who experienced an anterior myocardial infarction (AMI) underwent coronary angiography and coronary-artery bypass graft surgery at significantly lower rates than did men. Once women undergo coronary arteriography, they are as likely to undergo PCTA than are men [316].

Variability in clinical response to inhaled short-acting β_2 adrenergic agonists has been documented and may contribute to the increase in morbidity seen in women with asthma [317]. Differences in the nonbronchodilatory β_2 -(AR) response have varied with gender [318], and differences in β -AR sensitivity have been postulated. As discussed earlier, the influence of hormones on β_2 -AR density may have a role. Variability that is related to β -adrenergic polymorphisms has been described. Two polymorphic loci within the coding region of the β_2 -AR have been described at amino acids 16 and 27 [319]. Marked differences in the prevalence of positive responses to bronchodilators based on these β_2 -AR polymorphisms have been reported [320,321]. Polymorphisms may influence airway response to regular inhaled β -agonist treatment as compared with response to as-needed treatment [322] and may affect asthma severity [323,324].

Although there are no reports of differential expression of the β_2 -AR polymorphisms on the basis of gender, Barr et al reported that BMI and the Arg16->Gly polymorphism of the β_2 -AR are associated with incident asthma, but only in a subset of sedentary women. This finding suggests that there may be complex gene-by-environment effects on incident asthma, involving AR polymorphisms, BMI, activity level, and gender [325].

Summary

The evidence reviewed brings to light the complexity of the interactions that exist between the varied manifestations of sex and gender with the development of and morbidity associated with asthma. The effects of sex are manifest throughout life, beginning during pregnancy. Although the effects of sex on asthma include hormonal differences between females and males, diverse effects have been noted, including influence on immune maturation, the balance of the immunologic response, amplification of the inflammatory state associated with obesity, and modification of the response to therapy through effects on the β_2 AR.

The complex interactions that occur between the effects of sex and gender (the socio-cultural effect of being female or male) are discussed. The influence of

psychosocial factors (eg, stress, cognitive factors, emotion, coping, identity) on the course and presentation of obstructive lung disease is examined compared between girls and women and boys and men.

To understand the disparities in asthma risk, the potential role of the complex interactions between various determinants of health should be understood. Understanding these interactions promises to lead to more effective therapies, including interventions aimed at educating individuals with asthma and their social supports and at helping individuals make behavioral changes. Documenting these multilevel determinants of health can shape changes at the institutional level, including policies that influence environmental exposures, and can remediate social inequities in resources.

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