The airway behavior of girls and women is different from that of boys and men, and these differences vary in strength and in direction across different ages and time windows. Physiologists interested in structure–function relationships have, in general, explored these differences more thoroughly than have clinicians, despite the fact that airway behavior is an important determinant of the clinical manifestations of airway disease. In this review we examine the determinants of airway behavior, focusing on sex differences, and propose an approach to analyzing their relevance for clinical and public health practice as well as for research into the origins of airway disease.

BACKGROUND

Interest in sex and gender differences in airway behavior and disease is not new. This is illustrated by three remarkable documents published in the nineteenth century. The first, published in 1846 by a London surgeon, J. Hutchinson, was entitled “On the Capacity of the Lungs and on the Respiratory Function with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer” (Figure 53-1). The spirometer is an instrument that he developed to measure “vital capacity” (VC), a term he introduced to describe the maximum amount of air that could be blown out after the deepest possible breath in. Based on his observations of over 2,000 men aged 15 to 65 years drawn from all walks of life (including soldiers and guardsmen, gentlemen, giants, and dwarfs) and 26 young girls, he identified height, weight, and age as determinants of VC in what was probably the first epidemiologic study of lung function. Although his spirometer was not useful for the purpose for which he developed it—to “distinguish disease”—it was put to good use by others.

In 1890, Professor Ott set out to measure the physiologic as opposed to the psychological and emotional processes that accompanied menstrual bleeding in 60 women in good health studied over a 3-month period covering 68 cycles. He combined measurements of body temperature, muscular force, VC using Hutchinson’s spirometer, and reflex action into a composite index that he called the “fonction physiologique de l’organisme feminin” (the physiologic function of the female organism), which was expressed on a scale of 0 to 100% (Figure 53-2). This index was about 52% at midcycle, peaked at about 80% 3 days before menstrual bleeding started, began to fall immediately prior to the onset of bleeding, and fell to a low of about 35% during bleeding.
before returning to its midcycle level. He cited evidence that such fluctuations were not seen in prepubertal girls or in postmenopausal women and interpreted his results as evidence that his index was driven by the female organs of reproduction during a woman’s reproductive years. Of interest to the chest physician or physiologist is the fact that Ott’s composite index included a measure of lung function, suggesting that sex hormones influence airway behavior.

More than a century later, questions about sex differences in the nonreproductive area of biology continue to challenge this field of research. In 2001, the Institute of Medicine in a report entitled “Exploring the Biological Contributions to Human Health: Does Sex Matter?” noted that many normal physiologic functions “are influenced directly or indirectly by sex-based differences in biology,” and the authors reminded their readers that “every cell has sex.”¹⁸ In their view, appreciation of this fact had been slow in coming because of the recent emphasis on differences between women and men at the societal level (in Havelock Ellis’s words),¹¹ the classification of living things as male or female according to their organs of reproduction” and gender as “a person’s self representation as male or female or how that person is responded to by social institutions on the basis of the individual’s gender presentation.”

DEFINITIONS

The definitions of the terms sex and gender used in this chapter are those used in the 2001 Institute of Medicine report,¹⁸ definitions that are also in conformity with those used by Ellis in 1894.¹¹ Airway behavior refers to “the dimensions, structure and functions of the lung, their relationship to each other and to the mechanical properties of the lung” and determinant to “any factor, event, characteristic or other definable entity that brings about change in a health characteristic or other defined entity.”¹⁹ Determinants may increase or decrease risk; they may also be established or putative.

Much of the material published on sex and gender differences in airway behavior and disease is limited to specific ages or time windows. Studies of children usually reflect the methods of study used in pediatrics and the clinical experience of pediatricians, studies of adolescents those of physicians in sports medicine, studies of adults those of internists, and studies of the elderly those of geriatricians. Since this chapter focuses on changes across the human life span, the material cited relies heavily on the findings from the few population-based studies in which sex- and gender-based differences in airway behavior and disease have been examined using the same methodology to gather information over the human life span.¹⁰⁻¹²

BIOLOGIC DETERMINANTS OF AIRWAY BEHAVIOR

The biologic determinants of airway behavior include (1) dimensional factors, which are described in morphometric and physiologic terms and yield information on lung structure–function relationships, and generally favor the female lung; (2) immunologic factors, of particular importance in diseases such as asthma; and (3) hormonal factors attributable to the cyclical changes in female sex hormones that occur during the reproductive years of a woman’s life. Because these factors contribute to different degrees and often in different directions over different age and time windows, they are considered separately below.

DIMENSIONAL DETERMINANTS OF AIRWAY BEHAVIOR

The dimensional determinants of airway behavior are summarized for different ages in Table 53-1.¹³⁻¹⁰ The structure of the lungs is an important determinant of their ventilatory
Table 53-1  Sex Differences in Airway Behavior across the Human Life Span, Reflected in Lung Structure–Function Relationships

<table>
<thead>
<tr>
<th>Period</th>
<th>Lung growth, development, and aging</th>
<th>Sex differences in lung structure–function relationships</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy: peri- and postnatal up to 1 yr</td>
<td>Alveolar multiplication occurs from ~36 wk through 1 yr or more. Lung vasculature develops in relation to the bronchial tree before birth and to multiplying alveoli after birth</td>
<td>Female neonates less likely than male neonates to develop transient hyperpnea or respiratory distress syndrome and more responsive to hormone accelerators of surfactant. Lungs of infant girls are smaller than those of infant boys but have higher absolute and size-corrected flow rates.</td>
</tr>
<tr>
<td>Childhood: age 1–10 yr</td>
<td>Alveolar multiplication continues up to ~2 yr; somatic growth is more or less linear with age up to ~10 yr. Airway-parenchyma-somatic growth is complex and exhibits dysanapsis.</td>
<td>Based on morphometry, lungs of girls remain smaller than those of boys, yet they have lower specific airway resistance at any given height. Maximum forced expiratory volume is higher in girls than boys and increases after a deep inspiration in girls but not in boys. Large airways grow proportionately to lung volumes in girls but lag in boys, whereas small airways grow faster than lung volumes in girls but proportionately in boys.</td>
</tr>
<tr>
<td>Early adolescence: from 10 yr to midteens</td>
<td>Somatic and lung growth accelerate with age. Peak velocity for somatic growth precedes that for lung growth by 1–2 yr. FVC and TLC do not grow at the same rate.</td>
<td>Peak velocity for height growth in girls precedes that of boys by ~2 yr. Height ceases to increase at ~16 yr in girls but only slows at ~18 yr in boys. FEV_{1} and FEV_{1}/FVC% remain higher in girls than in boys, but not peak flow rates. Adolescent girls generate lower respiratory pressures than adolescent boys at all lung volumes.</td>
</tr>
<tr>
<td>Late adolescence: from mid-to late teens</td>
<td>Duration of adolescent growth spurt similar whether onset of maturity is early, middle, or late.</td>
<td>Growth velocity in adolescent girls plateaus after height ceases to increase but continues at a slower pace in adolescent boys until the mid-20s. This is attributed to a “muscularity effect” in boys, in particular of the shoulder girdle, caused by male sex hormones; growth of TLC and of flow rates relative to TLC are slower in adolescent girls than boys; specific airway resistance decreases up to ~18 yr in girls but not boys, while FEV_{1} in relation to height and FEV_{1}/FVC % remains higher in adolescent girls than boys.</td>
</tr>
<tr>
<td>Early adulthood: from late teens to mid-20s</td>
<td>Linear age-related increase in lung function slows with the end of the adolescent growth spurt. Height stabilizes, but weight increases.</td>
<td>Growth velocity for adolescent young men continues at a slower pace until the mid-20s, attributed to “muscularity effect” (see late adolescence). Once height stabilizes, weight becomes a determinant of lung volumes and flow rates in young men and women. Sex differences in tracheal area (measured by acoustic reflection) vs lung volume suggest that the configuration of the adult female lung is the result of proportional growth of airways vs parenchyma, but in the adult male lung growth of the airways has lagged behind that of the parenchyma, ie, has been dysanaptic.</td>
</tr>
<tr>
<td>Adulthood through old age: from ~30 yr</td>
<td>Age-related loss of lung function is linear up to ~50 yr and accelerates thereafter. With age, alveolar air volume decreases, and alveolar duct air and lung connective tissue increase, altering the lungs’ mechanical properties.</td>
<td>Changes related to aging of the lungs’ mechanical properties develop later and proceed more slowly in women than men. Age-related changes result in increases in lung compliance, decreases in maximal expiratory flow rates, and airway closure at higher lung volumes. With increasing age, the large airways of men also lose elastic recoil, which may counteract the loss of parenchymal recoil and explain the relative preservation of their peak flow rates.</td>
</tr>
</tbody>
</table>

FEV_{1} = forced expiratory volume in 1 second; FVC% = forced vital capacity; TLC = total lung capacity.
Adapted from Kauffman F et al,1 Becklake MR and Kauffmann F2 and Kauffmann F and Becklake MR.3
function through its effects on the lungs' mechanical properties. These, in turn, are reflected in the relationships of flow, volume, and time during a forced expiratory maneuver. Thus, the relationship of lung volume (a measure of lung size) to forced expiratory volume (a measure of airway size) is also a measure of the structure-function relationship. Despite the lungs of girls and women being smaller than those of boys and men of the same height, they exhibit higher values for forced expiratory flow (FEF) rates and for forced expiratory volume in 1 second (FEV)2/FVC% over the human life span. These sex-based differences in airway dimensions are thought to be the consequence of disproportionate growth between the airways, whose number is fixed by about 16 weeks gestation, and the air spaces (alveoli), which continue to multiply up to the age of about 2 years and perhaps longer, a phenomenon characterized by Mead as dysanapsis.17 Mead also pointed out that this loose coupling between airways and air spaces favors the smaller lungs of girls and women compared with the larger lungs of boys and men whose gas drainage systems are, relatively speaking, both narrower and longer.17 These dimensional advantages of female over male lungs are also reflected in the reference (predicted) values used routinely by clinical laboratories. For instance FEV2/FVC% prediction formulae generated from the study of different populations in different countries on different continents are consistent in showing higher values in girls and women than in boys and men.31-34

Sex differences in lung structure—function relationships by age are described in greater detail in Table 53-1. For the reader's convenience, it is summarized here.

1. Prenatal (from conception): Mouth movements, reflecting fetal breathing,18 are more advanced and phospholipid profiles19 more mature in female than male fetuses.

2. Infancy (peri- and postnatal period to age 1 year): Female neonates are less likely than male neonates to develop transient tachypnea25 or the respiratory distress syndrome of the newborn, and they are more responsive to hormone accelerators of surfactant production.19

3. Childhood (from age 1 to 10 years): Based on morphometry, the lungs of girls remain smaller than those of boys, yet they have lower values for specific airway resistance at any given height.22 Large airways grow proportionately to lung volumes in girls but lag in boys, whereas small airways grow faster than lung volumes in girls but proportionately in boys.22

4. Early adolescence (from age 10 years to midteens): FEV1 and FEV2/FVC% remain higher in girls than in boys, but not peak flow rates.29 Adolescent girls generate lower maximal respiratory pressures than adolescent boys at all lung volumes. These sex differences, described as a "muscularity effect" involving the muscles of the shoulder girdle, start with the onset of puberty and have been attributed to the puberty-associated increases in male sex hormones.29

5. Late adolescence (from mid-to late teens): Growth of total lung capacity (TLC) and of flow rates relative to TLC is slower in adolescent girls than in adolescent boys.27,30 Specific airway resistance decreases up to about age 18 years in girls but not in boys,22 differences attributed to a muscularity effect (see early adolescence above).29

6. Early adulthood (from late teens to midtwenties): After height stabilizes, weight becomes a determinant of lung volumes in young men and women. Sex differences in tracheal area (measured by acoustic reflection) vis-a-vis lung volumes26 suggest that configuration of the adult female lung is the result of proportional growth of airways and parenchyma, but in the adult male lung, growth of the airways has lagged behind that of the parenchyma (ie, has been dysanaptic).17,36

7. Adulthood through old age (from about age 30 years): Aging of the lungs' mechanical properties occurs later and proceeds more slowly in women than in men.32 Age-related changes in lung structure and function result in increases in lung compliance, decreases in maximal expiratory flow rates, and airway closure at higher lung volumes. With increasing age, the large airways of men (measured by acoustic techniques) lose elastic recoil. This may counteract the loss of parenchymal recoil and explain the relative preservation of their peak flow rates.36,37

**IMMUNOLOGIC DETERMINANTS OF AIRWAY BEHAVIOR**

Sex-based differences in the immune system are reflected in the manifestations of allergy,2 and atopy, a marker of allergic status, is an important determinant of airway behavior as well as an important host risk factor for asthma.38 Atopy has been defined as that form of immunologic activity in which "IgE antibody is readily produced in response to common allergens of the subject's environment."2 Phenotype markers of atopy used in population-based studies include skin prick reactivity to common allergens, total or specific serum immunoglobulin (IgE), blood eosinophil counts, and, in children up to 2 years of age, mononuclear proliferative and cytokine responses to specific allergens and tetanus toxoid.2 These biomarkers of atopy differ in their evolution with age, their relationship to each other is complex, and, although sex-based differences in the immune system have long been recognized, there have been few studies that have examined specific time windows by sex and age. In addition, account needs to be taken of between-study differences in methodology, for instance, in the test batteries of allergens used for assessing skin prick reactivity and in the criteria for reading a skin test as positive.

**Total and Allergen-Specific Serum IgE**

Sex differences in the manifestations of allergy assessed by total serum IgE have been reported across the human life span, with levels in girls and women being lower than those in boys and men in most, but not all, studies.2 In the Tucson study, one of few community-based cohort studies covering the human life span using the same methodology, the differences in IgE levels were consistent from childhood through old age (lower in girls and women than in boys and men) and followed a similar pattern over time in both sexes (Table 53-2).10,12 These differences are obviously biologically determined, although for reasons that are not clear.38 By contrast,
sex-based differences in allergen-specific IgE are less consistent across studies and are likely to be related to local differences in prevalent outdoor and indoor antigens. For instance, in a community-based Norwegian study of 1,512 adults aged 18 to 78 years, prevalence odds ratios, adjusted for potential confounders, were significantly higher in men than in women for only one of three serum-specific IgE antibodies to the indoor allergens tested (the house dust mite) and not to the two others (cat and mold) or to the two outdoor allergens tested (birch and timothy grass). A plausible explanation is that allergen-specific T-cell memory develops prenatally or in early infancy. Thus, in the Norwegian study, sensitization to house dust mite likely occurred in the first year of life, when infant boys are more at risk for sensitization than are infant girls.

**Skin Test Reactivity** In contrast to the sex-based differences in total serum IgE that are consistent in direction from childhood through old age (lower in girls than in boys and men), sex-based differences in the prevalence of skin test reactivity to a panel of allergens differ in direction in different time windows. In the Tucson study, rates in childhood up to the midteens were higher in boys than girls, but throughout their reproductive years women exhibited higher rates than men, although not after the menopause (see Table 53-2). Because these sex differences in rates for total serum IgE were consistent across the age strata studied, the average differences (25.5% vs 42.1% in females vs males, respectively) are an accurate reflection of the sex differences. However, although the average sex differences for the prevalence of skin test positivity are similar (50.3% vs 51.2% for females vs males, respectively), they are clearly not an accurate reflection of the complexity of the relationship of skin test positivity with age. The authors concluded that “the (skin) reaction rate in men and women is virtually identical” but that “depending on the age and the number of subjects, an apparent, but probably spurious sex difference may be noted.” In other words, the authors failed to recognize this evidence of important interactions between the immune and reproductive systems of women in their childbearing years. Subsequently published data confirmed that these sex differences were indeed not spurious.

### Immune Status of Fetus and Mother during Pregnancy

Pregnancy involves two physiologies, that of the fetus and that of the mother. Although the placenta is a barrier to most blood constituents, transfer of IgG is a normal feature of pregnancy. There is also a bidirectional interaction between the mother’s immune and reproductive systems, the mother’s immune response either enhancing or inhibiting the development of the fetal-placental unit, and the success of the pregnancy depends on the maternal immune system to facilitate ovule implantation and to develop tolerance to the fetus, a semiallograft. Thus, the mother’s immune system is biased toward humoral (T helper cell type 1; ie, Th1) responsiveness and the fetal–placental immune system toward a cell-mediated (T helper cell type 2; ie, Th2) responsiveness, due to cytokines produced by the amnion and placenta, and spontaneous abortion is likely to occur if this immune profile does not develop in time. T cells from the cord blood of babies born to atopic mothers respond to food and inhaled antigens to which the mother was exposed during pregnancy. In addition, estrogen levels, as they increase during pregnancy, have been shown to have multiple effects on cytokine production and on the fetal–maternal immune system. Whether the sex of the fetus affects these relationships does not appear to have been studied.

### Early Life Events as Primers of the Immune System

Pre- and early postnatal events appear to be important as primers of the human immune system when it hangs in the balance between Th2 and Th1 responsiveness, that is, between developing atopy and the asthma phenotype or not. Besides a family history, early life events associated with a decreased risk of developing childhood allergy or asthma include breast-feeding, having older siblings, having recurrent early childhood respiratory or gastrointestinal infections, and having been inoculated with certain vaccines, such as BCG. By contrast, migration and urbanization are associated with an increased risk of developing atopy and asthma. Only one study commented on sex differences in immune programming by the mother, in 777 newborn infants in Detroit, Michigan. An association between a maternal history of asthma and an elevated cord blood IgE was found for newborn girls but not for the newborn boys.

### Hormonal Determinants of Airway Behavior

Despite the evidence cited by Havelock Ellis over 100 years ago that female sex hormones influence airway behavior, and despite the recognition by physiologists in the early twentieth century that the hyperventilation of pregnancy was largely driven by progesterone, the role of hormonal factors as determinants of airway behavior is still poorly understood. There is, however, compelling evidence that, during their reproductive years, the airways of women respond to the cyclical variations in sex hormones. This has been demonstrated in the context of circadian and menstrual rhythms and the use of oral contraceptives, as well as
in pregnancy and the menopause and postmenopausal hor-
mine replacement therapy (HRT).\textsuperscript{1} Much of the information
comes from studies of subjects with asthma, although a few,
such as the classic study by Ott,\textsuperscript{7} included nonasthmatic
subjects.\textsuperscript{53,54} Many studies did not, however, distinguish
whether the cycles studied were natural or experienced by
women on oral contraceptives. Research interest also is now
shifting to understanding the role of sex hormones in the
genesis of other respiratory diseases, such as chronic
obstructive pulmonary disease, lung cancer, and obstructive
sleep apnea (OSA).\textsuperscript{55}

**Circadian and Menstrual Rhythms and
Contraceptive Use**

*Studies in Nonasthmatic Subjects* There is increasing evi-
dence supporting the hypothesis that hormones exert
important biologic effects on the respiratory tract.
Progesterone has long been identified as a potent stimulant
of ventilatory drive.\textsuperscript{52,56,57} In addition, progesterone and
estrogen have been shown to act by decreasing bronchial
smooth muscle tone.\textsuperscript{58-60} Circadian rhythms affect airway
responsiveness to inhaled challenges, as well as skin prick reac-
tivity, in diurnally active nonasthmatic men and women,
both being least at about noon and greatest around mid-
night.\textsuperscript{61} Skin reactivity also exhibits marked menstrual vari-
ability. Other cyclical variations that occur over the
menstrual cycle include airway responsiveness to metha-
choline, which has been shown to increase in the luteal
compared with the follicular phase of the cycle,\textsuperscript{62} and diffus-
ing capacity for carbon monoxide, which has been shown to
be reduced by about 8% in the pre- or perimenstrual period
compared with midcycle levels.\textsuperscript{63} Clearance of theophylline
has also been shown to be significantly higher in the luteal
than the follicular phase of the cycle.\textsuperscript{64} The expired level of
nitric oxide (NO), reflecting the biologic level of the
endothelial relaxing factor, is also significantly higher
during the luteal than the follicular phase of the cycle.\textsuperscript{53}

*Studies in Asthmatic Subjects* The level of expired NO
has been interpreted as a marker of allergen-induced inflam-
ation and may explain premenstrual exacerbations of
asthma.\textsuperscript{53} Increased clearance of theophylline in the luteal
phase could have the same effect. Premenstrual aggravation
of asthma symptoms, which occurs in 30 to 40% of asth-
maic women, may be severe, even life threatening.\textsuperscript{65} In
some studies of women whose asthma is exacerbated pre-
menstrually, modest parallel decreases in spirometric lung
functions and increases in airway responsiveness have been
shown.\textsuperscript{66} The physiologic fall in progesterone and estradiol
production by the corpus luteum in the late luteal phase
may be responsible for the premenstrual worsening of
asthma symptoms.\textsuperscript{67,68} Secretion of progestins and estradiol
by the corpus luteum peaks at 5 to 7 days after ovulation
and then drops to baseline levels shortly before the onset of
menses. There is also some evidence that menstrual
rhythmicity in airway behavior is reduced or suppressed by
intramuscular progesterone\textsuperscript{69} or by the use of oral contra-
ceptives.\textsuperscript{53,64} Premenstrual exacerbation of asthma has been
attributed\textsuperscript{1-4} to (1) an increase in allergen-induced airway
inflammation, (2) a decrease in smooth muscle contractility,
(3) microvascular leak, (4) direct action of progesterone on
the airways, and (5) in a speculative paper entitled “Is
Asthma an Endocrine Disease?”\textsuperscript{70} to changing “Western life-
styles, including increasing use of oral contraceptives,
which, when withdrawn, still delays the success of subse-
quent efforts at conception.”

**Pregnancy** Pregnancy is accompanied by changes in chest
wall and lung mechanics, increases in the diffusing capacity
that stabilize at about 26 weeks,\textsuperscript{71} and an increase in ven-
tilation at rest and on effort of about 30%, attributable to
increased progesterone levels.\textsuperscript{3} Progesterone levels are esti-
mated to be approximately 900% higher by the end of gesta-
tion and estradiol levels are 100 times higher compared with
levels at conception.\textsuperscript{60} During pregnancy, asthma may
remain stable, improve, or get worse, in roughly similar pro-
portions.\textsuperscript{72-74} Acute attacks are more likely to be experi-
enced at 17 to 24 weeks,\textsuperscript{73} particularly in women at the end
of the reproductive period of their lives, whereas worsen-
ing of asthma symptoms is more likely to occur at 29 to 32
weeks.\textsuperscript{74} The variability of the effect of pregnancy on asthma
can be attributed to a number of factors. In the group of
patients with reduced exacerbations, the high level of circu-
lating progesterone may be the dominant influence. In the
subgroup of patients in whom symptoms worsen, the benefi-
cial effects of the circulating hormones on the airways may
be attenuated by the reduced functional residual capacity
and residual volume. Furthermore, gastroesophageal reflux
is not uncommon during pregnancy and may also be a fac-
tor in triggering exacerbations in certain patients. In none of
the studies cited above was the sex of the fetus reported or
apparently considered as potentially important on influenc-
ing the mother’s asthma. However, in one study carried out
in London on 34 pregnant asthmatic women, asthma symp-
toms improved if the fetus was male and remained
unchanged or increased if the fetus was female (Table 53-
3).\textsuperscript{57} Overall, few studies have objectively examined asth-
matic subjects who were pregnant, and to our knowledge,
none have followed patients from conception to delivery. In
future such studies will hopefully also control for other
confounding factors, such as physiologic changes in
pulmonary function during pregnancy, gastroesophageal
reflux, medication use, and access to health care.

**Menopause and HRT** Menopause is characterized by
significant reductions in circulating serum hormone levels.
Few studies have investigated the effect of menopause or of
HRT on the airways and pulmonary function. However,

| Table 53-3 Asthma Status in 34 Women during Pregnancy in Relation to the Sex of the Fetus |
|---------------------------------|-------------------------------|
| Asthma status       | Sex of fetus |
| Improved            | 8               | 1                                   |
| Unchanged           | 5               | 6                                   |
| Worse               | 5               | 9                                   |
|                         | Overall, 8 boys 1 girl |

Table shows the number of woman in each group. Based Beecroft N et al.\textsuperscript{75}
some data suggest that hormonal changes in menopause may have important pathophysiologic consequences in diseases such as asthma and OSA.

**HRT and Asthma** The Nurses Health Study reported that postmenopausal women who were never-users of HRT had a lower risk of asthma than premenopausal women (relative risk = 0.65; 95% confidence interval [CI] = 0.46 to 0.92). In addition, past and current users of HRT demonstrated increased risk of asthma when compared with women who never used HRT. The Cardiovascular Health Study reported different findings. In this longitudinal population-based study of 2,353 women aged 65 and older, FEV₁ and FVC values were higher among current HRT users compared with noncurrent users. In addition, women with asthma using HRT had a trend toward higher FEV₁ and FVC values than women with asthma who were not using HRT. To our knowledge, no prospective studies examining the influence of HRT on asthma control have included a preparation with a progesterone component. Furthermore, the actual doses of estrogen in the HRT preparations, which are significantly lower than in oral contraceptive pills, may be too low to exert a potent clinical effect on asthma control.

**HRT and OSA** Early epidemiologic studies of OSA suggested that this was a disease primarily confined to men. More recent data confirm that men are two to three times more likely to have sleep-disordered breathing than women and that the majority of women affected by OSA are postmenopausal, among whom the prevalence is at least double that in premenopausal women. The increased ventilatory chemoresponsiveness triggered by progesterone may be responsible for these phenomena. Female hormones may also promote activity of the dilator upper airway muscles. In a study of 14 morbidly obese subjects (7 men and 7 women) referred for gastric bypass surgery, none of the women desaturated during sleep, whereas 6 of the men had apneic episodes with desaturation. The one man in whom apneic events were not recorded had hypogonadism. These findings suggest that testosterone may also play an important role in the pathophysiology of this disorder in men.

**ENVIRONMENTAL AND SOCIOCULTURAL DETERMINANTS OF AIRWAY BEHAVIOR**

The environmental and sociocultural determinants of airway behavior, like the biologic determinants, may act with varying strength and on occasion in opposite directions within different ages. Their impact is likely to vary between communities, cultures, and countries, reflecting differences in environmental factors such as climate, natural resources, and levels of urbanization, industrialization, and affluence or poverty, as well as differences in sociocultural factors, such as acceptability of smoking among women and the degree to which they participate in the commercial, sporting, and entertainment life of their communities. There is also increasing evidence of complex interactions between the biological (sex-based) and sociocultural (gender-based) determinants of airway behavior (see below).

**ENVIRONMENTAL EXPOSURES**

In industrialized countries and increasingly in industrializing countries, exposures common to both genders include environmental (secondhand) tobacco smoke and alcohol use, usually more and less frequent in women than in men, respectively. On the other hand, for active smoking, rates have in the past been lower in girls and women than in boys and men, although this is fast changing as women and now adolescent girls take up the smoking habit. Workplace exposure to dusts, fumes, and vapors is likely to show similar trends as women move into traditionally male jobs. On the other hand, women are more likely than men to be exposed to home cleaning materials and to nitrogen dioxide fumes from gas cookers (potentially harmful to small airway function), as are young children in the home. There is also increasing evidence that women are more susceptible to the harmful effects of certain inhaled pollutants, tobacco smoke probably being the most important. The lung structures targeted by tobacco smoke may also be different in girls and women (lung vasculature) than in boys and men (airways in general, small airways in particular).

**SOCIOCULTURAL FACTORS**

Gender-based differences in the perception, reporting, and interpretation of respiratory symptoms have usually been attributed to sociocultural factors. For instance, shortness of breath is more commonly reported by women (and may be more socially acceptable to them than men), whereas cough, raising sputum, and snoring are less commonly reported by women (and may be less socially acceptable to them than to men). However, some markers of airway behavior attributed to gender (sociocultural differences) may in fact be sex based (biologically determined). This is illustrated in Figure 53-3, which shows that at all levels of FEV₁ (an objective marker of airway function), age-standardized, shortness of breath (a subjective marker of airway function) is more frequently reported by women than men. A plausible explanation is that their perception of breathlessness has been enhanced by the cyclical fluctuation of their airway caliber in response to the cyclical fluctuation of their sex hormones throughout their reproductive lives. As far as the symptoms of cough and raising sputum are concerned, women have consistently been shown to have a lower threshold to cough challenge tests than men, and this threshold is lower in pre- than postmenopausal women. These findings also illustrate the complexity of the potential interactions between the biologic and sociocultural determinants of airway behavior in women in their reproductive years.

**METHODOLOGIC ISSUES**

Studies of sex and gender differences in airway behavior are subject to methodologic sources of bias, which are particularly challenging to handle. For instance, inferences about sex or gender differences in susceptibility to tobacco smoke derived from epidemiologic studies are potentially subject to underestimation as a result of (1) selection bias from the “healthy” smoker effect (those whose airways are less able to sustain the habit remain nonsmokers); (2) information
bias (although reported levels of smoking may be similar for men and women, the effects of passive smoking, which are likely to be higher in women than in men, are not always taken into account in analysis); (3) diagnostic bias (symptoms such as shortness of breath and wheezing may attract a different diagnosis when reported by women than by men); (4) confounding bias (inferences are crucially dependent on how the reference, nonsmoking group is constituted, which, in turn, depends on the definition of “nonsmoker” and the reasons, usually very different, why men and women do not smoke). These and other methodologic issues will, for the most part, underestimate the effects of environmental and sociocultural determinants on airway behavior and disease in women and hence of the associated sex or gender differences.

**SUMMARY AND CONCLUSIONS**

To what extent are sex- and gender-based differences in airway behavior reflected in the clinical manifestations of airway disease? We addressed this question using, as the example, asthma based on data gathered in the **PAARC** (Pollution Atmosphériques et Affections Respiratoires Chroniques), a cross-sectional population-based study conducted in 1975 on over 20,000 adults aged 25 to 59 years, excluding subjects with reported respiratory or cardiovascular disease. The quintiles of FEV₁ were defined separately for women and men, age taking into account. Reproduced with permission from Kauffmann and Becklake.¹

![Graph showing Incidence of asthma per 100,000 in 5-year age periods in girls and women compared with boys and men.](image1)

![Graph showing Sex differences in reported shortness of breath (%).](image2)

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**FIGURE 53-3** Sex differences in reported shortness of breath (prevalence %) by quintiles of cc. Based on data gathered in the **PAARC** (Pollution Atmosphériques et Affections Respiratoires Chroniques), a cross-sectional population-based study conducted in 1975 on over 20,000 adults aged 25 to 59 years, excluding subjects with reported respiratory or cardiovascular disease. The quintiles of FEV₁ were defined separately for women and men, age taking into account. Reproduced with permission from Kauffmann and Becklake.¹

**FIGURE 53-4** Incidence of asthma per 100,000 in 5-year age periods in girls and women compared with boys and men. Based on data gathered in the **PAARC** (Pollution Atmosphériques et Affections Respiratoires Chroniques), a cross-sectional population-based study conducted in 1975 on over 20,000 adults aged 25 to 59 years, excluding subjects with reported respiratory or cardiovascular disease. Incidence of asthma was estimated retrospectively from age at onset as reported by the subjects. Reproduced with permission from Kauffmann and Becklake.¹

started to reverse, and from the age of 20 through 44 years (ie, throughout their reproductive years) incidence rates in women exceeded those in men. During this period, although women retained their dimensional advantages over men, their higher rates can be attributed to hormonal factors as well as interactions between immunologic and hormonal factors. From the age of 45 years, incidence rates again reversed; the rates in men increased, whereas those in women remained stable. The reasons for this are not clear but may be methodologic. After menopause, the airways of women appear to remain responsive to their sex hormones. Almost three decades after the **PAARC** study was carried out, the sex reversal rates of asthma during the reproductive period of women’s lives was confirmed by data gathered in the European Community Respiratory Health Survey (ECRHS) on a comparable number of subjects (18,000 to 19,000), although over a more limited age span (20 to 45 years of age). The pattern of distribution of asthma was similar within the 16 countries studied and was not affected by smoking.⁹⁰ In other studies, late-onset asthma was found to be largely confined to women and usually started around menopause.

Biologic (sex-based) and sociocultural (gender-based) differences in the airway behavior of girls and women compared with those of boys and men occur across the human life span. These differences, which vary in both strength and direction for different age spans, interact in a complex way to affect the clinical manifestations of airway disease. The biologic determinants of these differences include dimensional (lung structure–function relationships), immunologic, and hormonal factors. In childhood, the lungs of girls,
although smaller than those of boys, exhibit dimensional advantages compared with those of boys, measurable as higher flow rates in relation to lung size. From adolescence and throughout their child-bearing years, immunologic and hormonal factors exert important and interacting roles on the airway behavior of women and are probably responsible for the higher rates of asthma in women during the reproductive period of their lives. In addition, from late childhood through adolescence and into their adult life, airway behavior in women is influenced by environmental and sociocultural (gender-related) factors, some shared with men, some not. These act to modify how the symptoms of lung disease are perceived and reported by women compared with men, as well as how they are managed by their physicians. Results of studies on the effects of airway behavior on the manifestations of airway disease, whether clinical or epidemiologic, should be analyzed separately by sex and stratified by age prior to being combined, for instance, in clinical trials. In addition, the mechanisms of these sex-based differences should be the focus of research studies in the early years of the twenty-first century. We fully concur with the conclusion expressed by the authors of the 2001 Institute of Medicine report8: “Understanding [the] sex differences in health and illness merits serious scientific inquiry in all aspects of biomedical and health-related research.”

REFERENCES


