

Is Bronchial Hyperresponsiveness More Frequent in Women than in Men?

A Population-based Study

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To test the hypothesis that a greater proportion of women than men react to methacholine challenge and investigate the possible reasons for any differences observed, we recruited 495 subjects 20 to 44 yr of age (50.9% male) in Paris and 304 subjects (51.3% male) in Montpellier (France), as part of the European Community Respiratory Health Survey. The proportion of responders ($PD_{20} \leq 4$ mg methacholine) was 33.7% in women and 11.9% in men (odds ratio = 3.8; 95% confidence interval = 2.4–6.0) in Paris and 43.2% in women and 29.5% in men (odds ratio = 1.8; 95% confidence interval = 1.1–2.9) in Montpellier. These differences could not be explained by asthma, respiratory symptoms, atopy, or lung function parameters. In stepwise logistic regressions including sex, asthma, and asthma-like symptoms, nasal allergies, atopy, baseline FEV_1 , $FEV_1\%$ pred, FVC, and $FEV_1\%$ FVC, the odds-ratios for the effect of female sex on $PD_{20} \leq 4$ mg methacholine were 5.2 (3.0–9.0) in Paris and 2.2 (1.2–3.8) in Montpellier. Reacting to low doses of methacholine ($PD_{20} \leq 0.5$ mg) was associated with asthma and atopy in both men and women. In contrast, reacting to doses between 0.5 and 4 mg was associated with asthma and atopy only in men and with heavy tobacco consumption only in women. We conclude that the excess of hyperresponsiveness in women is not due to their having smaller lung size or airway caliber than men and may be related to a greater susceptibility to smoking. Leynaert B, Bousquet J, Henry C, Liard R, Neukirch F. Is bronchial hyperresponsiveness more frequent in women than in men?: a population-based study.

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Bronchial hyperresponsiveness to nonspecific bronchoconstrictor agents (BHR) is one of the main features of asthma. However, BHR is more prevalent than asthma and epidemiologic studies show that it is also observed in subjects without asthma or asthma-like symptoms (1). BHR is a risk factor for accelerated decline in pulmonary function and, hence, development of chronic obstructive pulmonary disease in nonasthmatics (2, 3). Several population studies of risk factors associated with BHR report a higher responsiveness in women than in men: either the proportion of reactors for a given dose of bronchoconstrictor was greater (4–8) or the dose-response slope was steeper (9, 10). This greater responsiveness of women was especially evident in young to middle-aged groups (6, 8, 9).

It has been suggested that the excess of responsiveness in women may be an artifact attributable to their having a

smaller airway caliber than men (6, 10). To explore the independent effect of gender, several investigators have tried to take airway caliber into account by adjusting for various lung function indices. Although an independent gender effect was observed in some cases (9, 10), factors possibly related to greater responsiveness in women have not been analyzed.

The objectives of this study were (1) to compare the frequency of BHR in men and women 20 to 44 yr of age recruited in a population-based study and (2) to investigate the possible reasons for any differences observed.

METHODS

Subjects

Data for 20- to 44-yr-old subjects were collected between September 1991 and June 1993 as part of the European Community Respiratory Health Survey (ECRHS). The method of this international two-stage survey has been described elsewhere (11). Briefly, 4,299 subjects from the eighteenth district of Paris and 5,619 subjects from the town of Montpellier were randomly selected from electoral rolls and were sent a self-administered questionnaire on asthma and asthma-like symptoms derived from the bronchial symptoms questions of the International Union Against Tuberculosis and Lung Disease questionnaire (11) (Stage I). Fully completed postal questionnaires were returned by 3,151 people in Paris and 3,774 in Montpellier. These subjects were then asked to attend the university clinic to be administered subsidiary tests. A total of 660 subjects in Paris and 456 subjects in Montpellier participated in Stage II of the ECRHS. Complete data on all tests were available for 495 individuals examined in the Paris center and

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These results are from a local analysis of data collected for the European Community Respiratory Health Survey. Any final international comparison may use a different form of analysis.

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TABLE 1
FREQUENCY OF SYMPTOMS AND ASTHMA REPORTED IN THE POSTAL QUESTIONNAIRE BY THE SUBJECTS INCLUDED IN THE ANALYSIS (TESTED) COMPARED WITH THOSE WHO PARTICIPATED ONLY IN STAGE I

	Paris				Montpellier			
	Men		Women		Men		Women	
	Tested (n = 252)	Stage I Only (n = 1,210)	Tested (n = 243)	Stage I Only (n = 1,446)	Tested (n = 156)	Stage I Only (n = 1,743)	Tested (n = 148)	Stage I Only (n = 1,727)
Wheezing in chest*	16.3	14.3	16.5	13.8	18.6	14.4	17.6	12.8
Awakening with chest tightness*	16.3	14.8	24.0	17.0 [†]	20.5	13.9 [‡]	28.6	18.1 [†]
Woken by shortness of breath*	4.4	4.2	5.9	4.8	4.5	3.6	6.2	4.4
Asthma attack*	4.0	4.1	3.7	4.0	6.4	2.9 [‡]	7.5	3.5 [‡]
Asthma ever	10.0	9.5	11.7	8.8	12.2	9.0	14.3	8.8 [‡]
Nasal allergies (hay fever)	31.8	30.1	39.4	29.8 [†]	36.5	32.6	44.2	35.0 [‡]

* During the last 12 mo.

[†] $p < 0.01$.

[‡] $0.01 \leq p < 0.05$.

304 individuals of the Montpellier center. The sex ratio was about 1:1 in all samples. Although the prevalence of symptoms was often higher in the subjects tested than in those who participated only in Stage I (Table 1), self-selection towards participation in testing was not associated with sex (the interaction test for a greater proportion of symptomatic subjects in one sex than in the other was not significant).

Methods

Subjects included in Stage II answered the main questionnaire administered by trained interviewers and performed lung function tests, including methacholine challenge and allergen skin tests. The main questionnaire included detailed questions on symptoms and medical history, medication and use of services, occupation and occupational exposure, and home environment. The questions on smoking habit were adapted from the American Thoracic Society Questionnaire (11). FVC and FEV₁ were measured with a water-sealed bell spirometer (Biomedin srl, Padova, Italy), and the best of five satisfactory maneuvers was used in the analysis. Predicted FEV₁ values were calculated from age and height for men and women using ECSC reference equations (12). A Mefar MB3 dosimeter (Mefar srl, Bovezzi, Italy) was used for the administration of methacholine. Criteria of exclusion from the methacholine challenge test were defined in the ECRHS international protocol. In particular, methacholine was not given to subjects with a baseline FEV₁ < 70% of the predicted value or < 1.5 L (three men and zero women in Paris; four men and four women in Montpellier) or a post-saline FEV₁ < 90% of initial FEV₁ (zero men and four women in Paris; two men and five women in Montpellier). After phosphate-buffered saline was inhaled, subjects were administered methacholine until FEV₁ had fallen by 20% or more from the post-saline value or until the maximum cumulative dose of 4 mg had been given: this dose was greater than the maximum dose defined in the ECRHS protocol (1 or 2 mg). Subjects with a past history of asthma or wheezing were started on a dose of 0.0078 mg, which was doubled for each subsequent administration. In other subjects, the following cumulative doses were administered: 0.0156, 0.0625, 0.25, 1, 2, 4 mg, changing to 2-fold steps if FEV₁ fell by 10% or more. Allergen skin sensitivity to 11 allergens was assessed using Phazets (Pharmacia Diagnostic AB, Uppsala, Sweden), with a positive control (histamine) Phazet and a negative control Phazet (11). Each wheal was measured as the mean of the largest diameter of the wheal and the right-angled diameter.

The protocol was approved by the French Ethics Committee for human research and by the National Committee for Data Processing and Freedom. Informed written consent was obtained from all the subjects.

Analysis

Subjects were categorized as reactors if they had a decline from post-saline FEV₁ of $\geq 20\%$ at the last dose (PD₂₀ ≤ 4 mg methacholine). The methacholine provocative dose (PD₂₀) was calculated by interpolation between the results of the last two inhaled doses of methacholine.

The two-point dose-response slope was calculated as the percent decline in FEV₁ from the post-saline value to that at the final cumulative dose administered divided by the final cumulative dose. The analysis was performed using $\log(\text{slope} + 1)$. Subjects with at least one mean skin wheal diameter ≥ 3 mm larger than the negative control were defined as atopic. Subjects who reported having smoked more than 1 g tobacco a day for 1 yr or more were defined as heavy smokers if they currently smoked more than 20 g tobacco a day and as moderate smokers otherwise. Those who had stopped at least 1 yr before the examination were defined as ex-smokers. The SAS-PC statistical package was used for statistical analysis; p values < 0.05 were considered significant. Contingency tables were analyzed using chi-square tests or the Fisher exact test when sample size was small. Continuous variables were analyzed by t test.

Univariate and multivariate logistic regressions with BHR status as the dependent variable were used to study the effect of sex taking bronchial airway caliber into account. In addition to sex, several indices that are linked to airway caliber were included in the models: height, weight/height², baseline FEV₁, predicted FEV₁, FEV₁%pred, FVC, and FEV₁%FVC. A forward stepwise logistic regression was also run with significance levels for entry or retention in the model, both set at $p = 0.05$; the variables included in the model were sex, smoking habits, and all the variables that were significantly associated to BHR in univariate analysis. We used multiple linear regressions when the dose-response slope was the dependent variable.

RESULTS

Study Population

Characteristics of the subjects included in the study are shown in Table 2. Past smoking was slightly more frequent among men than women, and mean daily tobacco consumption was higher by male than female current smokers ($p < 0.01$ in Paris; $p = 0.06$ in Montpellier). Men were more exposed to vapors, gas, dust, or fumes at work. There was no significant difference between the prevalence of symptoms reported by men and that by women. The proportion of men who reacted to skin-prick tests was higher than that of women but the difference was of borderline significance ($p = 0.06$) in Paris and not significant in Montpellier. Men were of similar age, were taller, and had a greater mean baseline FEV₁ than women but there was no difference in FEV₁%pred or FEV₁%FVC. The prevalence of PD₂₀ ≤ 4 mg was higher in women than in men (odds ratio [OR] = 3.77, 95% confidence interval [95% CI] = 2.37–6.00 in Paris; OR = 1.82, 95% CI = 1.14–2.93 in Montpellier). The dose-response slope was greater in women than in men in both towns.

TABLE 2
CHARACTERISTICS OF THE STUDY POPULATION BY SEX AND TOWN

	Paris		Montpellier	
	Men (n = 252)	Women (n = 243)	Men (n = 156)	Women (n = 148)
Age, yr (mean ± SD)	36.25 ± 6.78	35.27 ± 7.25	34.58 ± 6.74	35.22 ± 7.27
Height, m (mean ± SD)	1.76 ± 0.07	1.64 ± 0.06 [†]	1.75 ± 0.06	1.63 ± 0.06 [†]
Smoking habit, %				
Nonsmoker	34.5	42.4 [‡]	48.7	51.4
Ex-smoker	25.8	21.0	19.9	22.3
Moderate smoker (< 20 g/d)	18.7	24.7	12.8	15.5
Heavy smoker (≥ 20 g/d)	21.0	11.9	18.6	10.8
Occupational exposure to vapors, gas, dust, or fumes, %	37.8	17.4 [†]	17.5	6.8 [†]
Subjects with symptoms (Stage II), %				
Wheezing in chest*	17.5	18.5	25.6	21.6
Awakening with chest tightness*	17.5	21.0	23.7	25.7
Woken by shortness of breath*	3.2	5.8	10.9	9.5
Asthma attack*	2.8	2.9	8.3	8.1
Atopy, %	34.1	26.3	36.5	30.4
FEV ₁ , L/s (mean ± SD)	4.23 ± 0.59	3.09 ± 0.47 [†]	4.35 ± 0.54	3.20 ± 0.42 [†]
FEV ₁ %pred (mean ± SD)	105.8 ± 12.4	103.9 ± 11.7	108.2 ± 10.7	108.7 ± 10.5
FEV ₁ %FVC (mean ± SD)	85.3 ± 5.7	85.5 ± 6.4	92.2 ± 5.6	92.5 ± 5.3
Subjects with PD ₂₀ ≤ 4 mg, %	11.9	33.7 [†]	29.5	43.2 [§]
log(slope + 1) (mean ± SD)	0.19 ± 0.36	0.40 ± 0.53 [†]	0.37 ± 0.50	0.48 ± 0.56

* During the last 12 mo.

[†] p < 0.01 for the comparison between men and women.

[‡] p < 0.01 for the comparison between men and women by chi-square test with 3 degrees of freedom.

[§] 0.01 ≤ p < 0.05 for the comparison between men and women.

^{||} p = 0.07 for the comparison between men and women.

Associations between BHR and Risk Factors, Symptoms, and Pulmonary Function by Sex

A PD₂₀ ≤ 4 mg was not associated with smoking, with exposure to tobacco smoke (in nonsmokers), or with occupational exposure to vapors, gas, dust, or fumes for either men or women. The associations between PD₂₀ ≤ 4 mg and asthma, asthma-like symptoms, and allergy are shown in Table 3. The odds-ratios were generally greater for men than for women, indicating that the association between these conditions and BHR were stronger in men. Of all the responsive subjects, 28 (34%) women but only four (13%) men had neither asthma nor nasal allergy or respiratory symptoms (wheezing, awaken-

ing with chest tightness, or being woken by shortness of breath) in Paris (p = 0.03). These figures were 14 (22%) and five (11%), respectively, in Montpellier (p = 0.13). In both towns, reactive subjects had significantly lower levels of FEV₁%pred than nonreactors, and this association was similar for men and women (results not shown).

BHR Prevalence in Asymptomatic Subjects According to Sex

We tested whether there was an association between female sex and risk of BHR for nonsymptomatic subjects. In Paris, women were more likely than men to have a PD₂₀ ≤ 4 mg in

TABLE 3
ODDS RATIOS AND CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN RESPIRATORY SYMPTOMS, ASTHMA, AND ALLERGIES AND BHR

	Paris				Montpellier			
	Men		Women		Men		Women	
	OR of PD ₂₀ ≤ 4 mg	95% CI	OR of PD ₂₀ ≤ 4 mg	95% CI	OR of PD ₂₀ ≤ 4 mg	95% CI	OR of PD ₂₀ ≤ 4 mg	95% CI
Wheezing in chest*	4.71 [†]	2.08–10.65	4.39 [†]	2.23–8.66	7.54 [†]	3.40–16.71	3.88 [†]	1.68–8.96
Awakening with chest tightness*	2.29	0.96–5.41	2.28 [†]	1.21–4.28	8.14 [†]	3.59–18.45	2.58 [‡]	1.21–5.50
Woken by shortness of breath*	2.57	0.50–13.36	5.45 [†]	1.65–17.97	26.13 [†]	5.67–120.49	3.70 [‡]	1.11–12.42
Asthma ever	14.13 [†]	5.37–37.19	5.09 [†]	2.19–11.87	9.81 [†]	3.89–24.76	5.00 [†]	1.96–12.76
Nasal allergies (hay fever)	4.66 [†]	2.10–10.37	1.86 [‡]	1.07–3.24	6.05 [†]	2.86–12.83	2.89 [†]	1.47–5.68
Atopy	3.40 [†]	1.55–7.44	2.16 [‡]	1.20–3.88	6.68 [†]	3.13–14.24	2.34 [‡]	1.15–4.78

* During the last 12 mo.

[†] p < 0.01.

[‡] 0.01 ≤ p < 0.05.

the groups who: (1) had never had asthma ($n = 445$; $OR = 4.88$; $p < 0.01$), (2) had never had asthma and did not react to skin-prick tests ($n = 325$; $OR = 5.00$; $p < 0.01$), or (3) had never had asthma, did not react to skin-prick tests, and had never had nasal allergy ($n = 255$; $OR = 6.42$; $p < 0.01$). The difference between sexes was larger in the nonsmokers of the third subgroup ($n = 94$; $OR = 9.55$; $p < 0.01$). In Montpellier, the odds ratio for the association between female sex and $PD_{20} \leq 4$ mg was 2.24 ($p < 0.01$) for nonasthmatic subjects ($n = 249$), 3.64 ($p < 0.01$) for subjects who had never had asthma, atopy, or nasal allergy ($n = 146$), and 14.40 ($p < 0.01$) in nonsmokers with none of these conditions ($n = 68$).

Adjustment for Lung Function

Various logistic regressions were used in an attempt to adjust for airway caliber and lung size (Table 4). If sex and height were included in the model, women were at higher risk than men of $PD_{20} \leq 4$ mg. Similar results were observed after adjustment for height², for height³, or for the weight/height² ratio. When predicted FEV_1 was taken into account, women were still at higher risk of BHR than men. Women were also more reactive than men when adjusting for $FEV_1\%$ pred, FVC, or $FEV_1\%$ FVC. After adjustment for baseline FEV_1 alone, the difference between men and women did not reach statistical significance but the odds ratios were 1.57 in Paris and 1.41 in Montpellier. However, when both baseline FEV_1 and height were taken into account, the odds ratios were larger and became significant for the data from Paris. After adjusting for any combination of baseline FEV_1 , $FEV_1\%$ pred, and $FEV_1\%$ FVC, women were more responsive than men except for the model that adjusted for FEV_1 and $FEV_1\%$ FVC.

Stepwise logistic regressions were conducted (bottom of Table 4). For both centers, the model that best fitted the data showed that women were at higher risk than men of $PD_{20} \leq 4$ mg independently of other factors.

The analysis was entirely rerun using the dose-response slope instead of the categorical response reactors versus non-reactors. The results confirmed the categorical findings. In

multiple linear regressions including sex, wheezing, awakening with chest tightness, woken by shortness of breath, asthma ever, nasal allergies, atopy, baseline FEV_1 , $FEV_1\%$ pred, FVC, and $FEV_1\%$ FVC, mean $\log(\text{slope} + 1)$ was 0.17 ($SE = 0.04$) in men and 0.42 ($SE = 0.04$) in women ($p < 0.01$) in Paris and 0.31 ($SE = 0.05$) in men and 0.54 ($SE = 0.05$) in women ($p < 0.02$) in Montpellier.

Proportion of Reactors at Each Step of the Methacholine Challenge Test

The cumulative percentage of subjects with a 20% decline in FEV_1 from post-saline FEV_1 (PD_{20}) was then plotted against the cumulative methacholine dose administered, separately for men and women. To reach the same prevalence of PD_{20} in women as in men, the methacholine bronchoprovocation challenge should have been stopped at < 0.5 mg for women and 4 mg for men in Paris (Figure 1a) and < 1.5 mg and 4 mg, respectively, in Montpellier (Figure 1b). To assess the effects of bronchial caliber on BHR, we also compared the prevalence of BHR in short and tall subjects of the same sex. Subjects were divided into three equal groups according to height. We then plotted the cumulative percentage of subjects with PD_{20} against the cumulative methacholine dose received separately for women whose height was in the first tertile of the distribution (short women) and for women whose height was in the third tertile (tall women) (Figure 2). The proportions of reactors at each dose were the same in the two groups. We also compared women with high and low predicted FEV_1 (results not shown) and again detected no difference. Similar results were observed in men.

Using the dose-response slope instead of the reactor status did not show any difference in mean $\log(\text{slope} + 1)$ when comparing short to tall women or women with high and low predicted FEV_1 .

Level of Responsiveness

The percentage of female reactors at a methacholine dose of < 0.5 mg was the same as that of male reactors at 4 mg (data

TABLE 4
INDEPENDENT ODDS RATIOS AND CONFIDENCE INTERVALS FOR THE EFFECT OF FEMALE SEX
ON BHR ADJUSTED FOR VARIOUS INDICES OF AIRWAY CALIBER AND LUNG SIZE

	Paris ($n = 495$)		Montpellier ($n = 304$)	
	OR of $PD_{20} \leq 4$ mg for Female Sex	95% CI	OR of $PD_{20} \leq 4$ mg for Female Sex	95% CI
Adjusted for:				
Height	4.19 [†]	2.25–7.78	2.15 [‡]	1.08–4.29
Weight/height ²	3.65 [†]	2.27–5.87	1.81 [‡]	1.09–2.98
Predicted FEV_1	3.99 [†]	1.75–9.11	6.93 [†]	2.53–19.03
FEV_1	1.57	0.82–3.01	1.41	0.68–2.95
$FEV_1\%$ pred	3.74 [†]	2.32–6.03	1.93 [†]	1.18–3.14
$FEV_1\%$ FVC	4.02 [†]	2.50–6.47	1.91 [†]	1.18–3.09
FVC	2.63 [†]	1.37–5.04	2.06 [‡]	1.02–4.17
FEV_1 , height	2.11 [‡]	1.06–4.17	1.64	0.76–3.54
FEV_1 , $FEV_1\%$ pred	3.88 [†]	1.67–9.02	6.31 [†]	2.31–17.22
FEV_1 , $FEV_1\%$ FVC	1.93	0.98–3.81	1.48	0.70–3.13
$FEV_1\%$ pred, $FEV_1\%$ FVC	3.91 [†]	2.41–6.35	2.00 [†]	1.22–3.28
FEV_1 , $FEV_1\%$ pred, $FEV_1\%$ FVC	3.94 [†]	1.67–9.31	5.93 [†]	2.16–16.28
Stepwise logistic regression*	5.17 [†]	2.98–8.97	2.17 [†]	1.24–3.80

* The variables included in the model were sex, wheezing, awakening with chest tightness, woken by shortness of breath, asthma ever, nasal allergies, atopy, baseline FEV_1 , $FEV_1\%$ pred, FVC, and $FEV_1\%$ FVC for both centers. The variables kept in the final model were sex, wheezing, asthma ever, nasal allergies, and $FEV_1\%$ pred for both centers plus atopy and $FEV_1\%$ FVC (Paris center) and awakening with chest tightness (Montpellier center).

[†] $p < 0.01$.

[‡] $0.01 \leq p < 0.05$.

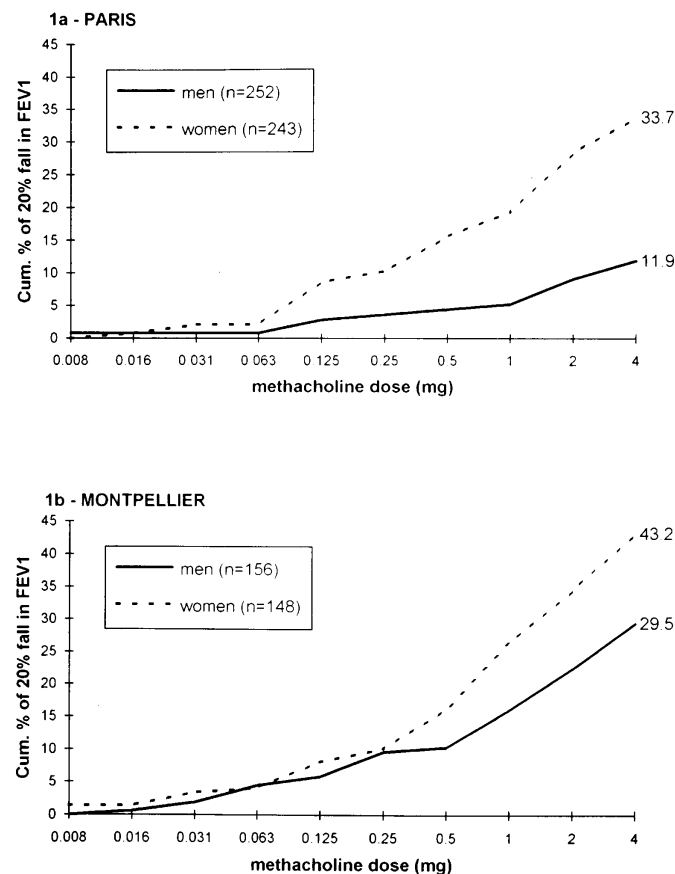


Figure 1. Cumulative percentage of men (solid line) and women (dotted line) with a 20% fall in FEV₁ at various doses of methacholine (a: data from Paris; b: data from Montpellier).

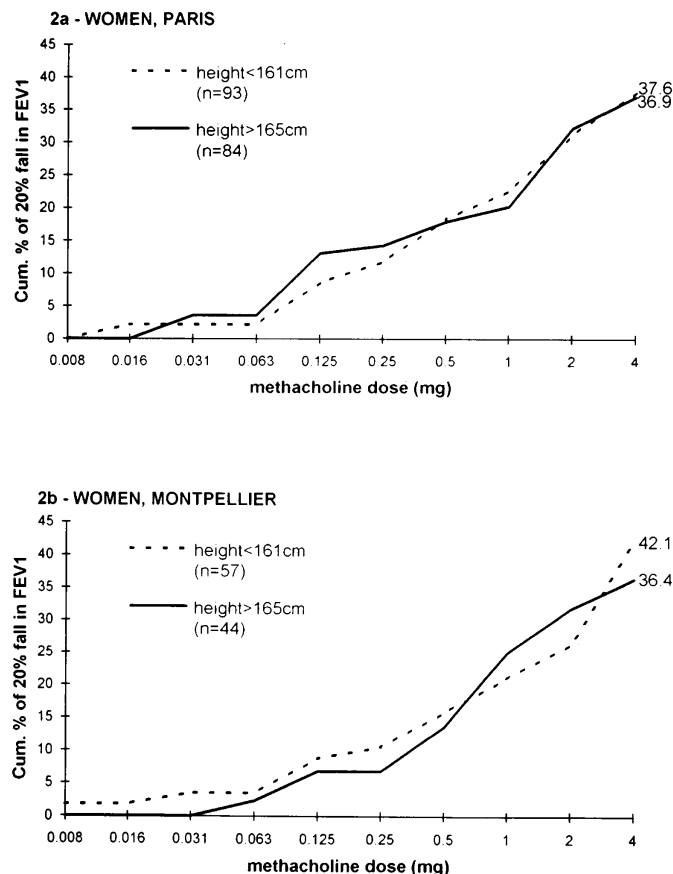


Figure 2. Cumulative percentage of women with height in the first tertile (solid line) and women with height in the third tertile (dotted line) with a 20% fall in FEV₁ at various doses of methacholine (a: data from Paris; b: data from Montpellier).

from Paris). We therefore ran separate analyses for subjects with $PD_{20} \leq 0.5$ mg and those with PD_{20} between 0.5 and 4 mg in both towns. Because the results were similar in Paris and Montpellier (no significant interaction) and the numbers of subjects were relatively small, we pooled the data of the two towns. In men, the conditions reported in Table 3 were significantly associated with both levels of BHR. In women, low-dose responsiveness was strongly associated with asthma-like symptoms; the odds ratio for asthma, nasal allergy, and atopy increased toward or became even greater than those observed in the whole group of men. In contrast, the associations between these conditions and PD_{20} between 0.5 and 4 mg were weak and generally not significant (Table 5). In women as in men, there was no association between either level of BHR and occupational exposure to vapors, gas, dust, or fumes or passive smoking. In men, no association was found between smoking status and either level of responsiveness. In women, the risk of having low-dose BHR was not related to smoking status. In contrast, the risk of reacting at doses between 0.5 and 4 mg was greater for heavy smokers than moderate smokers. The prevalence of PD_{20} between 0.5 and 4 mg among women was 31% in heavy smokers versus 12% in moderate smokers (OR = 3.26, 95% CI = 0.99–10.74) in Paris and 50% versus 13% (OR = 7.00, 95% CI = 1.14–42.97) in Montpellier.

DISCUSSION

In our population-based sample of subjects 20 to 44 yr of age, the prevalence of BHR to methacholine was higher among

women than men both in Paris and Montpellier. This could not be explained by a higher prevalence of respiratory symptoms among women and indeed the difference was even greater in nonsymptomatic subjects. Several variables were used to adjust for airway caliber and lung size. Adjusting for any of height, body mass index, predicted FEV₁, FEV₁%pred, FVC, or FEV₁%FVC, or FEV₁%pred and FEV₁%FVC together did not abolish the observed difference between sexes. Only adjusting for baseline FEV₁ led to the difference not being statistically significant, but the adjusted odds-ratio for increased risk of BHR in women was still > 1.4. Moreover, shorter women were not more reactive than taller ones. These results suggest that the greater responsiveness observed in women was not due to women receiving a dose of methacholine relatively large for their size. In men, both $PD_{20} \leq 0.5$ mg and PD_{20} between 0.5 and 4 mg were significantly associated with asthma, asthma-like symptoms, and allergy, whereas in women only low-dose BHR was strongly associated with these conditions. Among factors that could explain women's BHR, heavy tobacco consumption was associated with reacting to doses between 0.5 and 4 mg.

Although the data were collected independently, the results obtained in Paris and Montpellier are very similar. In both towns, the postal questionnaire was sent to a sample of subjects randomly selected from electoral rolls (Stage I). The representativity of the subjects who answered the initial postal questionnaire has been shown elsewhere (13). The prevalence

TABLE 5
ODDS RATIOS AND CONFIDENCE INTERVAL FOR THE ASSOCIATION BETWEEN
RESPIRATORY SYMPTOMS, ASTHMA, ALLERGIES, AND BHR IN WOMEN
ACCORDING TO THE LEVEL OF RESPONSIVENESS

	OR for $PD_{20} \leq 0.5 \text{ mg}^\dagger$	95% CI	OR for $0.5 < PD_{20} \leq 4 \text{ mg}^\ddagger$	95% CI
Wheezing in chest*	9.19 [§]	4.85–17.41	2.05	1.05–3.99
Awakening with chest tightness*	4.10 [§]	2.24–7.48	1.56	0.85–2.84
Woken by shortness of breath*	9.46 [§]	3.79–23.57	1.88	0.60–5.90
Asthma ever	12.58 [§]	6.18–25.61	1.93	0.84–4.45
Nasal allergies (hay fever)	3.73 [§]	2.09–6.66	1.60	0.96–2.68
Atopy	4.12 [§]	2.30–7.39	1.37	0.77–2.41
Smoking habits				
Heavy smokers versus nonsmokers	0.71	0.25–2.00	1.48	0.71–3.07
Heavy smokers versus moderate smokers	0.68	0.23–2.05	4.35 [§]	1.64–11.57

* During the last 12 mo.

† Sixty-two women with $PD_{20} \leq 0.5 \text{ mg}$ were compared with 245 nonreactive women.

‡ Eighty-four women with $0.5 \text{ mg} < PD_{20} \leq 4 \text{ mg}$ versus 245 nonreactive women.

§ $p < 0.01$.

|| $0.01 \leq p < 0.05$

of symptoms was generally higher among the subjects tested than in those who participated only in Stage I. However, the symptom prevalence was similarly higher for both men and women and the interaction test for a greater increase in one sex than the other was not significant. We do not think that self-selection of symptomatic subjects may have biased our results since the prevalence of symptoms was similar in the men and women tested and the difference in BHR between sexes was even greater in nonsymptomatic subjects.

Most previous studies of adults report a higher responsiveness of women to nonspecific bronchoconstrictor stimuli. In 100 healthy nonsmokers equally distributed for sex, Malo and coworkers found that the number of subjects with $PC_{20} \leq 128 \text{ mg/ml}$ was greater in women than men (4). In general population-based samples, the crude prevalence of subjects with an observed 20% decrease in FEV_1 was almost always reported to be higher in women than in men (6, 8). Only Burney and colleagues reported a higher prevalence of $PD_{20}FEV_1 \leq 8 \mu\text{mol}$ in men, but the difference was not significant when skin sensitivity, smoking, and age were taken into account (1). Women were also more hyperresponsive than men in samples of smokers with mild to moderate airflow limitation (14) or in patients with asthma (15). Using a 15% decrease in FEV_1 to define responsiveness, women were also shown to be more reactive than men in studies of Italian normal nonsmokers (5), French blue-collar workers (16), or an Australian general population (7). No significant sex effect was detected when a 10% or smaller decline in FEV_1 was used to define BHR: Rijcken and associates reported a similar prevalence of subjects with a persistent 10% decrease of FEV_1 or inspiratory vital capacity in both sexes (17), and Malo and coworkers failed to find a significant difference when $PC_6 \leq 128 \text{ mg/ml}$ was used instead of $PC_{20} \leq 128 \text{ mg/ml}$ (4). Women have also been found to have steeper dose-response slopes than men (9).

It has been suggested that the higher BHR observed in women may be due to their having smaller airway caliber (6, 10). The resistance to the flow in a tube is inversely proportional to the fourth power of its radius. Therefore, a given degree of circumferential bronchial smooth muscle shortening will cause a greater increase in airway resistance in a narrower than a wider airway. Consequently, subjects with small airway caliber are expected to show a greater fall in FEV_1 . Baseline FEV_1 is frequently used to adjust for airway caliber. However, this procedure is debatable. Adjusting for baseline FEV_1 may bias the results, since it is equivalent to comparing BHR in

men and women with similar FEV_1 . Rather than adjusting for FEV_1 , we compared the prevalence of BHR in men and women with FEV_1 between 3 and 3.5 L/s: the prevalence of BHR was higher in women than in men in both Paris (25.6% versus 17.9%) and Montpellier (45.1% versus 33.3%), but the difference was not significant (results not shown). However, among subjects with FEV_1 between 3.0 and 3.5 L/s, women had higher $FEV_1\%$ pred than men (106.4 ± 7.9 versus 89.8 ± 9.0 ; $p < 0.01$). Results were similar in subjects with FEV_1 between 3.5 and 4.0 L/s. Since baseline FEV_1 is physiologically greater in men than women, comparing men and women with the same level of FEV_1 is to compare men who are at higher risk of BHR than the average to women who are at lower risk of BHR. If women are really more responsive than men, this selection bias may artificially remove or even reverse the sex difference in BHR. This may partly explain why in some studies the significance of the sex difference was lost after adjustment for baseline FEV_1 (10). In others, this adjustment led to a higher risk in men (6, 17). The effects of such an adjustment may depend on the characteristics (health status and age) of the population studied. In 21- to 55-yr-old subjects from a general population, Paoletti and coworkers found a higher level of BHR in women than in men that was still significant after FEV_1 was taken into account (9). In contrast, in the over-65-yr age group, the adjustment for FEV_1 resulted in slightly lower mean values of the ln-slope in women than in men. In most studies, after adjustment for other lung function indices alone or with baseline FEV_1 , women were found to be more responsive than men (9, 10, 17). In our study, the sex difference was significant after adjustment for either $FEV_1\%$ pred or $FEV_1\%$ -FVC or both. To adjust for variables that are linked to airway caliber but that are not impaired in reactive subjects, we measured the sex effect on risk of BHR after adjustment for either morphometric variables or predicted FEV_1 . These analyses showed that women were more responsive than men when any of height, body mass index (weight/height²), or predicted FEV_1 were taken into account. Moreover, BHR was not related to height for either men or women, indicating that the higher BHR of women cannot be explained by a dilution effect of methacholine by lung size. Adjusting for FVC, another surrogate measurement for lung size (18), did not modify the results. The difference in BHR between women and men might also be explained by women's having smaller airways relative to lung size than men (concept of dysanapsis proposed by Mead [19]). This possible bias seems unlikely since FEV_1 /

FVC was the same in women and men in both towns and, in stepwise regressions including variables linked to airway caliber and to lung size, BHR was more frequent in women than in men. Finally, plotting the cumulative percentage of reactive subjects against the cumulative methacholine dose administered showed that the percentage of reactors was the same for 4 mg methacholine in men and < 1.5 mg in women (0.5 mg in Paris). So large a difference is unlikely to be due only to a difference in parameters such as lung size or airway caliber. The higher prevalence of BHR in women could not either be explained by a higher prevalence of asthma-like symptoms, asthma, atopy, or nasal allergy. BHR seems therefore to be actually more frequent in women than in men.

Women have also been demonstrated to be more sensitive than men to inhaled capsaicin. Airway sensitivity to that cough stimulant was assessed in a recently published experimental study of young and middle-aged subjects (20). The cough threshold was 3- to 5-fold lower in women than in men in both age groups. Pulmonary function, age, height, and weight were not significant predicting factors for the cough sensitivity. The investigators concluded that the airway cough reflex in response to inhaled capsaicin, probably mediated directly or indirectly by C-fiber endings, was more sensitive in females than in males. C-fibers play a role in inflammatory processes of the airways and are involved in the mechanisms of cough, mucus hypersecretion, and bronchoconstriction (21). Fujimara and associates suggested that the sex difference in cough sensitivity may have resulted from female hormones (20). However, they found that the menstrual cycle did not influence the capsaicin cough threshold in young women.

The question of whether hormone levels affect asthma manifestations and bronchial airway reactivity has been addressed in various studies. Several investigators have shown significant associations between hormone levels and asthma onset (22), asthma symptoms (23, 24), or airway reactivity to adenosine 5'-monophosphate in asthmatics (25). In contrast, no association has been found between BHR to histamine or methacholine and physiologic changes in hormone levels during the menstrual cycle, in either asthmatic or healthy women (23, 24, 26). Therefore, to date, there does not seem to be any evidence that female sex hormones could explain the higher prevalence of BHR in women in our population sample.

Since it has been suggested that BHR has an inheritable component (27), another hypothesis is that the greater sensitivity of women might be due to a complex system involving a gene located on chromosome X.

Various factors are potentially associated with BHR in nonasthmatics. These include smoking habits, which have been investigated by several researchers. Most studies report an association between smoking and BHR, especially for heavy cigarette consumption (6, 8, 17). The association between cigarette smoking and increased responsiveness was sometimes only observed in restricted subgroups of subjects: O'Connor and coworkers found steeper dose-response slopes for subjects with at least one positive skin-test reaction (28); Burney and colleagues found that smoking was the most important determinant of BHR in older subjects but not in young, suggesting that the effect of smoking on BHR may only be detectable in subjects with high sensitivity (1). In some studies, smoking was reported to be associated to BHR in women but not in men (9, 14). In our study, reacting at doses between 0.5 and 4 mg methacholine was associated with heavy cigarette consumption in women but not in men. The associations were significant for the comparison to moderate smokers and not to nonsmokers, probably because of a "healthy smoker effect" (17). The higher prevalence of BHR in women might be re-

lated to smoking, and our results are consistent with the view that women are more susceptible than men to the effect of tobacco smoke. In two previous studies, we found that the prevalence of respiratory symptoms increased more sharply with the number of cigarettes smoked in female than in male subjects and that there was a dose-response relationship between smoking and lower levels of height-adjusted FEV₁, both in adults (29) and in teenagers (30). In a cross-sectional study in Canada, women had greater lung function deficits than men per pack-year of cigarettes smoked (31). A more recent longitudinal study of 10- to 18-yr-old adolescents suggested that girls may be more vulnerable than boys to the effects of smoking on the development of lung function (32). Women are also more susceptible than men to other environmental factors. Jarvis and associates reported that the use of gas for cooking is associated with an increased risk of respiratory symptoms and impaired lung function in young women but not in men in three English centers participating in the ECRHS (33). In another analysis of the ECRHS data from Paris and Montpellier, we also found that there was no significant relationship between gas cooking and respiratory symptoms in men, whereas in women gas cooking was associated with asthma-like symptoms, usual morning phlegm and usual morning cough (34). Increased vulnerability of women to the effects of ozone has also been suggested (35).

We conclude that women are actually more hyperresponsive than men and that the excess of BHR in women may partly be related to a greater susceptibility to tobacco smoking. BHR should not be neglected since it has been shown to be an independent risk factor for an accelerated decline in FEV₁ and, hence, for the development of COPD (1, 2).

The mechanisms involved in the higher airway responsiveness observed in women should be investigated and follow-up studies implemented to determine the predictive value of BHR not related to asthma.

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