Prospective Study of Postmenopausal Hormone Use and Newly Diagnosed Asthma and Chronic Obstructive Pulmonary Disease

R. Graham Barr, MD, DrPH; Catherine C. Wentowski, MPH; Francine Grodstein, ScD; Samuel C. Somers, MD; Meir J. Stampfer, MD, DrPH; Joel Schwartz, PhD; Frank E. Speizer, MD; Carlos A. Camargo, Jr, MD, DrPH

Background: Female reproductive hormones appear to influence asthma, although data are conflicting, and may modulate development of chronic obstructive pulmonary disease (COPD). Therefore, in a prospective cohort study, we evaluated whether postmenopausal hormone use was associated with an increased rate of newly diagnosed asthma and, separately, newly diagnosed COPD.

Methods: Postmenopausal hormone use was assessed by questionnaire biennially from 1976 onward. New physician diagnoses of asthma or COPD were reported on questionnaires from 1988 to 1996 and confirmed in 1998 using supplementary questionnaires. Grades of diagnostic certainty were established from reports of medication use and pulmonary function using validated definitions.

Results: During 546,259 person-years of follow-up, current use of estrogen alone was associated with an increased rate of asthma (multivariate rate ratio, 2.29; 95% confidence interval [CI], 1.59-3.29) compared with those who never used hormones. Current users of estrogen plus progestin had a similarly increased rate of newly diagnosed asthma. Rate ratios increased with certainty of diagnosis of asthma. In contrast, rates of newly diagnosed COPD were the same among hormone users and nonusers (multivariate rate ratio, 1.05; 95% CI, 0.80-1.37).

Conclusions: Postmenopausal hormone use was associated with an increased rate of newly diagnosed asthma but not newly diagnosed COPD. Female reproductive hormones may contribute to the onset of asthma among adult women, but do not appear to hasten the development of COPD.

Arch Intern Med. 2004;164:379-386

©2004 American Medical Association. All rights reserved.
However, that analysis included insufficient cases to differentiate current from past hormone use and did not examine COPD. We therefore undertook this prospective study to examine postmenopausal hormone use and new physician diagnoses of asthma (with 6 additional years of follow-up) and COPD. We hypothesized that hormone use would predict higher rates of newly diagnosed asthma and COPD.

**METHODS**

In 1976, the Nurses’ Health Study enrolled 121,700 married, female registered nurses, aged 30 to 55 years, who resided in 1 of 11 US states and who completed a mailed questionnaire on hormone use and medical history. We updated the information with biennial follow-up questionnaires and inquired about a physician diagnosis of asthma and, separately, COPD from 1988 onward. Follow-up of the original cohort in 1998 was greater than 90%.

**ASCERTAINMENT OF HORMONE USE**

In 1976 and thereafter, all participants were asked whether they used hormones after menopause and, if so, the duration of use. We collected information on the type of hormone therapy beginning in 1978 and the dose of oral conjugated estrogen from 1980 onward.

**DEFINITIONS OF ASThma AND COPD**

From 1988 through 1996, 10,496 women reported a physician diagnosis of asthma, and 8,105 women reported a physician diagnosis of COPD, with an overlap of 3,066 cases (ie, a total of 15,535 reports, 48% reported asthma only, 32% reported COPD only, and 20% reported both). These initial reports were verified by supplemental questionnaires or by review of death records (death certificates, hospital admission summaries, and autopsies). We sent supplemental questionnaires in 1998 detailing respiratory symptoms, medication use, and diagnostic tests to 9,836 women who reported asthma and 7,226 who reported COPD, excluding those who died (n = 863) or were lost to follow-up (n = 400). A further 378 died during follow-up. For asthma, 8,192 (85%) responded; for COPD, 5,561 (79%) responded. We reviewed all deaths in the Nurses’ Health Study for which death records were available (10,054 [98%] of 10,248 deaths) for a diagnosis of COPD and found an additional 359 cases among participants who had previously reported a physician diagnosis of COPD. Overall ascertainment was complete for 78% of 10,496 original reports of asthma and 82% of 8,105 original reports of COPD.

Since we were unable to obtain spirometry or clinical measures for this large number of geographically dispersed participants, we used questionnaire-based case definitions of possible, probable, and definite disease with increasing certainty of case definition. Possible asthma required reports of physician diagnosis of asthma on the original (1988-1996) and supplementary (1998) questionnaires and use of an asthma medication ever. Probable asthma required reports of physician diagnosis on both questionnaires, plus use of an asthma medication in the previous year. Definite asthma required reports of physician diagnosis on both questionnaires, plus use of an asthma controller medication (inhaled or systemic corticosteroid, theophylline, leukotriene modifier, or Cromolyn sodium) in the previous year. Cases reporting a comorbid pulmonary disease (eg, sarcoidosis) were excluded.

For COPD, the possible case definition required a report on the original (1988-1996) and supplementary COPD questionnaires (1998) of physician-diagnosed COPD, emphysema, or chronic bronchitis. If a participant reported chronic bronchitis only (ie, no emphysema or COPD), we also required symptoms diagnostic of chronic bronchitis (≥3 months of productive cough in ≥2 consecutive years). Probable COPD required the preceding criteria, plus a report of spirometry or radiography or computed tomography of the chest at the time of diagnosis or documentation of COPD on death records. Participants who met the possible case criteria and reported abnormal results of pulmonary function testing (FEV<sub>1</sub> < 80% predicted) in the year before the supplemental questionnaire were classified as definite cases. Cases who reported normal FEV<sub>1</sub> results, age at diagnosis of younger than 35 years, or comorbid pulmonary disease were excluded.

We validated these disease definitions against medical records in random subsamples. Of 100 randomly selected women with self-reported incident definite asthma in a related study, we confirmed that all carried a physician diagnosis of asthma; 91% had strong, consistent evidence of asthma; 4% had transient asthma; and 5% had some evidence of a questionable diagnosis. In a random sample of 273 patients who reported COPD, the primary end point of incident probable COPD was confirmed by medical record review for 84% of cases. Incident possible COPD was confirmed for 83% of cases, and definite COPD was confirmed for 90% of cases.

**STUDY SAMPLE**

Follow-up for this analysis began in July 1986, because data on a physician diagnosis of asthma and COPD were not available for 2-year intervals before the 1986 questionnaire cycle, and continued through June 1996. Participants who were postmenopausal on or before July 1986 were included in the analysis as of that date; participants who later reached menopause were included beginning at the time of menopause.

Participants were classified as postmenopausal at the time of a report of natural menopause or hysterectomy with bilateral oophorectomy. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for smokers and 56 years for nonsmokers). Age at menopause and type of menopause were reported accurately in this cohort.

To examine only new diagnoses of asthma and COPD in incident analyses, women who reported asthma or COPD first diagnosed before 1986 were excluded. Women with a history of cardiovascular disease (myocardial infarction, angina, or coronary revascularization) or cancer (except nonmelanoma skin cancer) before 1986 were excluded, because these conditions may have altered patterns of hormone use. Women who, on later questionnaires, reported asthma, COPD, cardiovascular disease, or cancer were excluded from subsequent follow-up in incident analyses. In 1986, 51,947 postmenopausal women were included; another 19,018 women were added during follow-up as they became postmenopausal.

**STATISTICAL ANALYSIS**

For each participant, person-months were allocated to categories of hormone use, updated every 2 years. Follow-up ended when asthma or COPD was first diagnosed, when an exclusion diagnosis was reported, when the participant died, or when the last questionnaire was returned.

Incidence rates were calculated as the number of cases divided by the person-time in each category of exposure, and rate ratios (RRs) were defined as the incidence rate of asthma or COPD among the exposed divided by the corresponding incidence rate among the unexposed. Age-adjusted rates were es-
timated with 5-year categories, and corresponding Mantel-Haenszel RRs\textsuperscript{23} and 95% confidence intervals (CIs) were calculated.\textsuperscript{24} Rate differences and 95% CIs were also estimated.

Cox proportional hazards models were used to estimate the RRs for asthma and, separately, COPD after adjustment for other covariates.\textsuperscript{25} Smoking status, pack-years, and body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) were treated as time-varying covariates, updated in 2-year periods. Intake of n-3 omega fatty acids and calories were ascertainment at 4-year intervals by means of validated, food-frequency questionnaire items\textsuperscript{26,27} and were also treated as time varying. Pack-years, BMI, and n-3 omega fatty acid and caloric intake were modeled flexibly with polynomial splines. The analysis was stratified jointly by age in months at the start of follow-up and calendar year of the current questionnaire cycle. Departures from the proportional hazards assumption (ie, effect modification by age and/or calendar time) were tested by means of likelihood ratio tests comparing models with and without the age or calendar time by covariate interaction terms. Effect modification of RRs was tested with multiplicative interaction terms in regression models. All P values were 2-tailed, with P < .05 considered statistically significant. Analyses were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

During 546 259 person-years of follow-up from 1986 to 1996, there were 609 new physician diagnoses of possible asthma, 461 of probable asthma, and 342 of definite asthma among postmenopausal women in the Nurses’ Health Study. During the same period, there were 513 possible, 414 probable, and 47 definite new physician diagnoses of COPD. The overall rate of new possible asthma in this cohort during follow-up was 112/100 000 person-years, and the rate of new possible COPD was 94/100 000 person-years. Because of the small number of cases of definite COPD, this group was combined with probable COPD as the primary outcome for COPD analyses (n = 421). Pulmonary function testing at diagnosis or in the previous year was reported by 60% with probable/definite COPD, and chest radiography or computed tomography was reported by 68%.

Those who never used hormones accounted for 33% of follow-up time, past users for 18%, and current users for 30%. Of current users, 44% of participants used estrogen alone and 31% used estrogen plus progestin. For the remaining person-time, information on hormone use was missing. Current hormone use smokers less than those who had ever used hormones and generally had healthier habits (Table 1). Current users had a lower BMI than those who never used hormones and were of somewhat higher socioeconomic status, as measured by the spouse’s educational attainment.

NEW PHYSICIAN DIAGNOSES OF ASTHMA

The age-adjusted RR for newly diagnosed definite asthma among current users of estrogen alone compared with the reference group of women who had never used hormones was 2.30 (95% CI, 1.69-3.14) (Table 2). The rate difference was 61/100 000 person-years (95% CI, 32/100 000-90/100 000 person-years) for definite asthma. Multivariate adjustment for age, time period of diagnosis, race/ethnicity, socioeconomic status, region, smoking, secondhand smoke exposure, BMI, birth weight, type of menopause, and past oral contraceptive use did not materially alter associations and yielded an RR of 2.29 (95% CI, 1.59-3.29). There was no effect modification of the estrogen effect by progestin (P = .54 for interaction), and women who used estrogen with progestin had a similarly increased rate of a new diagnosis of definite asthma (Table 2). New diagnoses of probable and possible asthma were also associated with hormone use, although the RRs were smaller, consistent with the likely greater misclassification of these end points. Inclusion of participants with cancer and cardiovascular disease yielded similar RRs for estrogen (2.13; 95% CI, 1.53-2.97) and estrogen plus progestin (2.04; 95% CI, 1.45-2.88).

In subsequent analyses of asthma rates, users of estrogen and estrogen plus progestin were combined as current hormone users. Among this group, the RR for newly diagnosed definite asthma did not vary appreciably with duration of current hormone use (P = .40; Figure 1A). After cessation of hormone use, the rate of newly diagnosed definite asthma among women who had used hormones in the past diminished over time (P < .001) to become similar to the rate among women who had never used hormones (Figure 2A).

We stratified the association of hormone use and asthma by BMI because obese postmenopausal women have higher levels of endogenous estrogen than nonobese women. Among obese women (BMI, > 30), the RR for newly diagnosed definite asthma among current hormone users was 1.38 (95% CI, 0.92-2.74), whereas among women with BMI of no greater than 25, the RR was 3.09 (95% CI, 1.83-5.21).

Since hormone users must see a physician for prescriptions, they may be more likely to be diagnosed with asthma and COPD than nonusers. We therefore repeated the analysis excluding women who had not visited physicians (data available from 1988, 1990, and 1992). Rate ratios were marginally reduced by this exclusion (eg, RR for definite asthma for current estrogen use, 2.03 [95% CI, 1.39-2.96]), and estimates for past hormone use lost statistical significance (eg, RR for definite asthma, 1.32 [95% CI, 0.92-1.90]).

In the overall cohort, misclassification of asthma, operationally defined as the number of definite cases divided by the number of possible cases, did not differ between hormone users and nonusers (57% and 54%, respectively; P = .69). Additional analyses restricted to women with natural menopause, nonsmokers, and those with asthma diagnoses after 1992 did not change results appreciably (data not shown).

NEW PHYSICIAN DIAGNOSES OF COPD

In contrast to findings for asthma, we found an inverse association of hormone use and newly diagnosed COPD in age-adjusted analyses, which became null after adjustment for covariates. The age-adjusted RR for the probable/definite COPD among current users of oral conju-
gated estrogen alone was 0.64 (95% CI, 0.46-0.90) compared with the reference group of women who had never used hormones (Table 3). The rate difference was −35/100000 person-years (95% CI, −58/100000 to −12/100000 person-years) for probable/definite COPD. Multivariate adjustment for smoking and other confounders, however, rendered this inverse association null (RR, 0.88; 95% CI, 0.60-1.27). Age-adjusted and multivariate rates of newly diagnosed COPD among users of estrogen plus progestin did not differ significantly from the null, and there was no significant effect modification of the estrogen effect by progestin (P = .12 for interaction). Overall, the RR for newly diagnosed probable/definite COPD among all current hormone users (estrogen and estrogen plus progestin) was 0.71 (95% CI, 0.56-0.91) in age-adjusted analyses and 1.05 (95% CI, 0.80-1.37) after controlling for smoking and other confounders. Findings for definite COPD were similar (age-adjusted RR, 0.42 [95% CI, 0.19-0.89] and multivariate RR, 0.53 [95% CI, 0.23-1.24]) as were findings for possible COPD (Table 3). Inclusion of participants with cancer and cardiovascular disease yielded similar RRs for probable/definite COPD for use of estrogen (0.86; 95% CI, 0.62-1.19) and estrogen plus progestin (1.22; 95% CI, 0.87-1.70).

The adjusted rates of newly diagnosed COPD did not deviate from the null, even among long-term users of hormones (Figure 1B), and was consistent after cessation of hormones (Figure 2B). Misclassification of
COPD, operationally defined as the number of probable/definite cases divided by the number of possible cases, did not differ between hormone users and nonusers (86% and 81%, respectively; \( P = .45 \)). The proportion of cases confirmed on medical record review (ie, 1−false-positive proportion) did not differ between users and non-users (86% and 90%, respectively, for probable/definite COPD \( P = .30 \) and 84% and 85%, respectively, for possible COPD \( P = .69 \)). Analyses restricted to women with natural menopause, who reported physician visits and COPD diagnosed after 1992, and analyses excluding

<table>
<thead>
<tr>
<th>Asthma Category*</th>
<th>Never Used</th>
<th>Used in Past</th>
<th>Current User</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Estrogen Alone</td>
</tr>
<tr>
<td>Definite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (n = 279)</td>
<td>86</td>
<td>59</td>
<td>80</td>
</tr>
<tr>
<td>Person-years</td>
<td>177,658</td>
<td>95,711</td>
<td>73,104</td>
</tr>
<tr>
<td>Age-adjusted rate ratio (95% CI)</td>
<td>1.00</td>
<td>1.44 (1.02-2.02)</td>
<td>2.30 (1.69-3.14)</td>
</tr>
<tr>
<td>Multivariate rate ratio† (95% CI)</td>
<td>1.00</td>
<td>1.48 (1.04-2.08)</td>
<td>2.29 (1.59-3.29)</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (n = 375)</td>
<td>116</td>
<td>82</td>
<td>103</td>
</tr>
<tr>
<td>Age-adjusted rate ratio (95% CI)</td>
<td>1.00</td>
<td>1.49 (1.12-1.99)</td>
<td>2.20 (1.68-2.87)</td>
</tr>
<tr>
<td>Multivariate rate ratio† (95% CI)</td>
<td>1.00</td>
<td>1.46 (1.09-1.96)</td>
<td>2.00 (1.47-2.75)</td>
</tr>
<tr>
<td>Possible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases (n = 494)</td>
<td>158</td>
<td>112</td>
<td>131</td>
</tr>
<tr>
<td>Age-adjusted rate ratio (95% CI)</td>
<td>1.00</td>
<td>1.46 (1.14-1.87)</td>
<td>2.03 (1.61-2.57)</td>
</tr>
<tr>
<td>Multivariate rate ratio† (95% CI)</td>
<td>1.00</td>
<td>1.43 (1.11-1.84)</td>
<td>1.82 (1.39-2.40)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NHS, Nurses’ Health Study.

*Categories of asthma are described in the “Definitions of Asthma and COPD” subsection of the “Methods” section.

†Multivariate rate ratios (1.00 indicates reference) were adjusted for age, period of diagnosis, race/ethnicity, husband’s educational attainment, region, smoking status, secondhand smoke exposure, birth weight, body mass index, type of menopause, and past oral contraceptive use.

Figure 1. Adjusted rate ratios for new physician diagnoses of asthma (A) and chronic obstructive pulmonary disease (COPD) (B) among current hormone users, according to duration of use. The solid line represents the rate ratio; dashed lines, 95% confidence intervals. The reference group consists of those who never used postmenopausal hormones.

Figure 2. Adjusted rate ratios for new physician diagnoses of asthma (A) and chronic obstructive pulmonary disease (COPD) (B) among past hormone users, according to the interval between last postmenopausal hormone use and time of diagnosis of asthma or COPD. The solid line represents the rate ratio; dashed lines, 95% confidence intervals. The reference group consists of those who never used postmenopausal hormones.
COMMENT

During 546,259 person-years of follow-up of postmenopausal women in the Nurses’ Health Study, we found postmenopausal hormone use to be associated with an increased rate of new physician diagnosis of asthma. In contrast, postmenopausal hormone use was not associated with an increased rate of newly diagnosed COPD.

A putative mechanism of hormonal effects in asthma may be inferred from results of tests of bronchoreactivity. Bronchoconstriction induced by inhalation of direct bronchoconstrictors (eg, methacholine chloride and histamine phosphate) does not vary during the menstrual cycle. It does, but bronchoconstriction from inhalation of indirect bronchoconstrictors (eg, adenosine phosphate) does. This suggests bronchoconstriction by causing mediator release from mast cells, indicating that female reproductive hormones may sensitize mast cells. Animal studies show that mast cells contain plentiful estrogen receptors, and estrogen up-regulates mast cell cell proliferation and activity at physiological doses. Such effects are more important in asthma than COPD, consistent with our findings.

Estrogen also has multiple systemic proinflammatory and anti-inflammatory effects that may be important to bronchospasm and lung function. Randomized clinical trials, in agreement with observational data, have shown that estrogen alone and estrogen plus progesterin increase C-reactive protein levels by approximately 85%. Because inflammatory responses differ between asthma and COPD, modulation of these responses by postmenopausal hormone therapy may also differ between asthma and COPD.

Other pulmonary effects of estrogen may relate to its role in the stimulation of endothelial nitric oxide synthase. Nitric oxide has been implicated in the pathogenesis of asthma, and levels vary with the menstrual cycle. Estrogen also causes edema throughout the body. Airway edema has been hypothesized to cause airflow limitation by limiting the ability of lung inflation to stretch the airway and may predispose airways to hyperresponsiveness.

A recent meta-regression of population-based studies funded by the National Heart, Lung, and Blood Institute that totaled more than 40,000 participants showed no sex differences in decline in FEV1. Most longitudinal studies suggest that lung function decline is similar among men and women after adjustment for smoking, occupational and environmental exposures, and differential “healthy smoker” effects. A cross-sectional study recently reported that FEV1 was higher among hormone users than nonusers. That association, however, may reflect reverse causality (women with higher FEV1 were more likely to use hormones) and incomplete adjustment for smoking history, which was assessed only once in that study.

Inferences about the effect of hormone use on asthma would ideally be drawn from randomized trials. However, to date, clinical studies of postmenopausal hormone use in women with asthma have been small, unblinded, and nonrandomized. Our findings are consistent with observations of a mild worsening of peak expiratory flow rate and FEV1 among postmenopausal asthmatic women taking estrogen and clinical reports of severe bronchospasm after challenge and rechallenge with estrogen. A more recent report, however, found no difference in peak flow and FEV1 with hormone use. A potentially important difference between these 2 studies was the positive study’s exclusion of previous hormone users and the negative study’s requirement of greater than 6 months of prior hormone use.

Although prospective, our study was observational; unmeasured confounding may therefore have biased our results. The elevated rate of asthma associated with hormone use returned to the null within approximately 4 years of discontinuation of hormone therapy, suggesting that, with respect to asthma rates and after multivariable adjustment, women who had ever used hormones may not have differed systematically from women who used them recently.
who had never used hormones. Additional analyses showed that the rate of newly diagnosed definite asthma in the years leading up to menopause was approximately 23% higher among participants who subsequently took hormones than among women who did not subsequently take hormones. This difference was much smaller than the 129% increase observed with current estrogen use.

Unmeasured confounding often biases effect estimates by modest amounts. To produce the large effect observed for asthma, a potential unmeasured confounder would have to strongly affect asthma, be common in the study population, and be strongly associated with hormone use. For example, smoking is an extremely strong cause of COPD and common in the study population, yet adjustment of RRs for postmenopausal hormones and COPD changed effect estimates by a magnitude that was considerably smaller than the observed effect estimate for asthma.

Consistent with this expectation, the Women’s Health Initiative and other randomized trials of postmenopausal hormones have confirmed earlier reports from the Nurses’ Health Study of increased risk for stroke, breast cancer, pulmonary embolism, and cholecystectomy and decreased risk for hip fracture and colon cancer. Results for secondary prevention of coronary disease in this cohort are concordant with those of the Heart and Estrogen/Progestin Replacement Study randomized trial. The discordant results from the Women’s Health Initiative and the Nurses’ Health Study for primary prevention of coronary disease may be due to unmeasured confounders that were selective to coronary disease, measurement error, or other differences such as the timing of initiation of hormone therapy relative to menopause. Approximately 80% of hormone users in the Nurses’ Health Study initiated postmenopausal hormone therapy at menopause, whereas the mean age at initiation of hormone therapy in the Women’s Health Initiative was 63 years, a difference that may have important mechanistic implications.

Information biases might also lead to nonetiologic differences in rates of asthma and COPD between hormone users and nonusers. When we restricted analyses to women who had visited their physicians during the study period (a surrogate marker for medicalization) and to nonsmokers to help address diagnostic biases, the results changed little. Misclassification of asthma and COPD, operationally defined herein, was similar between hormone users and nonusers. In addition, a previous population-based cross-sectional study showed that hormone use was associated with self-reported asthma and also with symptoms of wheeze and exertional cough that should be less subject to diagnostic bias.

Obstructive airways disease is underdiagnosed in the general population, therefore, even with perfect reporting by participants, false-negative cases occurred. The inevitable presence of such false-negative cases, however, should not have severely biased our estimations of RR, given person-time sampling and nondifferential disease misclassification between hormone users and nonusers (false-negative cases do bias the rate difference, and the reported rate differences should be interpreted with caution). The false-positive proportions of asthma and COPD cases were not related to hormone use.

Our results suggest a hormonal effect on the onset of asthma among adult women. The clinical implications are mitigated by recent changes in postmenopausal hormone use and by the fact that incident asthma is rare after menopause. Female reproductive hormones may contribute to the onset of asthma among adult women, but hormones do not appear to hasten the development of COPD.

Accepted for publication March 25, 2003.

This study was supported by grants HL-07427, PE-11001, HL-63841, CA-87969, and AI52338 from the National Institutes of Health, Bethesda, Md, and a Robert Wood Johnson Generalist Physician Faculty Scholar Award, Princeton, NJ (Dr Barr).

We thank Karen Corsano and Gary Chase for invaluable assistance with the implementation of the study.

Corresponding author: R. Graham Barr, MD, DrPH, Division of General Medicine, PH-9E 105, Columbia Presbyterian Medical Center, 622 W 168th St, New York, NY 10032 (e-mail: rgb9@columbia.edu).

REFERENCES


12. Silverman EK, Weiss ST, Drazen JM, et al. Gender-related differences in severe,
35. Wilhelm M, King B, Silverman AJ, Silver R. Gonadal steroids regulate the num-

37. Cushman M, Legault C, Barrett-Connor E, et al. Effect of postmenopausal hor-


41. Kirsch EA, Yuhanna IS, Chen Z, German Z, Sherman TS, Shaul PW. Estrogen

21. Willett WC, Stampfer MJ, Bain C. Cigarette smoking, relative weight, and meno-

20. Barr RG, Herbstman J, Speizer FE. Validation of self-reported smoking status in a

10. Weiss ST, Zhang S, Willett WC, Speizer FE, Camargo CA Jr. Prospective study of

19. Camargo CA Jr, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of


15. Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Longitudinal methods for de-

13. Xu X, Weiss ST, Rickert RN, Chu KH, Grodstein F. Influence of the menstrual

8. Alving KE, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in ex-

7. Xie W, Weiss ST, Brunnemann KD, Gersh BJ, Grodstein F. Changes in smoking habits,

4. Zilberberg MI, Guralnik JM, Branch Rickey Foundation, Inc. Prospective study of

3. Zilberberg MI, Guralnik JM, Branch Rickey Foundation, Inc. Prospective study of

2. Zilberberg MI, Guralnik JM, Branch Rickey Foundation, Inc. Prospective study of

1. Zilberberg MI, Guralnik JM, Branch Rickey Foundation, Inc. Prospective study of

0. Zilberberg MI, Guralnik JM, Branch Rickey Foundation, Inc. Prospective study of

©2004 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/pdfaccess.ashx?url=/data/journals/intemed/5475/ on 04/10/2017