

Postmenopausal Hormone Use and Symptoms of Gastroesophageal Reflux

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Background: Previous studies suggest that elevated levels of estrogen and progesterone, either through endogenous or exogenous sources, increase gastroesophageal reflux.

Methods: To evaluate the relationship between symptoms of gastroesophageal reflux disease (GERD) and postmenopausal hormone (PMH) therapy, including the use of selective estrogen receptor modulators and over-the-counter (OTC) hormone preparations, we performed a prospective cohort study of 51 637 postmenopausal women enrolled in the Nurses' Health Study who provided data on the use of PMH therapy biennially since 1976, and information about symptoms of GERD in 2002.

Results: Among eligible participants, 12 018 women (23%) reported GERD symptoms. Compared with women who never used PMHs, the multivariate odds ratio (OR) for the risk of GERD symptoms was 1.46 (95% confidence interval [CI], 1.36-1.56) for past hormone users,

1.66 (95% CI, 1.54-1.79) for current users of estrogen only, and 1.41 (95% CI, 1.29-1.54) for current users of combined estrogen and progesterone. The risk of GERD symptoms increased significantly with increasing estrogen dosage ($P < .001$) and increasing duration of estrogen use ($P < .001$). Moreover, current selective estrogen receptor modulator users experienced an OR of 1.39 (95% CI, 1.22-1.59) for GERD symptoms, and women currently using OTC hormone preparations had an OR of 1.37 (95% CI, 1.16-1.62).

Conclusions: Postmenopausal use of estrogens, selective estrogen receptor modulators, or OTC hormone preparations is associated with a greater likelihood of symptoms of GERD. This suggests a hormonal component to the pathophysiologic characteristics of GERD in women.

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GASTROESOPHAGEAL REFLUX disease (GERD) affects up to 60% of persons during the course of a year and 20% to 30% of persons at least weekly.^{1,2} The condition is marked by heartburn and acid regurgitation³ and accounts for substantial utilization of health care resources.⁴ Previous studies suggest that elevated levels of estrogen and progesterone increase gastroesophageal reflux.⁵⁻¹¹ Support for this theory includes observations that lower esophageal sphincter (LES) pressures decrease during pregnancy⁹ and with the use of sequential oral contraceptives.⁶ In addition, postmenopausal hormone (PMH) use may increase the risk of GERD symptoms among overweight and obese women.¹¹

We sought to further clarify the relationship between exogenous hormone use and symptoms of GERD. In particular, we were interested in determining the risk of GERD symptoms among postmenopausal women using PMHs, selective estrogen receptor modulators (SERMs), or over-the-counter (OTC) hormone prepa-

rations. To accomplish this, we utilized the resources of the Nurses' Health Study (NHS), a large prospective cohort in which detailed information on hormone use and other health-related factors have been collected over 26 years.

METHODS

NHS COHORT

The NHS cohort was established in 1976 when 121 700 female registered nurses, 30 to 55 years of age, completed a questionnaire about risk factors for cancer and cardiovascular disease. Participants have received follow-up questionnaires every 2 years to obtain information about personal habits (including detailed dietary information every 4 years), medical diagnoses, and medication use.

DEFINITION OF CASES AND NONCASES

In 2002, the NHS questionnaire asked the 106 310 surviving participants if they ever regularly experienced "heartburn/acid reflux" 1 or more times a week, how often in the past year they had experienced these symptoms, and for

how many years. Possible responses included none in the past year, less than once a month, about once a month, about once a week, several times a week, and daily.

We considered participants reporting heartburn or acid reflux at least once a week as having GERD symptoms and defined them as cases. Women without GERD symptoms in the past year served as controls. We excluded 15 705 women with a history of cancer, 3456 women who were premenopausal, 18 362 who were missing data about hormone therapy on the 2002 questionnaire, 6570 who failed to answer the question about GERD symptoms, and 2505 who failed to report their symptom frequency. To avoid misclassification bias, we also excluded 6947 women who reported GERD symptoms but with frequencies of less than once a week (3947 women experienced symptoms less than once a month, and 3000 experienced symptoms about once a month). Finally, we excluded 1128 women who reported no GERD symptoms in the previous year but also reported regular use of proton pump inhibitors (PPIs) or histamine type 2 receptor antagonists (H2RAs). This left 51 637 participants eligible for analysis.

ASCERTAINMENT OF EXPOSURES

We determined body mass index (BMI)—calculated as weight in kilograms divided by height in meters squared—from measurements of height provided by participants in 1976 and from measurements of weight in 1998. Smoking status, menopausal status, history of cancer, and history of diabetes mellitus were assessed in 1976 and updated every 2 years thereafter. Participants were first queried about PMH use in 1976, including duration of use. Information on the types of PMH used was collected beginning in 1978 and included the dosage of oral conjugated estrogen from 1980 onward. Duration of PMH use was the summation of PMH use across questionnaire cycles. From 1978 on, respondents were asked about the number of months they used hormones since the previous 2-year cycle. In 2002, participants were asked if they currently used the SERMs raloxifene hydrochloride or tamoxifen citrate. They were also asked about current use of “OTC (eg, herbal, natural, or soy-based) preparations for hormone replacement or to treat postmenopausal symptoms.” Response options included “soy estrogen products,” “natural progesterone cream or wild yam cream,” or “other.” When considering OTC preparations, participants were specifically asked not to include food sources like tofu and soy milk.

Other medication use, including PPIs, H2RAs, calcium channel blockers, bronchodilators, benzodiazepines, and antidepressants, was assessed in 2002. That year, women were also asked if they had had a physical examination or colonoscopy or sigmoidoscopy within the past 2 years. Dietary information, including intake of coffee, tea, alcohol, carbonated soft drinks, and chocolate, was obtained in 1998, whereas physical activity was assessed in 2000. Each activity reported was measured in metabolic equivalent task (MET) hours per week. One MET represents the energy expended during 1 hour of rest. Self-reported BMI, dietary information, and physical activity in this cohort have been validated previously.¹²⁻¹⁴

STATISTICAL ANALYSES

We used age-, age- and BMI-, and multivariate-adjusted unconditional logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of GERD symptoms among postmenopausal women using exogenous hormone therapies, including transdermal formulations of estrogen and progesterone. For these analyses, postmenopausal women who reported never using PMH therapy served as the reference population. We cal-

culated risks for symptoms based on increasing dosages and durations of ongoing estrogen therapy (dosages were not available for transdermal formulations). In these analyses, a test for trend was calculated using the median value in each category as an ordinal variable in the multivariate model.

In addition to analyses of estrogen- and progesterone-based hormone therapies, we also analyzed the risk for GERD symptoms among users of the SERMs tamoxifen and raloxifene, and OTC hormone preparations, including soy-based estrogens and natural progesterone creams. Because women with a history of breast cancer were excluded from this analysis, tamoxifen and raloxifene were presumably taken for breast cancer prevention or treatment of osteoporosis. For these analyses, postmenopausal women who reported never using PMH therapy, SERMs, or OTC hormone preparations served as the reference population. We conducted a secondary analysis defining a case as any woman reporting GERD symptoms several times a week or daily. To address the potential for reverse causality, we limited another analysis to women reporting GERD symptoms for 5 years or less, whereas we defined current PMH use as use for at least 6 years. To detect effect modification, other analyses were stratified by BMI, cigarette use, having had a physical examination within the past 2 years, and regular use within the past 2 years of medications that may decrease the pressure of the LES. Finally, we calculated the risk of GERD symptoms based on the duration of time since cessation of estrogen-only therapy, using current users as the reference population.

The attributable risks of GERD symptoms resulting from PMH use were calculated with multivariate relative risks (in this case, ORs) using the formula $(RR - 1)/RR$, where RR is the relative risk, and with women who never used PMH therapy as the referent. We calculated the attributable risks of ever using PMH therapy (ever use; combining past and current users) and current estrogen-only use. All subgroup comparisons were preplanned based on findings of previous investigators or by our own a priori assumptions. We conducted all analyses using SAS statistical software (version 9.0; SAS Inc, Cary, North Carolina); 2-sided *P* values < .05 were considered significant. The study was approved by the institutional review boards of Brigham and Women's Hospital and the Boston University Medical Center, Boston, Massachusetts.

RESULTS

Among 51 637 participants eligible for analysis, 12 018 women (23%) reported heartburn or acid reflux at least once a week and were defined as cases. Among eligible participants, 12 579 (24%) reported never using PMH, 20 170 (39%) were former PMH users, 11 149 (22%) were currently using estrogen-only therapy, and 7739 (15%) were currently using combined estrogen plus progesterone therapies. There were 2331 women (5%) who reported current use of a SERM and 1600 (3%) who reported current use of some form of OTC hormonal preparation.

PATIENT CHARACTERISTICS

Characteristics of participants according to PMH use are presented in **Table 1**. Compared with women who never used PMH, current users were slightly younger, leaner, and less likely to be active smokers, yet had gained more weight since menopause. Users of combination PMH were more physically active than other participants. Compared with women who never used PMH, those who ever used PMH

Table 1. Characteristics of 51 637 Postmenopausal Women in the Nurses' Health Study in 2002, According to Use of PMHs^a

Characteristic	PMH Use			
	Never Users (n=12 579)	Past Users (n=20 170)	Current Use of Estrogen (n=11 149)	Current Estrogen + Progesterone (n=7739)
Age, y	68 (7)	68 (7)	67 (7)	64 (6)
BMI	27 (6)	27 (5)	26 (5)	26 (5)
Weight gain since menopause, kg	3.6 (9.1)	5.0 (9.1)	6.4 (9.1)	3.6 (7.3)
Total activity, METs/wk	18 (22)	17 (21)	18 (22)	20 (25)
Cigarette use, %				
Never	45	44	48	44
Past	44	47	45	48
Current	11	9	6	8
Total caloric intake, kcal/d	1728 (546)	1716 (529)	1749 (526)	1755 (510)
Alcohol, drinks/d	0.4 (0.7)	0.4 (0.7)	0.4 (0.7)	0.5 (0.8)
Coffee, cups/d	1.8 (1.6)	1.6 (1.5)	1.6 (1.5)	1.8 (1.6)
Tea, cups/d	0.7 (1.1)	0.6 (1.1)	0.7 (1.1)	0.7 (1.1)
Carbonated soft drinks, cups/d	0.5 (0.8)	0.4 (0.8)	0.5 (0.8)	0.5 (0.9)
Chocolate, servings/d	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)
Patients who reported, %				
Use of medications that may decrease LES pressure ^b	15	21	23	19
Regular use of a PPI or H2RA	5	9	12	8
A physical examination within 2 y	87	93	95	95
Diabetes mellitus	10	8	7	6

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); H2RA, histamine type 2 receptor antagonists; LES, lower esophageal sphincter; METs, metabolic equivalent tasks; PMH, postmenopausal hormone; PPI, proton pump inhibitor.

^aData are given as mean (SD) unless otherwise indicated.

^bMedications that may decrease LES pressure included calcium channel blockers, bronchodilators, benzodiazepines, and antidepressants.

Table 2. Multivariate ORs for GERD Symptoms According to PMH Use

Participants	Cases, No.	Controls, No.	Rate, %	OR (95% CI)		
				Age-Adjusted	Age- and BMI-Adjusted	Multivariate ^a
Never users	2250	10 329	18	1 [Reference]	1 [Reference]	1 [Reference]
Past users	4968	15 202	25	1.50 (1.42-1.59)	1.57 (1.48-1.66)	1.46 (1.36-1.56)
Current estrogen use	3071	8078	28	1.73 (1.63-1.84)	1.87 (1.75-1.99)	1.66 (1.54-1.79)
Current estrogen + progesterone use	1729	6010	22	1.30 (1.21-1.40)	1.48 (1.37-1.59)	1.41 (1.29-1.54)

Abbreviations: BMI, body mass index; CI, confidence interval; GERD, gastroesophageal reflux disease; ORs, odds ratios; PMH, postmenopausal hormone.

^aAdjusted for age; BMI; change in weight since menopause; activity (metabolic equivalent tasks per week); smoking status (never, former, current); total caloric intake; intake of alcohol, coffee, tea, carbonated soft drinks, and chocolate; use of medications that may decrease the pressure of the lower esophageal sphincter (calcium channel blockers, bronchodilators, benzodiazepines, and antidepressants); having had a physical examination within 2 y; and history of diabetes mellitus. We defined GERD symptoms as regularly having heartburn or acid regurgitation at least once a week during the past year.

were more likely to be regular users of medications that may decrease the pressures of the LES, PPIs, or H2RAs and to have had a physical examination within the previous 2 years, but were less likely to have diabetes mellitus.

PMH USE AND RISK OF GERD SYMPTOMS

We examined the risk of GERD symptoms according to PMH use. Compared with women who never used PMH, the multivariate OR for the risk of GERD symptoms was 1.46 (95% CI, 1.36-1.56) for past PMH users, 1.66 (95% CI, 1.54-1.79) for current users of estrogens only, and 1.41 (95% CI, 1.29-1.54) for current users of combined estrogen and progesterone PMH (**Table 2**). Our findings were similar among age-adjusted, age- and BMI-adjusted, and multivariate models, suggesting minimal confounding by the other covariates tested.

Our findings were also similar using a case definition restricted to very frequent GERD symptoms occurring several times a week or daily (n=6936). Compared with women who never used PMH, the multivariate OR for very frequent symptoms was 1.57 (95% CI, 1.44-1.72) for past users, 1.74 (95% CI, 1.58-1.91) for current users of estrogen only, and 1.48 (95% CI, 1.33-1.66) for current users of combination therapy. Finally, to address the potential for reverse causality, we repeated our analysis defining cases as women reporting GERD symptoms of 5 or fewer years' duration, while defining current PMH use as use for at least 6 years (n=6222 cases). The multivariate OR for GERD symptoms was then 1.44 (95% CI, 1.31-1.58) for current users of estrogen only and 1.38 (95% CI, 1.23-1.55) for current users of combination therapy.

The risk of GERD symptoms associated with PMH use was significantly greater with increasing dosages of current

estrogen use and increasing durations of estrogen use (*P* value for trends, <.001; **Table 3**). Thirty-four percent of the increased risk of GERD symptoms among the entire cohort was accounted for by ever use of PMH therapy. For those women currently taking estrogen-only therapy, 40% of the increased risk could be accounted for by their PMH use.

The risk of GERD symptoms seemed to decrease with increasing time since discontinuation of estrogen use, although this trend was not significant (*P* value for trend, .27). Compared with current estrogen users, the OR for GERD symptoms was 0.88 (95% CI, 0.78-1.00) within the first 1.9 years after cessation of therapy, 1.30 (95% CI, 0.93-1.81) for 2.0 to 9.9 years after cessation of therapy, 0.61 (95% CI, 0.36-1.04) by 10.0 years after cessation of therapy, and 0.67 (95% CI, 0.58-0.78) for women who had never used PMH therapy. Therefore, the risk of GERD symptoms among past users did not seem to approach the risk of never users until more than 10 years following PMH cessation.

The increased risk of GERD symptoms did not seem to differ across strata of BMI, smoking status, use of medications that may decrease LES pressure, or between participants who had undergone a physical examination in the previous 2 years vs those who had not (**Table 4**). Furthermore, the effect of PMH use seemed similar regardless of weight changes after menopause and between those women who had undergone colonoscopy or sigmoidoscopy within the previous 2 years vs those who had not (data not shown).

SELECTIVE ESTROGEN RECEPTOR MODULATOR USE, OTC HORMONE USE, AND THE RISK OF GERD SYMPTOMS

Use of SERMs and OTC hormone preparations was significantly associated with an increased risk of GERD symptoms. Compared with women who never used PMH or SERMs, women currently using a SERM had an OR of 1.39 (95% CI, 1.22-1.59) for GERD symptoms. Among those specifically reporting current use of raloxifene (*n*=2041), the OR for GERD symptoms was 1.44 (95% CI, 1.26-1.66), whereas for those specifically using tamoxifen (*n*=302) the OR was 1.14 (95% CI, 0.82-1.59). Finally, compared with women who never used PMH or OTC hormone preparations, women currently using OTC hormone preparations had an OR for GERD symptoms of 1.37 (95% CI, 1.16-1.62). Among those specifically reporting current use of soy estrogen products (*n*=594), the OR was 1.57 (95% CI, 1.22-2.02), whereas for those specifically using progesterone creams (*n*=489) the OR was 1.27 (95% CI, 0.96-1.68).

COMMENT

We found a positive association between the use of PMH and GERD symptoms in a large cohort of postmenopausal women. The risk of GERD symptoms increased significantly with both increasing dosage and increasing duration of estrogen use (*P* value for trend, <.001). These associations persisted despite controlling for multiple potential confounders. In addition, the use of SERMs

Table 3. Multivariate ORs for GERD Symptoms According to Daily Dosage and Duration of Current PMH Use^a

Participants	Cases No.	Controls No.	Rate, %	Multivariate OR (95% CI) ^b
Estrogen dosage, mg				
Never user	2250	10 329	18	1 [Reference]
0.3	322	992	25	1.47 (1.26-1.73)
0.6	2008	5817	26	1.57 (1.45-1.71)
0.9	189	402	32	1.93 (1.56-2.39)
≥1.25	247	562	31	1.85 (1.53-2.23)
Duration of estrogen use, y				
Never user	2250	10 329	18	1 [Reference]
<1.0-1.9	30	118	20	1.13 (0.66-1.96)
2.0-4.9	284	1041	19	1.39 (1.17-1.65)
5.0-9.9	1077	3482	24	1.48 (1.33-1.64)
≥10.0	3409	9447	27	1.62 (1.50-1.74)

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; ORs, odds ratios; PMH, postmenopausal hormone.

^aIncludes estrogen-only users and estrogen plus progesterone users.

^bAdjusted for age; body mass index; change in weight since menopause; activity (metabolic equivalent tasks per week); smoking status (never, former, current); total caloric intake; intake of alcohol, coffee, tea, carbonated soft drinks, and chocolate; use of medications that may decrease the pressure of the lower esophageal sphincter (calcium channel blockers, bronchodilators, benzodiazepines, and antidepressants); having had a physical examination within 2 years; and history of diabetes mellitus. *P* value for trends, <.001.

and OTC hormone preparations was also associated with an increased risk of GERD symptoms.

Previous investigators⁵⁻¹¹ have postulated that endogenous and exogenous estrogen and progesterone are associated with GERD. For example, administration of estrogen and progesterone resulted in significant decreases in LES pressures in women.⁶ More recently, Nilsson et al¹¹ conducted a large case-control study demonstrating that PMH use significantly increased the risk of GERD symptoms as BMI increased. This further supports the suggestion that female sex hormones can potentiate the link between excess body mass and GERD in women. Nonetheless, in the current study, the effect of PMH use on GERD symptoms did not materially differ according to strata of BMI.

Our finding that the use of SERMs was associated with GERD symptoms has clinical implications because these therapies are widely prescribed. The SERMs are a diverse group of compounds that exert selective estrogen agonist or antagonist effects, depending on the target tissue, and are routinely recommended for the treatment or prevention of breast cancer.¹⁵ As SERM use continues, physicians, physician assistants, and nurse practitioners should be aware that patients may experience an increase in GERD symptoms. In fact, it is worth noting that raloxifene use was associated with a significantly increased risk of dyspepsia in a large, randomized, placebo-controlled trial assessing the effects of raloxifene on cardiovascular events and breast cancer.¹⁶ Similarly, many women have turned to complementary and alternative therapies for the management of menopause-related symptoms.¹⁷ However, many complementary and alternative therapies used for menopause-related symptoms are of unproven or limited benefit,^{17,18} suggesting that patients should at least be informed of potential adverse effects, such as GERD.

Table 4. Multivariate ORs (95% CIs) for GERD Symptoms According to PMH Use Stratified by BMI, Having Had a Physical Examination Within the Past 2 Years, Cigarette Smoking, and Use of Medications That May Decrease LES Pressures^a

Variable	PMH Use			
	Never User	Past User	Current Estrogen User	Current Estrogen + Progesterone
BMI				
<25.0				
Cases, No.	593	1624	1059	670
Controls, No.	4267	7064	4064	3294
Rate, %	12	19	21	17
OR (95% CI)	1 [Reference]	1.54 (1.37-1.74)	1.73 (1.52-1.97)	1.44 (1.24-1.66)
25.0-29.9				
Cases, No.	847	1877	1203	627
Controls, No.	3420	4906	2609	1807
Rate, %	20	28	32	26
OR (95% CI)	1 [Reference]	1.36 (1.22-1.51)	1.52 (1.35-1.71)	1.25 (1.10-1.45)
30.0-34.9				
Cases, No.	477	894	514	295
Controls, No.	1590	1920	894	583
Rate, %	23	32	37	34
OR (95% CI)	1 [Reference]	1.54 (1.31-1.80)	1.70 (1.42-2.04)	1.80 (1.46-2.23)
≥35.0				
Cases, No.	289	417	225	125
Controls, No.	850	861	366	231
Rate, %	25	33	38	35
OR (95% CI)	1 [Reference]	1.41 (1.13-1.75)	1.65 (1.27-2.14)	1.47 (1.08-2.01)
Recent physical examination				
Yes				
Cases, No.	2017	4680	2951	1653
Controls, No.	9005	14 112	7683	5706
Rate, %	18	25	28	22
OR (95% CI)	1 [Reference]	1.49 (1.40-1.58)	1.71 (1.60-1.84)	1.38 (1.27-1.49)
No				
Cases, No.	233	288	120	76
Controls, No.	1324	1090	395	304
Rate, %	15	21	23	20
OR (95% CI)	1 [Reference]	1.46 (1.18-1.80)	1.63 (1.24-2.14)	1.51 (1.10-2.08)
Cigarette smoking				
Never				
Cases, No.	944	2133	1405	720
Controls, No.	4777	6675	3961	2682
Rate, %	17	24	26	21
OR (95% CI)	1 [Reference]	1.61 (1.47-1.77)	1.76 (1.59-1.95)	1.42 (1.27-1.60)
Former				
Cases, No.	1141	2477	1493	872
Controls, No.	4347	7098	3565	2780
Rate, %	21	26	30	24
OR (95% CI)	1 [Reference]	1.35 (1.24-1.47)	1.62 (1.47-1.78)	1.31 (1.18-1.46)
Current				
Cases, No.	161	347	169	134
Controls, No.	1183	1403	541	537
Rate, %	12	20	24	20
OR (95% CI)	1 [Reference]	1.80 (1.44-2.25)	2.14 (1.65-2.78)	1.62 (1.23-2.13)
Use of medications that may decrease LES pressure				
Yes				
Cases, No.	479	1477	942	459
Controls, No.	1479	2828	1652	916
Rate, %	24	34	36	33
OR (95% CI)	1 [Reference]	1.68 (1.47-1.91)	1.79 (1.56-2.06)	1.53 (1.30-1.80)
No				
Cases, No.	1771	3491	2129	1270
Controls, No.	8850	12 374	6426	5094
Rate, %	17	22	25	20
OR (95% CI)	1 [Reference]	1.44 (1.34-1.54)	1.69 (1.57-1.83)	1.35 (1.24-1.47)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CIs, confidence intervals; GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; ORs, odds ratios.

^aAdjusted for age; BMI; change in weight since menopause; activity (metabolic equivalent tasks per week); smoking status (never, former, current); total caloric intake; intake of alcohol, coffee, tea, carbonated soft drinks, and chocolate; use of medications that may decrease the pressure of the LES (calcium channel blockers, bronchodilators, benzodiazepines, and antidepressants); having had a physical examination within 2 years; and history of diabetes mellitus.

The finding that use of PMH, SERMs, and OTC hormone preparations are all associated with an increased risk of GERD symptoms suggests a common mechanism. It is possible that weight gain associated with es-

trogen use results in excess GERD symptoms.¹⁹ Women reporting current estrogen use gained more weight after menopause than women in the other PMH categories. However, our findings were similar when we controlled

for weight gain after menopause and current BMI in our models, as well as when we stratified by these variables. This suggests an independent association with estrogen use. Previous investigators have suggested a role for nitric oxide as an intermediary between estrogens and GERD.¹¹ Postmenopausal use of estrogens is associated with increased plasma nitric oxide levels,²⁰ and nitric oxide is a principal neurotransmitter for relaxation of the LES.²¹ Nitric oxide is also associated with transient relaxations of the LES,²² one of the primary mechanisms underlying GERD in healthy volunteers²³ and in patients with reflux esophagitis.²⁴ Previously, it has been shown²⁵ that postmenopausal women taking unopposed estrogen had higher plasma nitric oxide levels than women taking the same dosage of estrogen coupled with the progestin levonorgestrel. This might explain our finding that women taking combined estrogen plus progesterone therapy had a lower risk of GERD symptoms than women taking unopposed estrogens.

Our study has several strengths, such as the large number of participants, the ability to control for several confounding variables, and the prospective manner in which many of those variables were collected. Nevertheless, a limitation of our study is the use of a questionnaire to define symptoms of GERD. However, several studies^{1,2,11,26-28} have demonstrated the validity and reliability of these questions in identifying cases of GERD. Symptoms assessed by questionnaire have correlated with objective complications of GERD, such as esophagitis and esophageal adenocarcinoma.^{29,30} Furthermore, to improve our specificity for GERD we restricted our primary end point to women who reported at least weekly symptoms. A secondary analysis, using a stricter definition of GERD symptoms (occurring >2 times/wk), produced similar results. Finally, any misclassification in defining GERD symptoms should have occurred randomly and not in relation to PMH use, thereby biasing our results toward the null hypothesis. We also could not exclude the possibility that women who use hormonal therapies are more likely to report, and seek therapy for, symptoms (be they GERD symptoms or menopause-related symptoms) than women who refrained from PMH use. Several of our findings, however, refute this interpretation. We observed significant trends with both increasing dosage and duration of estrogen use, suggesting that it is not simply the choice to use PMH that is associated with GERD symptoms ($P < .001$). We also found a similar association between PMH use and GERD symptoms regardless of whether women had had a physical examination or lower gastrointestinal endoscopy within the previous 2 years. This suggests that health-seeking behavior is less likely to account for the observed association. In addition, our findings were similar when our analyses were restricted to women reporting GERD symptoms of a more recent onset than their ongoing PMH use, establishing an appropriate temporal relationship between PMH use and subsequent symptoms. Finally, we found a similar association between SERM use and GERD symptoms. Unlike PMH and OTC hormone preparations, the SERMs are not used for symptoms; rather, they are used for bone health and breast cancer prevention.

In conclusion, we found evidence that exogenous estrogen and potential estrogen agonists are associated with an increased risk of GERD symptoms. These findings add to our understanding of the pathophysiologic characteristics of GERD. In addition, as the current US population ages, there may be increasing numbers of women seeking both medical and complementary therapies for menopause-related symptoms and breast cancer or osteoporosis prevention. These women should be counseled about the potential for symptoms of GERD associated with hormone therapies.

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