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Association of hormone therapy and incident gout: population-based case-control study

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Abstract

Objective: This study aims to assess the odds of developing incident gout in association with the use of postmenopausal estrogen-progestogen therapy, according to type, timing, duration, and route of administration of estrogen-progestogen therapy.

Methods: We conducted a retrospective population-based case-control analysis using the United Kingdom–based Clinical Practice Research Datalink. We identified women (aged 45 y or older) who had a first-time diagnosis of gout recorded between 1990 and 2010. We matched one female control with each case on age, general practice, calendar time, and years of active history in the database. We used multivariate conditional logistic regression to calculate odds ratios (ORs) with 95% CIs (adjusted for confounders).

Results: The adjusted OR for gout with current use of oral formulations of opposed estrogens (estrogen-progestogen) was 0.69 (95% CI, 0.56-0.86) compared with never use. Current use was associated with a decreased OR for gout in women without renal failure (adjusted OR, 0.71; 95% CI, 0.57-0.87) and hypertension (adjusted OR, 0.62; 95% CI, 0.44-0.87) compared with never use. Tibolone was associated with a decreased OR for gout (adjusted OR, 0.77; 95% CI, 0.63-0.95) compared with never use. Estrogens alone did not alter the OR for gout.

Conclusions: Current use of oral opposed estrogens, but not unopposed estrogens, is associated with a decreased OR for incident gout in women without renal failure and is more pronounced in women with hypertension. Use of tibolone is associated with a decreased OR for incident gout. The decreased OR for gout may be related to the progestogen component rather than the estrogen component.

Key Words: Gout – Hormone therapy – Clinical Practice Research Datalink – Epidemiology – Estrogens – Progestogens.

Gouty arthritis is a common painful inflammatory arthritis with sudden onset, characterized by deposition of monosodium urate crystals in affected joints and surrounding tissue.[1,2] Older age, male sex, hyperuricemia, obesity, and alcohol are important risk factors for gout.[3,4] Furthermore, arterial hypertension, renal failure, congestive heart failure, and use of diuretics or antihypertensive drugs have also been associated with increased risk of gout.[5,6]

The incidence of gout differs between men and women and is strongly related to age in women.[7,8] Gouty arthritis is rarely diagnosed in premenopausal women, but the incidence and prevalence of gout increase after menopause.[7-9] Several authors demonstrated that urate levels—an important risk factor for gout—substantially increase with age in women, but not in men.[10-12] This led to the notion that changes in serum levels of female sex hormones after menopause may be linked to increased urate levels and increased gout risk[13-15] and that female sex hormones may protect against the development of gouty arthritis.[7,16-18] Indeed, investigations showed that both estrogen and progestogen stimulate renal clearance of uric acid and thereby decrease serum urate levels.[11,12] Furthermore, postmenopausal hormone therapy (estrogen-progestogen therapy [EPT]) was shown to also reduce serum uric acid levels.[19,20] Finally, in a study conducted by Hak et al,[9] postmenopausal EPT use was associated with a modestly reduced gout risk, but they did not report on the dose, duration, or route of administration of EPT, or the possible differences between use of estrogens alone and use of opposed estrogens (ie, estrogens plus progestogen).

EPT is licensed for relief of climacteric symptoms and for prophylaxis against osteoporosis in perimenopausal and postmenopausal women.[21] Women with intact uteri usually take combination estrogen-progestogen therapy, whereas women who have had hysterectomy may receive unopposed

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estrogens.[21] We conducted a large case-control analysis using a well-validated primary care database to explore the risk of gout development in association with EPT use, with detailed analyses of the type, timing, duration, and route of administration of EPT.

METHODS

Data source

We derived data from the United Kingdom–based Clinical Practice Research Datalink (CPRD), a large primary care database established in 1987 that encompasses data from some 450 general practices on some 8 million individuals who are representative of the UK population[22,23] with regard to age, sex, geographic distribution, and annual turnover rate.[7,24,25] The CPRD holds information on participant demographics and characteristics, lifestyle variables (such as body mass index [BMI], smoking status, and alcohol consumption), symptoms, medical diagnoses, referrals to consultants, and hospitalizations, which is recorded by general practitioners as part of their daily routine when individuals consult them. General practitioners generate drug prescriptions directly with a computer using a coded drug dictionary. General practitioners have been trained to record medical information for research purposes using standard software and coding systems. The database has been described in detail[26,27] and has been validated extensively.[23,28-31] The CPRD has been the source of numerous epidemiological studies published in peer-reviewed journals, including research on gout.[6-8,32,33]

The Independent Scientific Advisory Committee for the Medicines and Healthcare Products Regulatory Agency database research approved the study.

Study population

Cases

Based on Read codes, we identified in the CPRD women (aged 45 y or older) who had a first-time diagnosis of gout recorded between 1990 and 2010. The date of the first diagnosis of gout was referred to as the "index date." Previous studies of gout in the CPRD[6-8,32,33] provided evidence that diagnoses—albeit, in most cases, clinical diagnoses by general practitioners—have high validity. In addition, we reviewed a large sample of participant records to verify the validity of inclusion and exclusion criteria, the incident recording of the disease, and the validity of recording according to treatment patterns and differential diagnoses around the index date.

Exclusion criteria

We excluded all cases with less than 3 years of recorded history before the index date to reduce the likelihood of including prevalent gout cases. We further excluded all women with a diagnosis of human immunodeficiency virus or cancer (except nonmelanoma skin cancer) before the index date and women with a diagnosis of hemochromatosis, septic arthritis, rheumatoid arthritis, or osteoarthritis at any time in participant records (to reduce the risk of misclassification; ie, inclusion of individuals with gout who, in fact, had another disease with similar symptoms). The diagnosis of gout in the CPRD has been validated in a previous study[32] in which similar case definitions were used.[6-8,33]

Control participants

We randomly identified from the CPRD a control group of women without evidence of gout. We applied the same exclusion criteria to controls as to cases. We matched (1:1) controls to cases on age, general practice, number of years of recorded history in the database, and index date.

Exposure

We identified EPT prescriptions before the index date and classified exposed women into "current users" (last prescription ending <90 d before the index date), "past users" (last prescription ending ≥ 90 d before the index date), or "never users." We determined a cutoff of 90 days for current use because this is the typical maximal length of a prescription in the United Kingdom. We further classified EPT users according to duration of use, with the number of EPT prescriptions (1-9, 10-19, ≥ 20 prescriptions) before the index date used as proxy for treatment duration. In addition, we distinguished opposed (estrogen-progestogen) from unopposed (estrogen only) EPT prescriptions and ran stratified analyses by route of administration (oral, transdermal patch, vaginal, or others, including gel, implant, nasal spray, and injection).

Covariates

We classified cases and controls according to their BMI (unknown, 12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, ≥ 45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, ≥ 20 units/wk], unknown), and number of general practitioner visits within the year immediately preceding the index date (0-2, 3-4, 5-9, ≥ 10). We assessed whether cases and controls had a recording of hysterectomy, osteoporosis, hypertension, renal failure, ischemic heart disease, congestive heart failure, stroke or transient ischemic attack, diabetes mellitus, or dyslipidemia at any time before the index date. Furthermore, we assessed the association of use of antihypertensive drugs (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and organic nitrates), statins, and low-dose acetylsalicylic acid within 180 days of the index date with gout. A cutoff of 180 days was chosen to better distinguish between current and past users because these substances are prescribed for long-term use, and many of these drugs are also available in packages containing more than 90 tablets.

Sensitivity analysis

We conducted various sensitivity analyses. First, we assessed the odds ratio (OR) for gout in association with EPT use in the subset of cases (and their matched controls) who were treated with nonsteroidal anti-inflammatory drugs,

colchicine, and/or corticosteroids within 7 days of the index date, or uricosuric/uricostatic drugs within 90 days of the index date. This was performed to reduce the risk of misclassification (ie, to increase the likelihood of including valid gout cases). In a second sensitivity analysis, we excluded women with a history of renal failure, congestive heart failure, or hypertension to eliminate residual confounding by these important risk factors for gout. In a third sensitivity analysis, we stratified the study population by the presence or absence of these comorbidities. In a fourth sensitivity analysis, we stratified the study population by hysterectomy status because increased gout risk has previously been reported in younger women who have had natural or surgical menopause.[9] In a fifth sensitivity analysis, we compared current EPT users to the reference group of past EPT users to limit the risk of potential confounding by indication. In a sixth sensitivity analysis, we restricted the data to incident users of EPT by excluding prevalent users to address potential prevalent user bias; incident users were women without any prescriptions for opposed or unopposed estrogens within the first year of their registered history. In a seventh sensitivity analysis, we assessed the ORs for gout (ever use vs never use) with EPT stratified by route of administration. Finally, we assessed the ORs for gout with EPT excluding tibolone because tibolone is a synthetic steroid with properties different from those of "simple" estrogens and progestogens.

Statistical analysis

We conducted multivariate conditional logistic regression analyses to compare the exposure prevalence of EPT between cases and controls. We present relative risk estimates as ORs with 95% CIs. Two-sided $P < 0.05$ was considered statistically significant. We conducted statistical analysis using the software program SAS version 9.3 (SAS Institute Inc, Cary, NC).

In analyzing the odds for exposure, we adjusted for participant characteristics, comorbidities, or concomitant drug use in multivariate analysis if these potential confounders were predictor variables for gout known a priori from the literature: BMI category (12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, $\geq$45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, $\geq$20 units/wk], unknown), and general practitioner visits within the last year preceding the index date (0-2, 3-4, 5-9, $\geq$10) for all analyses. When we explored the association between incident gout and baseline characteristics, including lifestyle factors (alcohol consumption and smoking status) and different comorbidities, we additionally adjusted our analyses for hysterectomy status (yes/no) and previous comorbidities such as hypertension (yes/no), congestive heart failure (yes/no), ischemic heart disease (yes/no), and renal failure (yes/no). For all other analyses, we simultaneously adjusted for use of diuretic and antihypertensive drugs, nitrates, statins, low-dose acetylsalicylic acid, and opposed or unopposed estrogens.

RESULTS

The study population encompassed 13,489 incident gout cases in women aged 45 years or older and the same number of matched controls. The mean (SD) age at index date was 70 (12.3) years. All adjusted factors were associated with an increased OR for incident gout in univariate analysis. Increasing BMI was associated with a higher OR for gout, as was current alcohol consumption in a dose-dependent manner. Comorbidities known to be associated with increased risk of gout, such as hypertension, renal failure, congestive heart failure, and ischemic heart disease, were all associated with an increased OR for incident gout (Table 1).

Current use of most antihypertensive drugs—except for calcium channel blockers, which were associated with a decreased OR for gout—was associated with an increased OR for gout compared with never use of these drugs (Table 1).

Compared with never use, current use of opposed estrogens (adjusted OR, 0.72; 95% CI, 0.59-0.88)—but not unopposed estrogens (adjusted OR, 1.21; 95% CI, 0.98-1.48)—was associated with a decreased OR for incident gout. ORs for gout did not materially change with increasing number of prescriptions among users of opposed or unopposed estrogens; however, an additional trend analysis using the number of prescriptions as a continuous variable showed a statistically significant P value of 0.0001 (Table 2).

Results from sensitivity analyses restricted to women with pharmacologically treated gout or women without evidence of renal failure, congestive heart failure, or hypertension did not materially differ from the main analysis (data not shown). When we stratified our analysis by renal failure, current use of opposed estrogens was associated with a decreased OR for gout in women without renal failure compared with never use (adjusted OR, 0.71; 95% CI, 0.57-0.87), whereas no such association was found in women with renal failure (adjusted OR, 0.99; 95% CI, 0.53-1.86). In the analysis stratified by hypertension, current use of opposed estrogens was associated with a stronger protective effect (adjusted OR, 0.62; 95% CI, 0.44-0.87) on women with hypertension, whereas the association was closer to null in cases and controls without hypertension (adjusted OR, 0.80; 95% CI, 0.63-1.02; Table 3). We additionally ran a χ^2 test for interaction and found no interaction ($P > 0.1$) for renal failure, hypertension, and users of opposed and unopposed estrogens. We could not stratify by the presence or absence of congestive heart failure as there were too few women with the disease. In the analysis stratified by hysterectomy status (21.4% of cases and 17.3% of controls had had hysterectomy), current use of opposed estrogens was associated with a decreased OR in women who have not had hysterectomy (OR, 0.71; 95% CI, 0.58-0.88), whereas no such association was found in women with recorded hysterectomy (data not shown). To address potential bias by indication, we compared current use of opposed or unopposed estrogens with past use of each and observed findings closely similar to those for the main model (data not shown). In the analysis restricted to current incident users of EPT compared with nonusers, the results were closely similar to the main findings (data not

TABLE 1. *Baseline characteristics of women: gout cases (n = 13,489) and matched controls (n = 13,489)*

Variable	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age group[a]				
45-49 y	786 (5.8)	786 (5.8)	NA	NA
50-54 y	984 (7.3)	988 (7.3)	NA	NA
55-59 y	1,264 (9.4)	1,256 (9.3)	NA	NA
60-64 y	1,442 (10.7)	1,440 (10.7)	NA	NA
65-69 y	1,304 (9.7)	1,319 (9.8)	NA	NA
70-74 y	1,527 (11.3)	1,525 (11.3)	NA	NA
75-79 y	1,600 (11.9)	1,609 (11.9)	NA	NA
≥80 y	4,582 (34.0)	4,566 (33.9)	NA	NA
BMI category[b]				
12.0-18.4 kg/m^2	165 (1.2)	303 (2.3)	0.80 (0.66-0.98)	0.78 (0.62-0.98)
18.5-24.9 kg/m^2	2,871 (21.3)	4,386 (32.5)	1.00 (referent)	1.00 (referent)
25.0-29.9 kg/m^2	3,772 (28.0)	3,300 (24.5)	1.83 (1.71-1.96)	1.58 (1.46-1.71)
30.0-34.9 kg/m^2	2,422 (18.0)	1,276 (9.5)	3.23 (2.95-3.53)	2.50 (2.27-2.77)
35.0-39.9 kg/m^2	1,054 (7.8)	390 (2.9)	4.51 (3.95-5.15)	3.20 (2.76-3.71)
40.0-44.9 kg/m^2	410 (3.0)	97 (0.7)	7.30 (5.75-9.26)	4.78 (3.69-6.20)
≥45.0 kg/m^2	214 (1.6)	41 (0.3)	8.95 (6.34-12.64)	5.17 (3.58-7.49)
Unknown	2,581 (19.1)	3,696 (27.4)	0.88 (0.82-0.96)	1.33 (1.19-1.49)
Smoking status[b]				
Nonsmoker	6,521 (48.3)	6,698 (49.7)	1.00 (referent)	1.00 (referent)
Current smoker	1,726 (12.8)	1,802 (13.4)	0.99 (0.91-1.07)	1.21 (1.11-1.33)
Ex-smoker	3,682 (27.3)	2,547 (18.9)	1.57 (1.48-1.68)	1.30 (1.20-1.40)
Unknown	1,560 (11.6)	2,442 (18.1)	0.54 (0.49-0.58)	1.15 (1.01-1.32)
Alcohol consumption[b,c]				
Never/past	3,016 (22.4)	2,750 (20.4)	1.00 (referent)	1.00 (referent)
Current, unknown units/wk	3,146 (23.3)	2,936 (21.8)	0.98 (0.91-1.06)	1.05 (0.96-1.15)
Current, 1-9 units/wk	3,238 (24.0)	3,160 (23.4)	0.95 (0.88-1.03)	1.13 (1.04-1.24)
Current, 10-19 units/wk	1,045 (7.8)	818 (6.1)	1.21 (1.08-1.35)	1.59 (1.39-1.81)
Current, ≥20 units/wk	501 (3.7)	261 (1.9)	1.80 (1.54-2.12)	2.03 (1.68-2.46)
Unknown	2,543 (18.9)	3,564 (26.4)	0.57 (0.53-0.62)	0.96 (0.85-1.09)
General practitioner visits within the last year[b]				
0-2	1,042 (7.7)	2,976 (22.1)	1.00 (referent)	1.00 (referent)
3-4	407 (3.0)	864 (6.4)	1.39 (1.20-1.61)	1.21 (1.03-1.41)
5-9	1,556 (11.5)	2,065 (15.3)	2.41 (2.17-2.68)	2.04 (1.81-2.29)
≥10	10,484 (77.7)	7,584 (56.2)	5.15 (4.71-5.64)	3.19 (2.87-3.53)
Comorbidities[b]				
Hysterectomy	2,882 (21.4)	2,337 (17.3)	1.32 (1.24-1.40)	1.18 (1.09-1.27)
Osteoporosis	817 (6.1)	894 (6.6)	0.91 (0.82-1.00)	0.93 (0.83-1.05)
Hypertension	8,186 (60.7)	4,833 (35.8)	3.18 (3.00-3.36)	2.09 (1.95-2.23)
Diabetes mellitus	1,721 (12.8)	900 (6.7)	2.08 (1.91-2.27)	1.05 (0.94-1.16)
Dyslipidemia	2,408 (17.9)	1,559 (11.6)	1.78 (1.65-1.91)	1.07 (0.98-1.17)
Renal failure	4,689 (34.8)	2,583 (19.2)	4.44 (4.07-4.85)	2.39 (2.16-2.63)
Congestive heart failure	1,646 (12.2)	505 (3.7)	3.98 (3.56-4.45)	2.91 (2.57-3.31)
Ischemic heart disease	2,544 (18.9)	1,308 (9.7)	2.27 (2.11-2.45)	1.42 (1.30-1.56)
Stroke/TIA	1,292 (9.6)	905 (6.7)	1.51 (1.38-1.65)	1.14 (1.02-1.27)
Comedications[d]				
ACE inhibitors	3,606 (26.7)	1,656 (12.3)	3.46 (3.21-3.72)	1.53 (1.40-1.68)
ARBs (excluding losartan)	1,009 (7.5)	415 (3.1)	2.90 (2.56-3.28)	1.24 (1.06-1.45)
Losartan	354 (2.6)	148 (1.1)	2.51 (2.07-3.05)	1.11 (0.69-1.77)
Loop diuretics	3,250 (24.1)	889 (6.6)	5.73 (5.23-6.29)	3.26 (2.92-3.63)
Thiazide diuretics	3,440 (25.5)	1,778 (13.2)	2.78 (2.59-2.98)	1.89 (1.73-2.06)
Potassium-sparing diuretics	557 (4.1)	117 (0.9)	5.31 (4.31-6.54)	2.33 (1.84-2.94)
β-Blockers	3,846 (28.5)	1,790 (13.3)	3.06 (2.86-3.28)	1.83 (1.68-1.99)
Calcium channel blockers	2,500 (18.5)	1,717 (12.7)	1.90 (1.77-2.05)	0.89 (0.82-0.98)
Nitrates	1,283 (9.5)	551 (4.1)	2.67 (2.40-2.97)	1.29 (1.13-1.47)
Statins	3,113 (23.1)	1,768 (13.1)	2.45 (2.27-2.64)	1.15 (1.04-1.26)
Low-dose acetylsalicylic acid	2,857 (21.2)	1,755 (13.0)	2.07 (1.92-2.22)	0.98 (0.89-1.07)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; NA, not applicable; OR, odds ratio; TIA, transient ischemic attack.

[a]Matching variables: age, sex, general practice, history on database, and index date.

[b]Adjusted for BMI category (12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, ≥45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, ≥20 units/wk], unknown), number of general practitioner visits within the last year (0-2, 3-4, 5-9, ≥10), hysterectomy (yes/no), hypertension (yes/no), renal failure (yes/no), congestive heart failure (yes/no), and ischemic heart disease (yes/no).

[c]One unit equals 10 mL of pure ethanol (8 g of ethanol).

[d]Adjusted for BMI category (12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, ≥45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, ≥20 units/wk], unknown), number of general practitioner visits within the last year (0-2, 3-4, 5-9, ≥10), hysterectomy (yes/no), and prior prescription for ACE inhibitors (yes/no), ARBs excluding losartan (yes/no), losartan (yes/no), loop diuretics (yes/no), thiazide diuretics (yes/no), potassium-sparing diuretics (yes/no), β-blockers (yes/no), calcium channel blockers (yes/no), nitrates (yes/no), statins (yes/no), low-dose acetylsalicylic acid (yes/no), opposed estrogens (yes/no), and unopposed estrogens (yes/no).

TABLE 2. *ORs for current use versus never use of hormone therapy in gout cases (n = 13,489) and matched controls (n = 13,489)*

Hormone therapy	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Opposed estrogens				
Never use	11,772 (87.3)	11,623 (86.2)	1.00 (referent)	1.00 (referent)
Current use				
Overall	267 (2.0)	332 (2.5)	0.78 (0.66-0.92)	0.72 (0.59-0.88)
1-9 prescriptions	85 (0.6)	113 (0.8)	0.72 (0.54-0.97)	0.68 (0.49-0.95)
10-19 prescriptions	67 (0.5)	78 (0.6)	0.82 (0.59-1.15)	0.77 (0.52-1.14)
≥20 prescriptions	115 (0.9)	141 (1.1)	0.79 (0.62-1.02)	0.72 (0.53-0.97)
Past use				
Overall	1,450 (10.8)	1,534 (11.4)	0.92 (0.84-1.00)	0.88 (0.79-0.97)
1-9 prescriptions	857 (6.4)	836 (6.2)	0.99 (0.90-1.10)	0.95 (0.83-1.07)
10-19 prescriptions	300 (2.2)	350 (2.6)	0.83 (0.71-0.98)	0.81 (0.67-0.98)
≥20 prescriptions	293 (2.2)	348 (2.6)	0.81 (0.69-0.96)	0.77 (0.63-0.94)
Unopposed estrogens				
Never use	12,021 (89.1)	12,268 (91.0)	1.00 (referent)	1.00 (referent)
Current use				
Overall	343 (2.5)	234 (1.7)	1.54 (1.30-1.83)	1.21 (0.98-1.48)
1-9 prescriptions	84 (0.6)	59 (0.4)	1.49 (1.06-2.09)	1.28 (0.87-1.89)
10-19 prescriptions	80 (0.6)	54 (0.4)	1.54 (1.08-2.18)	1.24 (0.83-1.87)
≥20 prescriptions	179 (1.3)	121 (0.9)	1.57 (1.23-1.99)	1.15 (0.87-1.53)
Past use				
Overall	1,125 (8.3)	987 (7.3)	1.19 (1.08-1.30)	1.02 (0.91-1.14)
1-9 prescriptions	638 (4.7)	603 (4.5)	1.10 (0.98-1.23)	0.96 (0.84-1.11)
10-19 prescriptions	217 (1.6)	180 (1.3)	1.27 (1.04-1.55)	1.16 (0.91-1.48)
≥20 prescriptions	270 (2.0)	204 (1.5)	1.38 (1.15-1.67)	1.09 (0.86-1.37)

OR, odds ratio.
[a]Adjusted for body mass index category (12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, ≥45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, ≥20 units/wk], unknown), number of general practitioner visits within the last year (0-2, 3-4, 5-9, ≥10), and prior prescription for angiotensin-converting enzyme inhibitors (yes/no), angiotensin receptor blockers excluding losartan (yes/no), losartan (yes/no), loop diuretics (yes/no), thiazide diuretics (yes/no), potassium-sparing diuretics (yes/no), β-blockers (yes/no), calcium channel blockers (yes/no), nitrates (yes/no), statins (yes/no), low-dose acetylsalicylic acid (yes/no), opposed estrogens (yes/no), and unopposed estrogens (yes/no).

shown). Finally, in the analysis of users of EPT without tibolone compared with nonusers, the results were closely similar to the main findings (data not shown).

Ever use of norethisterone acetate and estrogen, medroxyprogesterone acetate and estrogen, and tibolone was associated with a decreased OR for incident gout compared with

TABLE 3. *ORs for hormone therapy use, stratified by renal failure and hypertension, in gout cases (n = 13,489) and matched controls (n = 13,489)*

	With comorbidity before the index date				Without comorbidity before the index date			
	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Renal failure	4,689 (34.8)	2,583 (19.2)			8,800 (65.2)	10,906 (80.9)		
Opposed estrogens								
Nonuse	4,252 (31.5)	2,328 (17.3)	1.00 (referent)	1.00 (referent)	7,520 (55.8)	9,295 (68.9)	1.00 (referent)	1.00 (referent)
Current use	40 (0.3)	21 (0.2)	0.91 (0.52-1.60)	0.99 (0.53-1.86)	227 (1.7)	311 (2.3)	0.80 (0.66-0.96)	0.71 (0.57-0.87)
Past use	397 (2.9)	234 (1.7)	0.82 (0.68-0.98)	0.82 (0.66-1.02)	1,053 (7.8)	1,300 (9.6)	0.97 (0.88-1.07)	0.90 (0.80-1.01)
Unopposed estrogens								
Nonuse	4,250 (31.5)	2,363 (17.5)	1.00 (referent)	1.00 (referent)	7,771 (57.6)	9,905 (73.4)	1.00 (referent)	1.00 (referent)
Current use	46 (0.3)	18 (0.1)	1.05 (0.59-1.87)	1.30 (0.67-2.52)	297 (2.2)	216 (1.6)	1.68 (1.40-2.03)	1.23 (0.99-1.52)
Past use	393 (2.9)	202 (1.5)	1.08 (0.89-1.31)	1.05 (0.84-1.30)	732 (5.4)	785 (5.8)	1.25 (1.12-1.40)	1.04 (0.91-1.19)
Hypertension	8,186 (60.7)	4,833 (35.8)			5,303 (39.3)	8,656 (64.2)		
Opposed estrogens								
Nonuse	7,290 (54.0)	4,267 (31.6)	1.00 (referent)	1.00 (referent)	4,482 (33.2)	7,356 (54.5)	1.00 (referent)	1.00 (referent)
Current use	104 (0.8)	79 (0.6)	0.65 (0.48-0.88)	0.62 (0.44-0.87)	163 (1.2)	253 (1.9)	0.92 (0.74-1.13)	0.80 (0.63-1.02)
Past use	792 (5.9)	487 (3.6)	0.90 (0.79-1.02)	0.77 (0.66-0.89)	658 (4.9)	1,047 (7.8)	1.00 (0.89-1.12)	1.00 (0.88-1.14)
Unopposed estrogens								
Nonuse	7,317 (54.2)	4,391 (32.6)	1.00 (referent)	1.00 (referent)	4,704 (34.9)	7,877 (58.4)	1.00 (referent)	1.00 (referent)
Current use	182 (1.4)	73 (0.5)	1.38 (1.03-1.84)	1.17 (0.84-1.61)	161 (1.2)	161 (1.2)	1.55 (1.23-1.96)	1.25 (0.96-1.62)
Past use	687 (5.1)	369 (2.7)	1.15 (1.00-1.32)	0.95 (0.81-1.12)	438 (3.3)	618 (4.6)	1.23 (1.07-1.41)	1.14 (0.98-1.33)

OR, odds ratio.
[a]Adjusted for body mass index category (12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, ≥45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, ≥20 units/wk], unknown), number of general practitioner visits within the last year (0-2, 3-4, 5-9, ≥10), and prior prescription for angiotensin-converting enzyme inhibitors (yes/no), angiotensin receptor blockers excluding losartan (yes/no), losartan (yes/no), loop diuretics (yes/no), thiazide diuretics (yes/no), potassium-sparing diuretics (yes/no), β-blockers (yes/no), calcium channel blockers (yes/no), nitrates (yes/no), statins (yes/no), low-dose acetylsalicylic acid (yes/no), opposed estrogens (yes/no), and unopposed estrogens (yes/no).

TABLE 4. *ORs for hormone therapy use, stratified by progesterone component (single substance), in gout cases (n = 13,489) and matched controls (n = 13,489)*

Hormone therapy	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Opposed estrogens				
Nonuse	11,807 (87.5)	11,652 (86.4)	1.00 (referent)	1.00 (referent)
Ever use, by substance				
Dydrogesterone and estrogen	65 (0.5)	70 (0.5)	0.90 (0.63-1.27)	0.97 (0.63-1.48)
Levonorgestrel and estrogen	87 (0.6)	95 (0.7)	0.89 (0.66-1.19)	0.77 (0.55-1.10)
Norethisterone and estrogen	607 (4.5)	671 (5.0)	0.88 (0.78-0.99)	0.81 (0.70-0.94)
Medroxyprogesterone acetate and estrogen	199 (1.5)	251 (1.9)	0.77 (0.63-0.93)	0.69 (0.54-0.87)
Norgestrel and estrogen	439 (3.3)	429 (3.2)	0.99 (0.86-1.14)	0.98 (0.83-1.17)
Raloxifene	35 (0.3)	39 (0.3)	0.88 (0.55-1.39)	1.23 (0.69-2.17)
Tibolone	250 (1.9)	282 (2.1)	0.86 (0.72-1.02)	0.77 (0.63-0.95)

OR, odds ratio.
[a]Adjusted for body mass index category (12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, ≥45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, ≥20 units/wk], unknown), number of general practitioner visits within the last year (0-2, 3-4, 5-9, ≥10), and prior prescription for angiotensin-converting enzyme inhibitors (yes/no), angiotensin receptor blockers excluding losartan (yes/no), losartan (yes/no), loop diuretics (yes/no), thiazide diuretics (yes/no), potassium-sparing diuretics (yes/no), β-blockers (yes/no), calcium channel blockers (yes/no), nitrates (yes/no), statins (yes/no), low-dose acetylsalicylic acid (yes/no), and unopposed estrogens (yes/no).

never use of these drugs (Table 4). Current use of oral opposed estrogens, but not of other routes of administration, was associated with a significantly decreased OR for incident gout (adjusted OR, 0.69; 95% CI, 0.56-0.86). Further results are displayed in Table 5.

DISCUSSION

In this large population-based case-control study, current use of opposed estrogens—but not unopposed estrogens—was associated with a decreased OR for incident gout (adjusted OR, 0.72; 95% CI, 0.59-0.88). The OR reduction was not dependent on the duration of EPT use. The decreased OR for gout among current users of opposed estrogens was only observed in women without renal failure. Of interest, when we stratified by arterial hypertension (another comorbidity that has been associated with an increased OR for gout in this study and in other studies),[5,6] the observed OR reduction was more pronounced in cases and controls with recorded arterial hypertension. Again, no such OR reduction was seen in users of unopposed estrogens. When we stratified by hysterectomy status, a protective effect of opposed estrogens was observed in women who have not had hysterectomy, whereas no association was observed in users of unopposed estrogens. When we stratified opposed estrogens by progestogen component, only

TABLE 5. *ORs for current use versus never use of hormone therapy, stratified by route of administration, in incident gout cases (n = 13,489) and matched controls (n = 13,489)*

Hormone therapy	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Opposed estrogens				
Never use	11,772 (87.3)	11,623 (86.2)	1.00 (referent)	1.00 (referent)
Current use, by route of administration				
Patch	24 (0.2)	28 (0.2)	0.82 (0.47-1.43)	0.95 (0.50-1.82)
Oral	236 (1.8)	298 (2.2)	0.77 (0.64-0.91)	0.69 (0.56-0.86)
Past use, by route of administration				
Patch	109 (0.8)	111 (0.8)	0.95 (0.73-1.24)	0.83 (0.60-1.16)
Oral	1,292 (9.6)	1,378 (10.2)	0.91 (0.83-0.99)	0.88 (0.79-0.98)
Others	56 (0.4)	51 (0.4)	1.07 (0.73-1.57)	1.03 (0.64-1.65)
Unopposed estrogens				
Never use	12,021 (89.1)	12,268 (91.0)	1.00 (referent)	1.00 (referent)
Current use, by route of administration				
Patch	73 (0.5)	62 (0.5)	1.27 (0.91-1.79)	1.02 (0.68-1.53)
Oral	216 (1.6)	124 (0.9)	1.85 (1.47-2.33)	1.37 (1.05-1.78)
Vaginal	37 (0.3)	34 (0.3)	1.10 (0.69-1.75)	0.87 (0.49-1.53)
Others	17 (0.1)	14 (0.1)	1.27 (0.62-2.57)	1.39 (0.63-3.10)
Past use, by route of administration				
Patch	320 (2.4)	267 (2.0)	1.25 (1.06-1.48)	0.98 (0.79-1.20)
Oral	536 (4.0)	423 (3.1)	1.32 (1.15-1.50)	1.17 (0.99-1.37)
Vaginal	189 (1.4)	243 (1.8)	0.80 (0.66-0.97)	0.75 (0.59-0.95)
Others	80 (0.6)	54 (0.4)	1.56 (1.10-2.21)	1.32 (0.86-2.02)

OR, odds ratio.
[a]Adjusted for body mass index category (12.0-18.4, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, 40.0-44.9, ≥45.0 kg/m^2), smoking status (nonsmoker, current smoker, ex-smoker, unknown), alcohol consumption (never/past, current [unknown, 1-9, 10-19, ≥20 units/wk], unknown), number of general practitioner visits within the last year (0-2, 3-4, 5-9, ≥10), and prior prescription for angiotensin-converting enzyme inhibitors (yes/no), angiotensin receptor blockers excluding losartan (yes/no), losartan (yes/no), loop diuretics (yes/no), thiazide diuretics (yes/no), potassium-sparing diuretics (yes/no), β-blockers (yes/no), calcium channel blockers (yes/no), nitrates (yes/no), statins (yes/no), low-dose acetylsalicylic acid (yes/no), and unopposed estrogens (yes/no).

norethisterone acetate and estrogen, and medroxyprogesterone acetate and estrogen were associated with a decreased OR for incident gout. Tibolone—a synthetic steroid hormone acting as a selective tissue estrogenic activity regulator acting as an estrogen receptor agonist[34] whose metabolites have estrogenic, androgenic, and progestogenic properties[35]—was also associated with a decreased OR for gout. The effect of tibolone might be explained by its progestogenic component. When we stratified by route of administration, current use of oral opposed estrogens was associated with a significantly decreased OR for incident gout, whereas transdermal patches were not associated with an altered OR. Taken together, our results suggest that the progestogen component in opposed estrogens may explain the observed relative decrease in the OR for gout in association with the use of opposed estrogens, an OR reduction that was only observed in the absence of renal failure and was more pronounced in the presence of diagnosed arterial hypertension, suggesting effect modification by these parameters.

To our best knowledge, the study conducted by Hak et al[9] is, to date, the only study to have explored the association between EPT use and risk of incident gout. They found a slightly decreased risk of gout in postmenopausal users of EPT (relative risk, 0.82; 95% CI, 0.70-0.96) compared with nonusers of EPT. However, they did not report findings on the type (opposed vs unopposed), duration, or route of administration of EPT.[9]

Serum uric acid levels increase in older postmenopausal women,[10] and decreased serum uric acid levels have been observed in users of EPT compared with postmenopausal women not using EPT.[10,19,20] In line with these observations, investigators showed that use of estrogens and progestogen leads to increased renal clearance of urate and therefore decreased serum urate levels.[11,12,20] However, the underlying causes of these age and sex differences remain unclear, and the number of participants analyzed was small.[11,12,20] In our study, use of opposed estrogens was not associated with a decreased OR for gout in women with renal failure (ie, a participant subgroup with reduced renal uric acid excretion). However, because use of unopposed estrogens was not associated with an altered OR for gout in either the main analyses or the stratified analyses, these findings do not support the hypothesis that altered renal uric acid handling alone explains our findings; this may be explained by the uricosuric effect of progestogens, but not of estrogens alone. Furthermore, hypertension also had an influence on the observed OR reduction seen for opposed estrogens.

Our large population-based study has several strengths. We were in a position to study a large number of cases with incident gout in a well-established primary care database.[23,28-31] Furthermore, we were able to analyze opposed and unopposed estrogens separately and to explore the OR for gout in association with duration and route of administration of EPT. We were able to run various sensitivity analyses to address potential biases. We further adjusted our analyses for important potential confounders such as BMI, smoking status, alcohol consumption, renal failure, hypertension, and concomitant drug therapies. Because information on diseases and drug exposure was prospectively entered in the CPRD in the absence of any study hypothesis, recall bias is not an issue.

Some limitations of our study have to be acknowledged. Misclassification of some gout cases may have occurred, although a previous study has shown that gout diagnoses are recorded in the CPRD with high validity.[32] To minimize misclassification, we excluded women with recorded diagnoses of other rheumatic disorders at any time within their history, and we further excluded all women with less than 3 years of recorded history in the database before the index date to reduce the risk of including prevalent rather than incident gout cases. We were not in a position to assess menopause because menopause status was not consistently recorded by general practitioners. However, EPT is prescribed mostly to postmenopausal women for symptomatic relief, usually as combined EPT in women with intact uterus.[21] The analysis stratified by hysterectomy status was consistent with results from the main analysis; we therefore assume that our study population is representative of postmenopausal women. Because the numbers of cases and controls among hormone therapy users in the stratified analyses were rather small for some agents, results have to be interpreted with caution. In addition, we were not able to adjust for all known potential risk factors for gout because, for example, dietary habits or physical activity[1,3] are not routinely recorded in the CPRD. However, we adjusted for BMI, a factor that is related to physical activity and dietary habits. Finally, we could not address potential confounding by socioeconomic status, but we partially controlled for this parameter by matching cases and controls on general practitioner because women from the same neighborhood tend to see the same general practitioner.

CONCLUSIONS

This large observational study provides evidence that current oral use of opposed estrogens is associated with a decreased OR for incident gout. OR reduction is only observed in women with normal renal function and is more pronounced in women with hypertension. Current use of oral unopposed estrogens is not associated with a decreased OR for gout in postmenopausal women. Thus, these findings provide evidence that the reduced OR for gout seen with EPT use may be related to the progestogen component rather than the estrogen component.

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REFERENCES

1. Choi HK, Mount DB, Reginato AM; American College of Physicians, American Physiological SocietyPathogenesis of gout. *Ann Intern Med* 2005;143:499-516.
2. Riches PL, Wright AF, Ralston SH. Recent insights into the pathogenesis of hyperuricaemia and gout. *Hum Mol Genet* 2009;18:R177-R184.
3. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Intern Med* 2005;165:742-748.
4. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet* 2004;363:1277-1281.

5. Choi HK, Soriano LC, Zhang Y, Rodríguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ* 2012;344:d8190.
6. Bruderer S, Bodmer M, Jick SS, Meier CR. Use of diuretics and risk of incident gout: a population-based case-control study. *Arthritis Rheumatol* 2014;66:185-196.
7. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. *Ann Rheum Dis* 2005;64:267-272.
8. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74:661-667.
9. Hak AE, Curhan GC, Grodstein F, Choi HK. Menopause, postmenopausal hormone use and risk of incident gout. *Ann Rheum Dis* 2010;69:1305-1309.
10. Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women—the Third National Health and Nutrition Examination Survey. *Arthritis Res Ther* 2008;10:R116.
11. Adamopoulos D, Vlassopoulos C, Seitanides B, Contoyiannis P, Vassilopoulos P. The relationship of sex steroids to uric acid levels in plasma and urine. *Acta Endocrinol* 1977;85:198-208.
12. Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. *Br Med J* 1973;1:449-451.
13. Lally EV, Ho G Jr, Kaplan SR. The clinical spectrum of gouty arthritis in women. *Arch Intern Med* 1986;146:2221-2225.
14. Puig JG, Michán AD, Jiménez ML, et al. Female gout. Clinical spectrum and uric acid metabolism. *Arch Intern Med* 1991;151:726-732.
15. De Souza A, Fernandes V, Ferrari AJ. Female gout: clinical and laboratory features. *J Rheumatol* 2005;32:2186-2188.
16. Mikkelsen WM, Dodge HJ, Valkenburg H. The distribution of serum uric acid values in a population unselected as to gout or hyperuricemia: Tecumseh, Michigan 1959-1960. *Am J Med* 1965;39:242-251.
17. Sturge RA, Scott JT, Kennedy AC, Hart DP, Buchanan WW. Serum uric acid in England and Scotland. *Ann Rheum Dis* 1977;36:420-427.
18. Akizuki S. Serum uric acid levels among thirty-four thousand people in Japan. *Ann Rheum Dis* 1982;41:272-274.
19. Simon JA, Lin F, Vittinghoff E, Bittner V; Heart, Estrogen-Progestin Replacement Study (HERS) Research Group. The relation of postmenopausal hormone therapy to serum uric acid and the risk of coronary heart disease events: the Heart and Estrogen-Progestin Replacement Study (HERS). *Ann Epidemiol* 2006;16:138-145.
20. Sumino H, Ichikawa S, Kanda T, Nakamura T, Sakamaki T. Reduction of serum uric acid by hormone replacement therapy in postmenopausal women with hyperuricaemia. *Lancet* 1999;354:650.
21. Bromley SE, de Vries CS, Farmer RD. Utilisation of hormone replacement therapy in the United Kingdom. A descriptive study using the General Practice Research Database. *BJOG* 2004;111:369-376.
22. Lawson DH, Sherman V, Hollowell J. The General Practice Research Database. Scientific and Ethical Advisory Group. *QJM* 1998;91:445-452.
23. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract* 2010;60:e128-e136.
24. García Rodríguez LA, Pérez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol* 1998;45:419-425.
25. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;12:171-177.
26. Jick H. A database worth saving. *Lancet* 1997;350:1045-1046.
27. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350:1097-1099.
28. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;302:766-768.
29. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the General Practice Research Database. *Pharmacotherapy* 2003;23:686-689.
30. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69:4-14.
31. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. *Pharmacoepidemiol Drug Saf* 1992;1:347-349.
32. Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. *Br J Clin Pharmacol* 1997;44:175-178.
33. Alonso A, Rodríguez LA, Logroscino G, Hernán MA. Gout and risk of Parkinson disease: a prospective study. *Neurology* 2007;69:1696-1700.
34. Reed MJ, Kloosterboer HJ. Tibolone: a selective tissue estrogenic activity regulator (STEAR). *Maturitas* 2004;48(suppl 1):S4-S6.
35. Biglia N, Maffei S, Lello S, Nappi RE. Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials. *Gynecol Endocrinol* 2010;26:804-814.

