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Psoriasis, Psoriati Arthritis, and Risk of Gout in U.S. Men and Women

Joseph F. Merola[*,1,2], **Shaowei Wu**[*,1,7], **Jiali Han**[1,3,4,5], **Hyon K. Choi**[3,6], and **Abrar A. Qureshi**[1,3,7]

[1]Department of Dermatology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[2]Department of Medicine, Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

[4]Department of Epidemiology, Fairbanks School of Public Health, Simon Cancer Center, Indiana University, Indianapolis, Indiana, USA

[5]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA

[6]Section of Rheumatology and the Clinical Epidemiology Unit, Boston University School of Medicine, Boston, Massachusetts, USA

[7]Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA

Abstract

Objective—Individuals with psoriasis have been found to have increased blood levels of uric acid. However, there is no prospective data on the association between psoriasis and uric acid levels and subsequent development of gout. In this study, we examined the risk of gout among individuals with psoriasis and psoriatic arthritis (PsA) in two cohorts of men and women, the Health Professionals Follow-up Study (HPFS) (1986-2010) and Nurses' Health Study (NHS) (1998-2010).

Corresponding author: Abrar A. Qureshi, MD, MPH, Department of Dermatology, Warren Alpert Medical School, Brown University, 339 Eddy St, Providence, RI 02903 USA, T (401) 444-7137, F (401) 444-7105, abrar_qureshi@brown.edu.
*Authors contributed equally to the manuscript.

Contributors: JFM, SW, AAQ have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors were involved in preparing this manuscript. JFM, SW, JH, AAQ were responsible for the overall study design, data analysis and interpretation of data, and wrote the initial draft of the manuscript. All authors contributed to the critical revision of the manuscript.

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Ethics approval: This study was approved by the Institutional Review Board of Brigham and Women's Hospital (IRB Protocol Title: Psoriasis in large cohort studies, IRB Protocol Number: 2006P001156).

Methods—A total of 27,751 men and 71,059 women were included in the analysis. Lifetime history of physician-diagnosed incident psoriasis and PsA was confirmed by validated supplementary questionnaires. Incident gout diagnoses were confirmed based on the American College of Rheumatology survey criteria. We used Cox proportional hazards models controlling for potential risk factors to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs) of incident gout while simultaneously adjusting for several common risk factors.

Results—We documented 2,217 incident cases of gout during the follow-up. Psoriasis was associated with an increased risk of subsequent gout with a multivariate HR of 1.71 [95% confidence interval (CI), 1.36-2.15] in the pooled analysis. Risk of gout was substantially augmented among those with psoriasis and concomitant PsA [pooled multivariate HR: 4.95, (95% CI, 2.72 to 9.01)] when compared to participants without psoriasis.

Conclusions—In this prospective study of US women and men, psoriasis and PsA were associated with an increased risk of gout.

Keywords

gout; psoriasis; psoriatic arthritis; uric acid

Introduction

Psoriasis is a chronic inflammatory skin disorder which may occur in isolation or together with psoriatic arthritis (PsA), an inflammatory seronegative arthritis. Psoriasis is a common disorder with a prevalence of 2-3%, and PsA has been reported to occur in upwards of 25% of those with a diagnosis of psoriasis [1-3]. Gout is an inflammatory crystal arthropathy caused by persistent hyperuricemia (elevation of serum uric acid levels) that deposits uric acid in the joints and soft tissues around the joints, leading to painful episodes of crystal-induced arthritis. The condition can become chronic and lead to joint erosions, damage and marked disability [4]. PsA and gout may occur in the same individual, sometimes concurrently, in those with a history of psoriasis [56].

Several studies have shown a correlation between psoriasis, PsA and elevated serum uric acid levels [7-10], with one study further demonstrating a correlation between uric acid levels and psoriasis severity on the psoriasis activity and severity index (PASI) [7]. Elevated serum uric acid levels correlate with systemic inflammatory markers and, in psoriasis, may be related to increased cell turnover as well as the known systemic inflammation associated with the disease state [911]. Uric acid has been shown to stimulate inflammatory pathways resulting in the secretion of chemokines and inflammatory markers [1213]. Coexisting psoriasis and gout has been documented in several case reports; however, no prospective data about the relation between a prior history of psoriasis and the risk of subsequent gout are available to date [14-17].

To address this issue, we investigated the association between psoriasis, with and without concomitant arthritis, and risk of subsequent gout using data from a cohort of men in the Health Professionals Follow-up Study (HPFS) and a cohort of women in the Nurses' Health Study (NHS).

Methods

Study population

Study participants were from 2 cohorts, the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS). The HPFS was established in 1986 when 51,529 male health professionals between the ages of 40 to 75 completed a baseline questionnaire. Information on medical history and lifestyle factors was collected biennially via mailed questionnaires in the two cohorts since baseline. The NHS was established in 1976 when 121,701 married female registered nurses ages 30-55 in the US completed a baseline questionnaire regarding their medical history and lifestyle risk factors. This study was approved by the Institutional Review Board of Brigham and Women's Hospital. The participants' completion and return of the self-administered questionnaires were considered as informed consent.

Assessment of exposures (psoriasis and psoriatic arthritis)

In 2008, we queried cohort participants about physician-diagnosed psoriasis and the diagnosis date in the HPFS (before 1986, 1986–1990, 1991–1995, 1996–2000, 2001–2004, or 2005 or later) and NHS (1997 or before, 1998–2001, 2002–2005, 2006–2007 or 2008). We confirmed self-reported psoriasis using the Psoriasis Screening Tool (PST) questionnaire, which inquired about the type of clinicians making the diagnosis and phenotypes [18]. A pilot study showed a sensitivity of 99% and a specificity of 94% for PST in psoriasis screening [18]. Diagnoses of psoriasis with concomitant PsA were confirmed using psoriatic arthritis screening and evaluation (PASE) questionnaire, which includes a symptom scale with seven items and a function scale with eight items [19]. Women chose one of five categories relating to agreement (strongly agree to strongly disagree) for each item. A total score of 47 or greater has been shown to identify PsA with a high sensitivity and specificity in our pilot studies as well as in cohort PsA diagnosis validation [18-20]. PASE has good test–retest reliability [21].

Assessment of outcome (gout)

We ascertained incident cases of gout using the American College of Rheumatology gout survey criteria, as previously described [922-24]. In HPFS, the participants were asked biennially since baseline whether they had received a physician diagnosis of gout and, if so, the date of first occurrence. In the NHS, the participants were asked for diagnoses of incident gout in 1982, 1984, 1986, 1988, 2002, and biennially thereafter. Starting in 2001, we mailed a supplementary questionnaire to participants with self-reported incident gout diagnosed during the follow-up to confirm the report and to ascertain whether the cases met the American College of Rheumatology gout survey criteria [25]. The primary end point in this study was incident cases of gout that met 6 or more of the 11 gout criteria (more than one attack of acute arthritis, maximum inflammation developed within one day, oligoarthritis attack, redness observed over joints, painful or swollen first metatarsophalangeal joint, unilateral first metatarsophalangeal joint attack, unilateral tarsal joint attack, tophus, hyperuricemia, asymmetric swelling within a joint, and complete termination of an attack) [923-26]. The overall response rate for the supplementary gout questionnaire was around 80% in both cohorts [924]. Two board-certified rheumatologists

reviewed the medical records from a sample of 76 men and 56 women in 2001. Of the76 men, 26 (34%) did not have relevant and complete records. Among the remaining 50 men, the rate of concordance between the diagnosis of gout according to the criteria of the American College of Rheumatology and the diagnosis of gout according to our review of the medical records was 94% (47 of 50) [9]. The concordance rate was similar in women (91%, 51/56) [24].

Covariates—Information on weight, smoking, diuretics use, aspirin use, and personal histories of type 2 diabetes and hypertension, and menopausal status and postmenopausal hormones use (for women) was collected biennially during the follow-up. Height was reported at cohort baseline. Body mass index was calculated as weight in kilograms divided by height in meters squared for each follow-up period. Physical activity was assessed biennially in the HPFS and in 1998, 2000, 2004 and 2008 in the NHS. Information on dietary intake was collected using a validated food-frequency questionnaire, and was available in 1986, 1990, 1994, 1998, 2002, and 2006 in the HPFS, and in 1998, 2002, and 2006 in the NHS [27-29].

Statistical analysis

Participants who did not respond to the psoriasis questions in 2008 or self-reported psoriasis that occurred before the baseline were excluded from the analysis. A total of 27,751 men and 71,059 women were included in the present analysis, and they contributed person-years of follow-up from the return date of the baseline questionnaire to the diagnosis date of gout or the end of follow-up (June 1, 2010), whichever came first. We ensured that the exposure (psoriasis/PsA) occurred before the outcome (gout).

We used Cox proportional hazards analyses to estimate the age- and multivariate-adjusted relative risks (HRs) and 95% confidence intervals (CIs) for the association between history of psoriasis/PsA and risk of incident gout. Multivariate-adjusted HRs were calculated after adjusting for age, BMI, alcohol, physical activity, smoking status, hypertension, type 2 diabetes, diuretics use, aspirin use, and daily average intakes of total vitamin C, coffee, total meats, seafood, total dairy foods, and free fructose. All the covariates were updated during follow-up to account for changes over time. For the pooled analysis, we tested the between-study heterogeneity and estimated the overall association from a random-effects model [30]. As a sensitivity analysis, we also examined the association of psoriasis history at baseline (1986 in the HPFS and 1998 in the NHS) and risk of indent gout during the entire follow-up. We further examined the association between history of other inflammatory arthritis (rheumatoid arthritis) and non-inflammatory arthritis (osteoarthritis) and risk of incident gout, and between history of gout and risk of incident psoriasis/PsA. All statistical analyses were performed using Statistical Analysis System software (SAS, version 9.2; SAS Institute Inc, Cary, NC). All statistical tests were 2-tailed, and the significance level was set at $P<0.05$.

Results

We documented a total of 2,217 incident cases of gout during the follow-up (1,368 cases in men and 849 cases in women, accounting for 4.9% men and 1.2% women included in the

study). There were 292 men and 1,329 women reported psoriasis at baseline. An additional 332 men and 1,002 women reported psoriasis during the follow-up. The baseline characteristics of study participants are shown in Table 1. Participants with psoriasis appeared to have higher BMIs, higher prevalence of smoking, hypertension, type 2 diabetes, and diuretics medication. Dietary factors were generally similar between those with psoriasis and without psoriasis.

Among participants who self-reported psoriasis, the multivariate-adjusted HRs for gout were 1.79 (95% CI: 1.30, 2.47) in men, 1.63 (95% CI: 1.17, 2.27) in women, and 1.71 (95% CI: 1.36, 2,15) in the pooled analysis (Table 2). Consistent with our results among self-reported psoriasis, we found that participants with confirmed psoriasis had a higher risk of gout in the pooled analysis (HR=1.95, 95% CI: 1.02, 3.75). The multivariate HR appeared to be higher among men with confirmed psoriasis (HR=2.72, 95% CI: 1.75, 4.25) than among women with confirmed psoriasis (HR=1.40, 95% CI: 0.90, 2.19).

We further examined psoriasis without and with concomitant PsA and subsequent risk of gout (Table 3). Of note, the risk of incident gout was substantially elevated among those with psoriasis and concomitant PsA (pooled multivariate-adjusted HR=4.95, 95% CI: 2.72, 9.01). The increased risk of gout in association with psoriasis with concomitant PsA was consistent among men and women.

Sensitivity analysis examining the association of baseline psoriasis with risk of incident gout during the follow-up showed similar results with the primary analyses (Table S1 and Table S2). Among those who had a confirmed diagnosis of psoriasis at baseline, the multivariate HR for gout was 1.84 (95% CI: 1.09, 3.09) in the pooled analysis. Risk of incident gout was also substantially increased among those with psoriasis and concomitant PsA at baseline (pooled multivariate HR=5.23, 95% CI: 2.70, 10.1).

In contrast to the strong association between history of psoriasis and risk of gout, there was only a marginal association between history of rheumatoid arthritis and risk of gout (pooled multivariate HR=1.15, 95% CI: 0.99, 1.35) (Table S3), and a significant but much weaker association between history of osteoarthritis and risk of gout (pooled multivariate HR=1.15, 95% CI: 1.04, 1.26) (Table S4). Heterogeneity test suggested that the association between history of psoriasis and risk of gout was significantly different from that between rheumatoid arthritis (P=0.005 for heterogeneity) and gout and between osteoarthritis and gout (P=0.002 for heterogeneity).

Interestingly, the associations between history of gout and risk of incident psoriasis and PsA were also significant but smaller in magnitude as compared to those between history of psoriasis and PsA and risk of incident gout (Table S5). Specifically, the pooled multivariate HRs were 1.53 (95% CI: 1.18, 2.00) for psoriasis and 3.43 (95% CI: 1.63, 7.18) for PsA among those who had a history of gout.

Discussion

Our findings represent the first prospective evidence demonstrating that a prior history of psoriasis as well as PsA is associated with an increased risk of incident gout based on data

from two large US cohorts of men and women. The associations between psoriasis, PsA and incident gout were generally consistent in different statistical analyses, though the risk estimates appeared to be higher among men than in women. This may be associated with gender heterogeneity since more frequent and severe gout were reported among male than among females [31]. Overall the risk estimates were substantial and demonstrate a clear association between a prior history of psoriasis, with or without concomitant PsA, and incident gout.

Our group has previously reported on musculoskeletal pain presentation among psoriasis patients presenting to a combined dermatology-rheumatology clinic [56]. Psoriasis patients with new onset musculoskeletal complaints were diagnosed with PsA, osteoarthritis, crystal arthopathy including gout and combinations of these diagnoses [56]. Clinically, an awareness of the relationship between psoriasis, PsA, and gout therefore is particularly important when evaluating the psoriasis patient for possible inflammatory arthritis symptoms. In those individuals presenting with an asymmetric, inflammatory synovitis, our findings clearly highlight the need to consider inflammatory crystal arthopathy in the differential diagnosis of psoriasis patients presenting with an acutely inflamed joint(s). Several case reports and series have reported the diagnostic challenge and often-missed clinical presentation of concomitant psoriasis, PsA and gout [14-17].

Psoriasis is a common inflammatory skin disorder with reports of up to 25% of patients having concomitant PsA [1-3]. Psoriasis disease activity has been variably associated with elevated serum uric acid levels in several studies [7103233]. One recent study compared 119 psoriasis subjects to an equal number of matched controls and found statistically significant higher serum uric acid levels and higher prevalence of asymptomatic hyperuricemia among psoriasis subjects, and psoriasis was the strongest predictor of hyperuricemia after adjusting for age, sex and metabolic syndrome features [34]. Both psoriasis and PsA have been associated with elevated serum uric acid levels, which have been attributed at least in part to the purine metabolites of increased cell turnover as seen in psoriasis skin disease [911]. Hyperuricemia has also been correlated with markers of systemic inflammation, including C-reactive protein (CRP) [35]. In one study, serum CRP and uric acid levels were increased among subjects with psoriasis (n=25) as compared to controls (n=50) [8]. CRP levels were up to 20-fold higher among those with psoriasis in this study, and serum uric acid levels were significantly higher compared to control groups, with nearly 25% of those with psoriasis having a uric acid level of more than 10 mg/dL. Among the psoriasis group, CRP decreased by nearly 50%, and a fall in uric acid was observed in nearly 80% of subjects, after 12 weeks of psoriasis treatment [8]. A cross-sectional study on the correlation of serum uric acid with psoriasis disease severity in 198 Korean patients found that serum uric acid in psoriasis patients is positively associated with PASI, extent of skin involvement and BMI for both genders independently [7]. Elevated serum uric acid levels were present in 45% of PsA patients in one observational study [36]. While no definitive unifying mechanism exists, one may speculate about immunologic stimulation of cellular pattern recognition receptors, which may drive systemic inflammation in psoriasis via tissue injury response [37]. In gout this may be further driven by response to urate crystals (themselves a known damage-associated molecular pattern – ‘DAMP’) [37].

Psoriasis, PsA, hyperuricemia and gout have all been tied to the metabolic syndrome and positively associated with cardiovascular risk [38]. Among individuals with PsA, a significant correlation between serum uric acid levels and subclinical atherosclerosis was found as indicated by increased carotid intima-medial thickness [323339]. Onat et al. showed that elevated uric acid levels correlate with a pro-inflammatory state and high-density lipoprotein (HDL) dysfunction and that risk of coronary heart disease is independently predicted by elevated uric acid levels in non-diabetic men, modulated by the metabolic syndrome and gender [40]. Elevated uric acid (hyperuricemia), the direct cause of gout, has also been independently associated with the development of diabetes and essential hypertension and has been identified as an independent risk factor for all-cause and cardiovascular mortality [3841]. Cassano et al evaluated the role of serum uric acid in conditioning the association of psoriasis with the metabolic syndrome [42]. In their study, serum uric acid levels were significantly higher among psoriasis subjects than controls and their results indicated a trend towards a correlation between serum uric acid levels and the risk of metabolic syndrome in psoriasis patients. Despite the metabolic syndrome risk factors commonly shared by those with gout and psoriasis, our findings demonstrated an independent association between psoriasis and gout even after adjusting for BMI, hypertension, diabetes, smoking and relevant dietary factors.

Strengths of our study include the use of two well-characterized, large, prospective cohorts to evaluate the association between psoriasis, psoriatic arthritis and incident gout. The exposures and outcomes of our study were confirmed by use of validated questionnaires, as described above. The development of gout, in the setting of hyperuricemia among those with psoriasis and/or psoriatic arthritis, is biologically plausible and supported by our data after adjusting for other known risk factors for gout in this population. The availability of detailed cohort follow-up information allowed us to control for a number of important confounders that may have influenced these associations.

We acknowledge some limitations of our study. While we accounted for multiple potential confounders known to be associated with gout, such as diet (e.g., seafood and fructose) and medication use (e.g., diuretics), it is possible that residual confounding may still remain. One recent study reported a lower sensitivity of PASE, raising the concern about possible misclassification of PsA cases [43]. Because PASE picks up individuals with active disease who are potentially more likely to have inflamed joints and increased systemic inflammation, it probably underestimates the number of PsA cases therefore leading to a conservative estimation of the association of interest.

In summary, our study found that among individuals with a prior history of psoriasis in two large cohorts of us men and women, there was an increased risk of incident gout.. The risk of gout was substantially augmented among those with psoriasis and concomitant PsA. The association between psoriasis, PsA, and gout appeared to be stronger in men than in women. These findings have important implications for clinical practice and for potential disease prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the study populations according to history of psoriasis[a]

	HPFS (1986-2010)		NHS (1998-2010)	
	No psoriasis	**Psoriasis**	**No psoriasis**	**Psoriasis**
No. of participants	27,459	292	69,730	1,329
Age, years, mean (SD)	50.5(8.1)	52.1(8.4)	63.0(6.8)	63.0(6.8)
White race, %	96.1	98.0	96.8	98.1
Body mass index, kg/m^2, mean (SD)	24.7(4.6)	25.0(4.6)	26.7(5.1)	27.7(5.7)
Physical activity, metabolic equivalent hrs/wk, mean (SD)	22.4(31.1)	24.6(37.4)	18.1(21.9)	16.4(19.8)
Current smoking, %	6.6	8.8	9.2	10.9
Hypertension, %	15.2	18.7	41.8	46.3
Type 2 diabetes, %	0.0	0.4	4.7	7.6
Diuretics use, %	5.9	7.4	10.5	13.9
Aspirin use, %	26.2	24.5	52.0	51.1
Menopausal status, %	-	-	93.0	93.1
Postmenopausal hormones use,[b] %	-	-	52.4	50.2
Alcohol intake, g/d, mean (SD)	10.8(14.3)	9.8(14.5)	5.1(8.9)	5.3(10.2)
Total energy, kcal/d, mean (SD)	1998(615)	2035(610)	1715(427)	1740(430)
Total vitamin C, mg/d, mean (SD)	415(451)	436(444)	352(312)	344(303)
Coffee intake, servings/d, mean (SD)	2.2(1.9)	2.3(2.0)	2.8(1.6)	2.9(1.6)
Total meat intake, servings/d, mean (SD)	1.5(0.8)	1.5(0.8)	1.4(0.5)	1.5(0.5)
Seafood intake, servings/d, mean (SD)	0.4(0.3)	0.4(0.3)	0.3(0.2)	0.3(0.2)
Total dairy intake, servings/d, mean (SD)	1.9(1.4)	2.0(1.3)	2.0(1.0)	2.1(1.0)
Free fructose, % of energy, mean (SD)	5.1(2.2)	5.0(2.2)	5.3(1.8)	5.2(1.7)

[a] Other than No. of participants and age, all variables are standardized to the age distribution of the study population.

[b] Percentages among postmenopausal women.

Table 2

Hazard ratios of incident gout according to a diagnosis of psoriasis

	Cases of gout (primary outcome)	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)
HPFS				
No psoriasis	1,329	634,372	1.00	1.00
Self-reported psoriasis	39	9,277	1.97 (1.43, 2.71)	1.79 (1.30, 2.47)
Confirmed psoriasis	20	3,184	3.01 (1.93, 4.68)	2.72 (1.75, 4.25)
NHS				
No psoriasis	812	813,880	1.00	1.00
Self-reported psoriasis	37	19,098	2.02 (1.45, 2.81)	1.63 (1.17, 2.27)
Confirmed psoriasis	20	13,070	1.64 (1.05, 2.56)	1.40 (0.90, 2.19)
HPFS/NHS				
No psoriasis	2,141	1,448,252	1.00	1.00
Self-reported psoriasis	76	28,375	2.00 (1.59, 2.51)	1.71 (1.36, 2.15)
Confirmed psoriasis	40	16,254	2.22 (1.22, 4.03)	1.95 (1.02, 3.75)

[a]Hazard ratios were further adjusted for BMI (<24.9, 25-29.9, 30-34.9, or ≥35 kg/m^2), alcohol intake (no, <5.0, 5.0-9.9, 10.0-19.9, or ≥20.0 g/d), physical activity (quintiles), smoking status (never, past, current smoking with 1-14, 15-24, or ≥25 cigarettes/day), hypertension (yes/no), type 2 diabetes (yes/no), diuretics use (yes/no), aspirin use (yes/no), and daily average intakes of total energy, total vitamin C, coffee, total meats, seafood, total dairy foods, and free fructose (all in quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormones use (premenopausal, postmenopausal never, past, or current use).

Table 3

Hazard ratios of incident gout according to a confirmed diagnosis of psoriasis without and with PsA

	Cases of gout (primary outcome)	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)
HPFS				
No psoriasis	1,329	634,372	1.00	1.00
Psoriasis only	14	2,743	2.44 (1.44, 4.14)	2.23 (1.32, 3.79)
Psoriasis with PsA	6	441	6.67 (2.97, 15.0)	5.60 (2.49, 12.6)
NHS				
No psoriasis	812	813,880	1.00	1.00
Psoriasis only	15	11,863	1.34 (0.80, 2.23)	1.14 (0.69, 1.91)
Psoriasis with PsA	5	1,207	5.01 (2.08, 12.1)	4.28 (1.77, 10.4)
HPFS/NHS				
No psoriasis	2,141	1,448,252	1.00	1.00
Psoriasis only	29	14,606	1.80 (1.00, 3.25)	1.59 (0.83, 3.07)
Psoriasis with PsA	11	1,648	5.85 (3.22, 10.6)	4.95 (2.72, 9.01)

[a]Hazard ratios were further adjusted for BMI (<24.9, 25-29.9, 30-34.9, or ≥35 kg/m^2), alcohol intake (no, <5.0, 5.0-9.9, 10.0-19.9, or ≥20.0 g/d), physical activity (quintiles), smoking status (never, past, current smoking with 1-14, 15-24, or ≥25 cigarettes/day), hypertension (yes/no), type 2 diabetes (yes/no), diuretics use (yes/no), aspirin use (yes/no), and daily average intakes of total energy, total vitamin C, coffee, total meats, seafood, total dairy foods, and free fructose (all in quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormones use (premenopausal, postmenopausal never, past, or current use).