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Hypertension, Anti-Hypertensive Medication Use, and Risk of Psoriasis

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Abstract

Importance—Individuals with psoriasis are shown to have an elevated risk of hypertension, and anti-hypertensive medications, especially beta-blockers, have been linked to psoriasis development. However, the association of prior existing hypertension and anti-hypertensive medications with risk of incident psoriasis has not been accessed using prospective data.

Objective—To evaluate the association of hypertension and anti-hypertensive medications with risk of psoriasis based on data from the Nurses' Health Study (NHS).

Design—Prospective cohort study (1996–2008).

Setting—Nurses' Health Study.

Participants—A total of 77,728 U.S. women who provided biennially updated data on hypertension and anti-hypertensive medications.

Main Outcome and Measure—Physician-diagnosed psoriasis.

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Results—We documented a total of 843 incident psoriasis cases during 1,066,339 person-years of follow-up. Compared to normotensive women, women with hypertension duration more than 6 years were at a higher risk of developing psoriasis [HR=1.27, 95% confidence interval (CI), 1.03–1.57]. In stratified analysis, the risk of psoriasis was higher among hypertensive women without medication [HR=1.49, 95% CI, 1.15–1.92] and among hypertensive women with current medication [HR=1.31, 95% CI, 1.10–1.55] when compared to normotensive participants without medication. Compared to women who never used beta-blockers, the multivariate HRs for psoriasis were 1.11 (95% CI, 0.82–1.51) for women who regularly used 1–2 years, 1.06 (95% CI, 0.79–1.40) for 3–5 years, and 1.39 (95% CI, 1.11–1.73) for 6 or more years (*P* for trend=0.009). There was no association between other individual anti-hypertensive drugs and risk of psoriasis.

Conclusions—Long-term hypertensive status is associated with an increased risk of psoriasis. Long-term regular use of beta-blockers may also increase the risk of psoriasis.

Introduction

Psoriasis is an immune-mediated chronic systemic disease that affects about 3% of the U.S. population and over 125 million patients worldwide[1–4]. Psoriasis has been associated with significant morbidity and substantial economic costs to both patients and the health care system[5]. Previous studies have demonstrated that psoriasis is associated with an increased risk of cardiovascular disease[6–8], and individuals with psoriasis are also at an increased risk of hypertension, a well-known risk factor of cardiovascular disease[9–15]. However, most of the previous studies are cross-sectional or case-control studies and thus limit clear investigation on the temporal relationship between psoriasis and hypertension. Based on the evidence that both psoriasis and hypertension may increase the risk of cardiovascular disease, and previous reports that individuals with psoriasis are more likely to have concurrent hypertension, it is reasonable to infer that hypertension may also be associated with the development of psoriasis. To our knowledge, no prospective data on the risk of incident psoriasis associated with hypertension is available to date.

In addition, medications for treating some comorbidities have been frequently reported to induce or exacerbate psoriasis, among which anti-hypertensive medications, especially beta-blockers, have received increasing attention[16–21]. However, findings from a previous large case-control study did not find a substantially altered risk of psoriasis for several widely used anti-hypertensive drugs [e.g., diuretics, beta-blockers, calcium-channel blockers, and angiotensin-converting enzyme (ACE) inhibitors][16]. Currently prospective data on the association between anti-hypertensive medications and risk of psoriasis are sparse, and whether there is a casual relationship between these drugs and psoriasis incidence needs further examination.

To address the hypothesis that prior histories of hypertension and related anti-hypertensive medication use may increase the risk of psoriasis, we investigated these associations based on prospective data from a large cohort in U.S. women, the Nurses' Health Study (NHS).

Methods

Study Population

The NHS was established in 1976 when 121,701 married, registered, female nurses aged 30–55 years and residing in the United States at the time of enrollment responded to a baseline questionnaire that included questions about their medical history and lifestyle risk factors. Information on risk factors and health data was updated by biennially mailed questionnaires and a response rate exceeding 90% has been achieved during each follow-up period. The institutional review board of Partners Health Care System approved this study. The completion and return of the self-administered questionnaire was considered as informed consent.

Case Ascertainment

In 2008, NHS participants responded to an item on the questionnaire that asked about any history of clinician-diagnosed psoriasis and the date of diagnosis (1997 or before, 1998–2001, 2002–2005, 2006–2007, or 2008). A total of 2,477 participants reported having been diagnosed with psoriasis, and 888 of those diagnoses occurred after 1997. We confirmed a subset of patients with self-reported psoriasis using the Psoriasis Screening Tool (PST) questionnaire, which inquires about the type of clinicians making the diagnosis and phenotypes[22]. A pilot study using the PST showed 99% sensitivity and 94% specificity for psoriasis screening[22]. The confirmation rate of self-reports reached 92%.

Assessment of Hypertension

Personal history of physician-diagnosed hypertension was assessed at cohort inception (1976) and updated every 2 years thereafter using biennial questionnaires. Once a participant reported physician-diagnosed hypertension, she was considered to have a positive history of hypertension until the end of the follow-up. Self-reported hypertension has a high accuracy in the cohort participants, with 100% self-reports confirmed by medical records[23].

Assessment of Anti-hypertensive Medications

Regular anti-hypertensive medication use during the past 2 years was assessed in the biennial questionnaires. Individual drugs included in the follow-up questionnaires were thiazide diuretics (1980, 1982, 1988, 1994, 1996, 1998, 2000, 2002, 2004, 2006); beta-blockers, calcium-channel blockers, other anti-hypertensive drugs (1988, 1994, 1996, 1998, 2000, 2002, 2004, 2006); and ACE inhibitors (1988, 1996, 1998, 2000, 2002, 2004, 2006).

Covariates

Information on weight, smoking, cardiovascular disease (including miocardial infarction and stroke), type 2 diabetes, hypercholesterolemia, menopausal status, postmenopausal hormones use, non-steroidal anti-inflammatory drugs (NSAIDs) use, multi-vitamins supplement, was collected biennially through the follow-up. Height was assessed in 1976. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Alcohol intake was available in 1994, 1998, 2002, and 2006. Physical activity was assessed in 1996, 1998, 2000, and 2004.

Statistical Analysis

Women who reported a baseline history of psoriasis were excluded from the analysis. Person-years of follow-up for each participant were calculated from the return date of baseline questionnaire to the date of diagnosis of psoriasis, date of death, time of loss to follow-up or the end of follow-up, whichever came first. Means with standard deviations (SD) for continuous characteristics and proportions for categorical characteristics were calculated by history of hypertension at baseline.

Cox proportional hazards analyses stratified by age and 2-year follow-up intervals were used to estimate the age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incident psoriasis associated with hypertension and anti-hypertensive medications. Selection of covariates in multivariate models was based on current knowledge on risk factors of psoriasis. Multivariate HRs were calculated after adjusting for age, BMI (<24.9, 25–29.9, 30–34.9, and ≥35 kg/m^2), alcohol intake (0, <5, 5–9.9, or ≥10 g/d), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, and ≥27 metabolic equivalent hours/week), smoking (never, past, current smoking with 1–14, 15–24, or ≥25 cigarettes/day), cardiovascular disease, type 2 diabetes, hypercholesterolemia, postmenopausal hormones use, NSAIDs use, and multi-vitamins supplement. Analyses for regular anti-hypertensive medication use or hypertension were additionally adjusted for hypertension or anti-hypertension medications in fully-adjusted models, respectively. All variables were coded as time-varying variables to account for potential changes over the follow-up. To differentiate the effect of hypertension from those of anti-hypertensive medications, we stratified the analysis for hypertension by status of regular anti-hypertensive medication use. We further evaluated the effects of duration of hypertension and anti-hypertensive medications (1–2 years, 3–5 years, and ≥6 years). We selected the duration of 6 years as the cutoff because we have a follow-up of 12 years (1996–2008). All statistical analyses were conducted 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 843 incident psoriasis cases among 77,728 participants over 1,066,339 person-years of follow-up. Table 1 shows the baseline characteristics of the study population. Women with hypertension tended to be older, had higher BMIs and proportionately higher prevalence rates of cardiovascular disease, type 2 diabetes and hypercholesterolemia, and were less physically active than those without hypertension.

Hypertension was associated with an elevated risk of psoriasis in multivariate-adjusted models (HR=1.21, 95% CI: 1.04–1.40) (Table 2). This association became insignificant with additional adjustment for anti-hypertensive medication use (HR=1.13, 95% CI: 0.93–1.37). However, there was a higher risk of psoriasis among women with hypertension duration of 6 or more years (fully-adjusted HR=1.27, 95% CI: 1.03–1.57) as compared to normotensive women (P for trend=0.03). In stratified analysis, we found a higher risk of psoriasis among hypertensive women without medication (HR=1.49, 95% CI, 1.15–1.92) and among hypertensive women with current medication (HR=1.31, 95% CI, 1.10–1.55) when compared to normotensive women without medication.

Analyses for anti-hypertensive medications suggest an association between regular anti-hypertensive medication use and risk of psoriasis (multivariate HR=1.19, 95% CI: 1.03–1.37) which became insignificant with additional adjustment for hypertension (fully-adjusted HR=1.10, 95% CI, 0.92–1.32) (Table 4). Among individual anti-hypertensive drugs, there was a marginal association between regular use of beta-blockers and risk of psoriasis in the multivariate model (multivariate HR=1.18, 95% CI, 0.99–1.40) which also became null with additional adjustment for hypertension (fully-adjusted HR=1.12, 95% CI, 0.93–1.34). Interestingly, this association persisted in a duration-dependent manner with a higher risk of psoriasis found among regular beta-blockers users with use duration of 6 or more years (HR=1.39, 95% CI: 1.11–1.73, *P* for trend=0.009) (Table 5). In contrast, there was no association between other individual anti-hypertensive drugs and risk of psoriasis.

Sensitivity analyses were performed among women without baseline cardiovascular disease and type 2 diabetes, and results were essentially changed (eTable 1 to eTable 3).

Discussion

Our study examined the association between hypertension and related anti-hypertensive medication use and risk of incident psoriasis using prospective data from a large cohort of U.S. women. After adjusting for a number of potential confounders, we found that a prior history of hypertension was associated with an increased risk of psoriasis among women with hypertension duration of 6 or more years. Specifically, both hypertensive women without medication and with current medication were more likely to develop psoriasis when compared to normotensive women without medication. Among the individual anti-hypertensive drugs, only beta-blockers were associated with an increased risk of psoriasis after regular use for an extended period of 6 or more years. In sensitivity analyses among women without baseline cardiovascular disease and type 2 diabetes, most findings as stated above were only slightly attenuated and remained statistically significant.

Psoriasis is a disease characterized by T-cell-mediated hyperproliferation of keratinocytes and inflammatory processes[3], and is classified as a T helper 1 (Th1) disease[24]. Hypertension is also characterized by increased oxidative stress and inflammation[25], and immune mechanisms are shown to involve in the development of hypertension with different T cells (Th1 and Th2 lymphocytes, T regulatory cells, etc.) participating respectively as pro- and anti-inflammatory cells[26]. Population-based studies have shown that chronic inflammation is associated with an increased risk of hypertension[27,28]. Therefore, hypertension may be associated with psoriasis development because of the shared inflammatory pathways. In the present study, we found that women with hypertension duration of 6 or more years were more likely to develop psoriasis whereas the risk was not apparent among women with hypertension duration of less than 6 years. This finding is consistent with the existing concept that psoriasis is associated with a chronic inflammatory state[1]. Hypertensive participants with longer disease durations may have a greater possibility to develop later on psoriasis because of the long-lasting increased levels of systemic oxidative stress and inflammation[25,26].

In addition, overall hypertension was associated with an increased risk of psoriasis in the multivariate model, and this association attenuated and became insignificant after additionally adjusting for anti-hypertensive medication use (Table 2). Interestingly, overall anti-hypertension medication use was also associated with an increased risk of psoriasis in the multivariate model, and this association attenuated and became insignificant after additionally adjusting for hypertension (Table 4). The results suggested that both hypertension and anti-hypertensive medication use may be associated with the development of psoriasis, though neither of them was associated with the risk individually. Stratified analyses gave a better overview on the relationship between hypertension, anti-hypertensive medication use, and risk of psoriasis. The risk of psoriasis associated with hypertension appeared to be specific to hypertensive women without medication and with current medication, and appeared to be specific to women with long-term duration of hypertension or anti-hypertensive medication use over 6 years. Therefore, special attention on psoriasis screening may be needed for hypertensive patients with long-term duration of hypertension and related anti-hypertensive medication in clinical practices.

A number of previous studies including case reports and case-control analyses have reported a possible association between induction/exacerbation of psoriasis and exposure to drugs such as beta-blockers, calcium-channel blockers, ACE inhibitors, lithium, and NSAIDs[16–21,29]. However, prospective data from population-based studies have not been available to date. Our detailed analyses on individual anti-hypertensive drugs revealed that only beta-blockers were associated an increased risk of psoriasis after regular use of 6 or more years. Therefore, it is likely that the association between hypertension and psoriasis among women with current medication was driven by beta-blockers. Previous case-control and case-crossover studies have shown evidence for the association between beta-blockers and psoriasis[17,20], though inconsistent results also exist[16]. Association of beta-blockers with risk of psoriasis has biological plausibility. Beta-blockers can block beta-adrenergic receptors in the skin, preventing beta-agonists from binding to the receptors. This subsequently leads to a decrease in cellular levels of cyclic adenosine monophosphate, an intracellular messenger in a pathway that simulates proteins responsible for differentiation and inhibition of proliferation[29]. A decrease of cyclic adenosine monophosphate further leads to a decrease in intracellular calcium and consequently increased cellular proliferation and lack of differentiation as seen in psoriasis[30]. Additionally, it has been reported that beta-blockers increase phosphorylation in T cells in psoriasis, which may be relevant to intracellular levels of calcium[31]. The results of blockade are marked by excessive release of enzymes from lymphocytes, neutrophils, and macrophages, which is believed to be responsible for the presence of hyperproliferation and psoriasiform change[32]. The blockade of beta-adrenergic receptors has been implicated in the pathogenesis of beta-blockers-provoked psoriasis[29].

Other widely used anti-hypertensive drugs, including thiazide diuretics, calcium-channel blockers, and ACE inhibitors, were not found to be associated with risk of psoriasis in the present study. Although analyses according to duration of regular medication use suggest trends towards increasing risk of psoriasis for these drugs, the risk estimates were largely insignificant. Therefore, these anti-hypertensive drugs may not be able to alter an individual’s risk of developing psoriasis on the basis of existing hypertensive status. It is

also possible that the previous findings on the induction or exacerbation of psoriasis associated with certain anti-hypertensive drugs were actually contributed by existing hypertensive status in part.

Our study has several strengths. First, we collected detailed, updated information on hypertension and anti-hypertensive medication use through the cohort follow-up, and thus avoided the potential recall bias of case-control studies which collected exposure data after incidence of psoriasis. Second, we were able to examine the effects of several widely used anti-hypertensive drugs (including thiazide diuretics, beta-blockers, calcium-channel blockers, and ACE inhibitors) separately over the cohort follow-up. Third, our participants were all registered health professionals, and the accuracy of self-reported hypertension and anti-hypertensive medication use is likely to be high as demonstrated previously[23]. Finally, we were able to control for a number of potential confounders which may have affected the association of interest based on detailed follow-up information.

Several study limitations should be noted when interpreting the results. First, survivorship bias would be a major concern on the selection of participants given that the psoriasis question was asked in 2008. We cannot obtain information from participants with psoriasis who died before the enquiry of outcome disease. However, the health-care–related professional background of our participants was reassuring and the relatively higher accuracy of their reports would have tended to cause nondifferential misclassification of psoriasis, resulting in a conservative estimate of HRs. In addition, we compared the baseline characteristics of women who responded to the 2008 psoriasis question with those who did not respond, and found that their main characteristics (e.g., age, BMI) were similar[33]. Therefore, it is unlikely that our results would change greatly due to response bias. Second, we only assessed regular anti-hypertensive medication use over the follow-up but did not have the drug dosage information which may be critical in determining the extent of disease risk. Third, our study participants were mostly white older women, and thus may limit generalizing the results to other gender and ethnicities.

In conclusion, our study provides evidence that a prior history of long-term hypertension over 6 years was associated with an increased risk of psoriasis. Among the individual anti-hypertensive drugs investigated in the study, only beta-blockers were associated with an increased risk of psoriasis after long-term regular use for 6 or more years. These findings provide novel insights into the relationship between hypertension, anti-hypertensive medications and psoriasis. However, further work is necessary to confirm our findings and elucidate the biological mechanisms underlying these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics[a] of the study population by history of hypertension

	No hypertension (n=47,897)	Hypertension (n=29,831)[b]
Age, years, mean (SD)	60.1(6.8)	62.6(6.7)
White race, %	97.3	95.5
Body mass index, kg/m^2, mean (SD)	25.5(4.5)	28.5(5.8)
Alcohol intake, g/d, mean (SD)	5.1(8.6)	4.8(9.2)
Physical activity, metabolic equivalent hrs/wk, mean (SD)	19.6(23.2)	16.4(21.0)
Current smoking, %	11.8	9.2
Cardiovascular disease, %	0.9	2.6
Type 2 diabetes, %	5.0	13.7
Hypercholesterolemia, %	45.9	63.9
Postmenopausal hormones use, %	43.0	43.6
NSAIDs use, %	52.8	59.7
Multi-vitamins supplement, %	52.8	51.5

Abbreviation: SD, standard deviation.

[a] All variables other than age have been standardized to the age distribution of the study population.

[b] Median hypertension duration time was 11 years.

Table 2

Hazard ratios of psoriasis according to hypertension

	Cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)	Multivariate-adjusted HR[b] (95% CI)
Hypertension					
No	366	540,694	1.00	1.00	1.00
Yes	477	525,645	1.34 (1.17–1.54)	1.21 (1.04–1.40)	1.13 (0.93–1.37)
Hypertension duration					
No	366	540,694	1.00	1.00	1.00
1–2 years	39	58,959	0.97 (0.70–1.35)	0.91 (0.65–1.27)	0.93 (0.65–1.33)
3–5 years	61	85,435	1.06 (0.80–1.39)	0.97 (0.74–1.28)	0.97 (0.71–1.31)
≥ 6 years	377	381,251	**1.47 (1.27–1.71)**	**1.32 (1.13–1.54)**	**1.27 (1.03–1.57)**
P for trend			<0.001	<0.001	0.03

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Simultaneously adjusted for age, body mass index, alcohol intake, physical activity, smoking status, cardiovascular disease, type 2 diabetes, hypercholesterolemia, postmenopausal hormones use, non-steroidal anti-inflammatory drugs use, and multi-vitamins supplement.

[b] Additionally adjusted for anti-hypertensive medication use.

Table 3

Hazard ratios of psoriasis according to hypertension stratified by status of anti-hypertensive medication use

	Cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)
No hypertension and no medication	282	445,705	1.00	1.00
Hypertension with no medication	77	78,445	**1.57 (1.22–2.02)**	**1.49 (1.15–1.92)**
Hypertension with past medication	38	55,883	1.10 (0.78–1.54)	0.97 (0.69–1.37)
Hypertension with current medication	359	386,026	**1.49 (1.27–1.75)**	**1.31 (1.10–1.55)**

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Simultaneously adjusted for age, body mass index, alcohol intake, physical activity, smoking status, cardiovascular disease, type 2 diabetes, hypercholesterolemia, postmenopausal hormones use, non-steroidal anti-inflammatory drugs use, and multi-vitamins supplement.

Table 4

Hazard ratios of psoriasis according to status of regular anti-hypertensive medication use

	Cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)	Multivariate-adjusted HR[b] (95% CI)
Overall anti-hypertensive medication					
Non-regular users	442	632,210	1.00	1.00	1.00
Regular users	401	434,129	1.32 (1.15–1.52)	1.19 (1.03–1.37)	1.10 (0.92–1.32)
Thiazide diuretics					
Non-regular users	710	923,449	1.00	1.00	1.00
Regular users	133	142,890	1.21 (1.00–1.45)	1.09 (0.90–1.32)	1.02 (0.83–1.24)
Beta-blockers					
Non-regular users	684	900,025	1.00	1.00	1.00
Regular users	159	166,314	1.25 (1.05–1.49)	1.18 (0.99–1.40)	1.12 (0.93–1.34)
Calcium-channel blockers					
Non-regular users	747	968,410	1.00	1.00	1.00
Regular users	96	97,929	1.26 (1.01–1.56)	1.15 (0.93–1.43)	1.09 (0.87–1.35)
ACE inhibitors					
Non-regular users	733	953,227	1.00	1.00	1.00
Regular users	110	113,112	1.26 (1.03–1.54)	1.16 (0.94–1.42)	1.08 (0.87–1.33)

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; HR, hazard ratio.

[a] Simultaneously adjusted for age, body mass index, alcohol intake, physical activity, smoking status, cardiovascular disease, type 2 diabetes, hypercholesterolemia, postmenopausal hormones use, non-steroidal anti-inflammatory drugs use, and multi-vitamins supplement.

[b] Additionally adjusted for hypertension.

Table 5

Hazard ratios of psoriasis according to duration of regular anti-hypertensive medication use

	Cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)	Multivariate-adjusted HR[b] (95% CI)
Overall anti-hypertensive medication					
0	359	524,150	1.00	1.00	1.00
1–2 y	52	73,920	1.03 (0.77–1.38)	0.94 (0.70–1.27)	0.87 (0.63–1.19)
3–5 y	87	104,463	1.21 (0.96–1.54)	1.10 (0.87–1.40)	1.02 (0.78–1.32)
≥ 6 y	286	293,094	1.43 (1.22–1.68)	1.26 (1.06–1.49)	1.15 (0.93–1.41)
P for trend			<0.001	0.01	0.16
Thiazide diuretics					
0	551	758,389	1.00	1.00	1.00
1–2 y	49	49,682	1.37 (1.02–1.84)	1.23 (0.92–1.66)	1.16 (0.85–1.57)
3–5 y	57	68,332	1.14 (0.87–1.50)	1.03 (0.78–1.35)	0.98 (0.74–1.29)
≥ 6 y	154	149,931	1.41 (1.18–1.69)	1.23 (1.02–1.49)	1.16 (0.95–1.41)
P for trend			<0.001	0.05	0.24
Beta-blockers					
0	592	799,129	1.00	1.00	1.00
1–2 y	48	52,453	1.24 (0.92–1.67)	1.17 (0.87–1.57)	1.11 (0.82–1.51)
3–5 y	55	62,679	1.18 (0.90–1.56)	1.11 (0.84–1.46)	1.06 (0.79–1.40)
≥ 6 y	105	91,251	**1.56 (1.26–1.92)**	**1.46 (1.18–1.81)**	**1.39 (1.11–1.73)**
P for trend			<0.001	0.001	0.009
Calcium-channel blockers					
0	670	877,735	1.00	1.00	1.00
1–2 y	34	35,865	1.23 (0.87–1.74)	1.14 (0.81–1.61)	1.07 (0.75–1.52)
3–5 y	58	48,415	1.55 (1.18–2.03)	1.43 (1.09–1.87)	1.34 (1.02–1.77)
≥ 6 y	51	53,360	1.25 (0.94–1.67)	1.13 (0.85–1.52)	1.08 (0.80–1.45)
P for trend			0.002	0.03	0.10
ACE inhibitors					
0	680	866,002	1.00	1.00	1.00
1–2 y	42	41,808	1.29 (0.94–1.77)	1.20 (0.87–1.65)	1.11 (0.80–1.53)
3–5 y	42	44,844	1.18 (0.86–1.61)	1.09 (0.80–1.49)	1.00 (0.72–1.37)

	Cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)	Multivariate-adjusted HR[b] (95% CI)
≥ 6 y	53	54,590	1.23 (0.93–1.64)	1.12 (0.84–1.49)	1.03 (0.77–1.38)
P for trend			0.03	0.23	0.64

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; HR, hazard ratio.

[a] Simultaneously adjusted for age, body mass index, alcohol intake, physical activity, smoking status, cardiovascular disease, type 2 diabetes, hypercholesterolemia, postmenopausal hormones use, non-steroidal anti-inflammatory drugs use, and multi-vitamins supplement.

[b] Additionally adjusted for hypertension.