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Psoriasis and risk of non-fatal cardiovascular disease in US women: a cohort study

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Abstract

Background—Psoriasis has been linked to cardiovascular co-morbidities in cross-sectional studies, but evidence regarding the association between psoriasis and incident cardiovascular disease (CVD) is limited.

Objective—To prospectively evaluate the association between psoriasis and risk of incident non-fatal CVD.

Methods—96,008 participants were included from the Nurses' Health Study II, and followed for 18 years. Information on physician-diagnosed psoriasis was obtained by self-report and diagnosis was confirmed by supplementary questionnaires. We included 2,463 individuals with self-reported psoriasis and a subsample of 1,242 with validated psoriasis. The main outcome was incident non-fatal CVD events (non-fatal myocardial infarction (MI) and non-fatal stroke), ascertained by biennial questionnaires and confirmed.

Results—During 1,709,069 person-years of follow-up, 713 incident non-fatal CVD events were confirmed. Psoriasis was associated with a significantly increased multivariate-adjusted hazard ratio (HR) of non-fatal CVD, 1.55 (95% confidence interval (CI): 1.04-2.31). HRs for non-fatal MI and stroke were 1.70 (95% CI: 1.01-2.84) and 1.45 (95% CI: 0.80-2.65) respectively. The association remained consistent in a sensitivity analysis of confirmed psoriasis (HR = 2.06, 95% CI: 1.31-3.26). For individuals with concomitant psoriatic arthritis, the risk of non-fatal CVD was even higher (HR 3.47; 95% CI: 1.85-6.51). Women diagnosed with psoriasis <40 years age or with duration of psoriasis ≥9 years had substantial elevations in CVD risk; HR 3.26 (95% CI: 1.21-8.75) and 3.09 (95% CI: 1.15-8.29) respectively.

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Conclusions—Psoriasis is an independent predictor for non-fatal CVD among women, with particularly high risk for those with longer duration of psoriasis and concomitant psoriatic arthritis.

Introduction

Psoriasis is a chronic inflammatory disease of the skin, with involvement of the joints (psoriatic arthritis, PsA) in 10-40% of cases.[1,2] It affects 1-3% of the population and poses a lifelong burden in spite of many treatment advances.[1-3]

Cardiovascular disease constitutes a severe public health concern in the United States.[4] Now recognized as a systemic inflammatory disorder, inflammation and increased prevalence of unhealthy lifestyle factors in psoriasis have been independently associated with an unfavorable cardiovascular risk profile.[5,6]

Although there have been studies investigating the association between individual types of CVD and psoriasis, most were cross-sectional or case-control studies.[7-18] Several studies were carried out based on the General Practice Research Database (GPRD), while the overall risk of cardiovascular outcome associated with psoriasis was not confirmed among these studies.[13-16] A Danish study by nationwide registers indicated increased risk of adverse cardiovascular events among individuals with psoriasis.[17] Contrarily, one Dutch study using administrative data and one US study did not support the association between psoriasis and CVD. [18,19] Therefore, the association remains to be elucidated. In this study, we investigated the association between psoriasis and non-fatal CVD in a population of 96,008 participants from the Nurses' Health Study II (NHS II). Furthermore, we evaluated whether the magnitude of the association varied for psoriasis with concomitant PsA, age at diagnosis of psoriasis, and duration of disease on incidence of non-fatal CVD.

Materials and methods

Study population

The NHS II was established in 1989 when 116,671 female registered nurses aged 25-42 years were enrolled using a mailed questionnaire which inquired about lifestyle practices and medical history. Biennially, this questionnaire was updated and a response rate exceeding 90% has been achieved.

The return of the completed self-administered questionnaire was considered to imply informed consent by the institutional review board of Partners Health Care System.

Assessment of main exposure

In 2005, the participants were asked about clinician-diagnosed psoriasis and the date of diagnosis (before 1991, 1991-1994, 1995-1998, 1999-2002, or 2003-2005). Of the 97,476 participants responding to the psoriasis question, a total of 2,529 women reported being diagnosed with psoriasis.

We confirmed a large subset of self-reported psoriasis by using the Psoriasis Screening Tool (PST) questionnaire, which inquires about the type of clinicians making the diagnosis and psoriasis phenotypes.[20] A pilot study using the PST showed 99% sensitivity and 94% specificity for psoriasis screening.[20] In our completed three waves of the validation study, the questionnaire was mailed to 1886 (75%) participants with self-reported psoriasis and 1637 (87%) responded, among which 1511 (92%) was finally confirmed. We are now working with the validation of the remaining self-reports.

We did not ask the question on PsA in our main questionnaire. Diagnosis of PsA was confirmed by using the Psoriatic Arthritis Screening and Evaluation questionnaire.[21] Therefore, we only have the information on confirmed PsA. Details of the instrument design and pilot studies have been described elsewhere.[21,22] A total score of ≥47 has been shown to identify PsA with 82% sensitivity and 73% specificity.[21]

Follow-up and assessment of outcome

The non-fatal CVD, specifically non-fatal MI and stroke, was set as the endpoint to avoid ascertainment bias from fatal events prior to 2005. On the biennial questionnaires, participants responded to questions on newly-diagnosed coronary heart disease or stroke.

We sought to access the medical records for reports of CVD during the time after return date of the 1991 questionnaire but before June 2009. Physicians blinded to exposure status reviewed the medical records. To confirm MI, we applied the World Health Organization criteria,[23] requiring typical symptoms plus either elevated cardiac enzyme levels or diagnostic electrocardiographic findings. To confirm stroke, according to the criteria of the National Survey of Stroke,[24] a diagnosis was confirmed if the medical records demonstrated a neurological deficit with sudden or rapid onset that persisted for >24 hours or until death. Cerebrovascular diseases due to infection, trauma, or malignancy, as well as silent strokes were excluded. Strokes included ischemic (thrombotic or embolic) and hemorrhagic (subarachnoid or intraparenchymal) strokes, as well as undetermined subtype. Computed tomography or magnetic resonance imaging reports were available for 89% of those with medical records. Those having confirmatory information but in which medical record release was refused or for which medical records were unavailable were classified as probable stroke of undetermined type. For this analysis, medical records were reviewed for 62.0% of the cases.

Assessment of covariates

Information on weight, smoking, menopausal status, use of postmenopausal hormones (PMH) and oral contraceptives, personal history of hypertension, hypercholesterolemia, diabetes, and cancer was collected biennially. Physical activity was assessed in 1991, 1997, 2001, and 2005. Use of aspirin was assessed in 1989 and biennially from 1993. Alcohol intake was available in 1991, 1995, 1999, and 2003. Family history of CVD (including MI or stroke of parents or siblings) was asked in 1989, 1993, 1997, 2001 and 2005. Race/ethnicity was reported in 1989. Height was assessed in 1989. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistical analysis

Participants who had a history of self-reported or confirmed CVD (n=942), diabetes (n=137) or cancer (n=332) before 1991, or psoriatics missing diagnosis time (n=57) were excluded. After exclusions, 96,008 participants (followed between 1991 and 2009) remained. Person-years of follow-up were calculated from the return date of 1991 questionnaire to the date of diagnosis of CVD, or the end of follow-up (June 2009), whichever came first. We conducted Cox proportional hazards analyses stratified by age and 2-year follow-up intervals to estimate the age- and multivariate-adjusted hazard ratio (HR) and 95% confidence interval (CI) for the association. The assumption of proportional hazards was tested and satisfied through addition of time-dependent variables to the models.

The time-varying variables were updated during follow-up. Multivariate HRs were calculated after adjusting for age, BMI, smoking, physical activity, alcohol intake, race, family history of CVD, hypertension, hypercholesterolemia, current aspirin use, multi-vitamin use, PMH use, and oral contraceptives use. We selected these variables because they

were well-accepted confounders or risk factors. Even though a given risk factor may be not statistically different by itself between psoriatics and non-psoriatics in our study, it may change the effect of the main exposure, or because it is a confounder only when included with other covariates[25].

Trend analyses were performed by diagnosis of PsA. Participants with no psoriasis, only psoriasis, and psoriasis with PsA were assigned 1, 2 and 3 respectively and the scores were entered into the Cox model as an ordinal term to calculate the *P*-value for trend (P_{trend}).

To evaluate the influence of age at psoriasis diagnosis or duration on incident non-fatal CVD, psoriatics before 1991 were excluded for unknown diagnosis date. We set 9 years as the cut point, because most PsA follows the development of psoriasis by 8-10 years [26] and we had a follow-up of 18 years. Similarly, we analyzed the HR for psoriasis diagnosed at age <40, or ≥40 years (because most of the Type 1 psoriatics occur before 40 years [2]). Interaction was evaluated by allowing for the interaction term in the models. As we did not reach significant association between psoriasis and stroke, we calculated the post-hoc statistical power.

Sensitivity analysis was carried out by including fatal CVD events occurring between 2005 and 2009 in the outcome. We also performed sensitivity analysis by including baseline cancer or diabetes cases, but adjusting for them in the analysis.

All statistical analyses were conducted in the Channing SAS/UNIX platform 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

A total of 96,008 participants were included with 2,463 psoriatics. Characteristics of the study population are listed in Table 1 by the diagnosis of psoriasis. Psoriatics tended to have a higher BMI, family history of CVD, personal history of hypertension or hypercholesterolemia, and lower physical activity. There were more current smokers among psoriatics.

During 1,709,069 person-years of follow-up, we identified 713 incident non-fatal CVD events, including 359 MI and 358 stroke cases, with 4 MI cases occurring in participants diagnosed with stroke. Psoriasis was associated with increased risk of non-fatal CVD, multivariate-adjusted HR 1.55 (95% CI: 1.04-2.31); HRs for MI and stroke were 1.70 (95% CI: 1.01-2.86) and 1.45 (95% CI: 0.80-2.65) respectively (Table 2). We found no significant association of psoriasis with hemorrhagic or ischemic stroke.

Individuals with confirmed psoriasis were at significantly increased risk of incident non-fatal CVD, HR 2.06 (95% CI: 1.31-3.26). HR was 2.63 (95% CI: 1.51-4.59) for MI and 1.61 (95% CI: 0.76-3.42) for stroke (Table 3).

Non-fatal CVD according to the diagnosis of PsA is listed in Table 4. Compared with psoriatics, increased risk of incident non-fatal CVD was only found among those with psoriasis plus PsA (HR = 3.47, 95% CI: 1.85-6.51), particularly for non-fatal MI (HR = 4.18, 95% CI: 1.96-8.90). There was a trend toward increased risk of non-fatal CVD when comparing participants with no psoriasis to psoriatics only and psoriatics with PsA (P_{trend} = 0.002).

We evaluated the influence of age at diagnosis or duration on incidence of non-fatal CVD. The HR was 3.26 (95% CI: 1.21-8.75) and 1.60 (95% CI: 0.66-3.88) for psoriasis diagnosed

at <40 years and ≥40 years respectively; while the HRs were 1.64 (95% CI: 0.68-3.96) for cases with duration time <9 and 3.09 (95% CI: 1.15-8.29) for duration ≥9 years (Table 5).

Stratified analyses showed the observed association existed among premenopausal women, and those with hypertension or hypercholesterolemia. We found an interaction of hypercholesterolemia and psoriasis on the risk of incident non-fatal CVD ($P_{interaction}$ = 0.04) (Supplementary table 1).

Sensitivity analysis was performed by including fatal CVD cases between 2005 and 2009 and no material change was noted (Supplementary table 2). We carried out secondary analysis by including subjects with baseline cancer or diabetes and no material change was noted (data not shown).

Discussion

Our study examined the association between psoriasis and incident non-fatal CVD in a large cohort of US women. The results demonstrated a considerably increased risk of non-fatal CVD, particularly MI, in women with psoriasis, even after adjusting for the traditional cardiovascular risk factors; the magnitude of the association was higher in those with concomitant PsA. However, we only have moderate power for the analysis on stroke.

Psoriasis is a Th1 and Th17-mediated autoimmune disease.[27,28] Activation of inflammation is crucial in the development of CVD with the up-regulation of Th1-mediated cytokine cascades as a trigger.[29] Therefore, chronic inflammation may be the biologically plausible mechanism underlying the association between psoriasis and increased risk of CVD.[30,31]

In our study, all cases with PsA had psoriasis simultaneously. Though there is still lack of evidence showing severe skin disease among those with PsA,[32] psoriasis skin lesions usually precede the onset of joint symptoms by 8-10 years.[26] Another study from our group has found that individuals with PsA reported more severe skin disease (unpublished data). Therefore, it is reasonable to propose that individuals with PsA tend to have a higher inflammatory burden. Based on published reports, we hypothesized that cumulative inflammatory burden and greater immune activity may be associated with elevated risk of CVD.[30,31] Consistent with this hypothesis, we found an increased risk of non-fatal CVD associated with psoriasis, especially among cases with PsA, and those with longer duration of psoriasis. Our results also suggested higher risk among psoriasis developing at an earlier age. A possible explanation lies in the recognition that psoriasis occurs in a bimodal age distribution.[2,33] Type 1 psoriasis is early onset with severe phenotypes, while type 2 is late onset (around 60 years) and less severe.[2] Among those diagnosed at a younger age, the majority may be type 1 which could have a higher risk of developing CVD.

Psoriasis and CVD share common risk factors. Smoking is a major environmental risk factor of CVD,[34] and has been related to psoriasis.[35] Obesity and other components of the metabolic syndrome, have been associated with both psoriasis and CVD.[36-39] The presence of these factors may create a pro-inflammatory environment and promote the development of CVD. A common genetic basis also may influence the connection, which has been shown in transgenic mice.[5]

There have been epidemiologic studies investigating the association between psoriasis and CVD, most of which used a case-control or cross-sectional study design. [7-16,18] Although some have suggested that CVD is more prevalent in psoriasis, the results have been mixed.[12,18] One study based on GPRD found that psoriasis may confer an independent risk of MI but the other did not find elevated MI risk for all psoriatics. [13,15] One Dutch study utilized administrative data rather than clinical health records did not show an increased risk

of ischemic heart disease, even among younger participants.[18] Another European study by linkage of nationwide registers suggested psoriasis as a clinically significant risk factor for cardiovascular death. [17] A US study did not observe increased CVD risk related to severe psoriasis.[19] Our study, based on a large cohort of women, advances previous findings and emphasizes the increased risk of incident non-fatal CVD among psoriatics.

We were able to analyze a large subset of confirmed psoriasis cases. [20] The sensitivity analysis showed that confirmed psoriasis was associated with significantly increased risk of incident non-fatal CVD and replicated the results from self-reported cases, demonstrating the reproducibility of our analyses.

The large cohort of health professionals provided reliable information on psoriasis as well as other covariates. The ascertainment of the outcome has been validated. The diagnosis of PsA and a large subset of psoriatics were confirmed. Moreover, we performed sensitivity analyses to ensure valid results. Previous studies have shown an increased risk of MI associated with psoriasis especially among young patients.[13,15] Our study was performed in a cohort with baseline age less than 45 years. Even at the end of follow-up, the majority were less than 60 years. Generally premenopausal women are not considered high risk for CVD, comparing with men or postmenopausal women. Further, in our study, individuals developing psoriasis at a younger age were at particularly higher risk of non-fatal CVD. It is also worth noting that this well-educated nurses' cohort minimizes the potential for confounding by socioeconomic status, and we were able to obtain high quality data with minimal loss to follow-up. Although the absolute rates of psoriasis and CVD may not be representative of a random sample of US women, the biological effects underlying the association should be similar. However, the majority of study participants are of European ancestry, which limits generalizing the results to other ethnicities.

Our study has other limitations. This is a prospective-retrospective mixed study. History of clinician-diagnosed psoriasis was asked in 2005. We cannot obtain information on psoriatics who died before the data collection. Although we have the complete datasets of those with fatal CVD prior to 2005, we were not able to investigate the association between psoriasis and fatal CVD. Hence, we used incidence of non-fatal CVD as the main outcome. Given that this is a younger cohort of women, the number of CVD deaths prior to 2005 was small. Furthermore, a sensitivity analysis was carried out by including the fatal CVD cases after 2005, and the magnitude of effect did not change materially. But it must be stated that the number of fatal CVD cases we have in present study was quite small. Misclassification could have arisen due to recall and response bias. However, a validation study showed a 92% accuracy of self-reported psoriatsis[20]. Our participants were young nurses who tended to have a higher accuracy of self-reports. We compared the characteristics between those responding and not-responding to the psoriasis question. The main characteristics, such as age, BMI, physical activity, and alcohol intake were similar although the responders had a slightly lower percentage of current smokers (Supplementary table 3). Further, the proportion of non-fatal CVD cases in responders to psoriasis item was 86.8% while the proportion of responders in the total participants was 83.5%. Therefore, it is less likely that our results were affected by response bias. Any misclassification would likely be non-differential and result in a conservative effect estimate. We cannot measure the effects of various systemic therapies for psoriasis on the incidence of CVD. However, evidence has shown that several commonly used medications may lower the risk of cardiovascular outcomes. [40,41] Moreover, systemic treatment in the US is limited to a small proportion of individuals with psoriasis who have moderate-severe psoriasis, hence the impact of systemic therapy would be minimal. Our study may have underestimated the association due to lack of information on therapy, but despite this an association was found. A 5-year trial found no evidence the use of the retinoid etretinate significantly increased the risk of cardiovascular

disease and the mortality associated with cardiovascular events was lower in patients receiving etretinate.[42] Acitretin was shown to induce hyperlipidemia.[43] Cyclosporine was reported to induce hypertension.[44] However, we adjusted for the roles of hypertension and hypercholesterolemia. Topical steroids may have a gluconeogenic impact. [45] However, systemic steroids are not the standard of care for psoriasis in the US and adherence to long-term use is generally low due to the well-known exacerbation of pustular psoriasis.[46,47] In addition, acitretin and cyclosporine were used only for management of severe psoriasis. Therefore, there is little concern about residual confounding by other therapies.

In conclusion, our prospective study, though the psoriasis collection is retrospective, provides further evidence that the presence of psoriasis is associated with increased risk of non-fatal CVD, particularly MI. Those with PsA, early onset, or long duration of psoriasis had a higher risk of CVD, supporting the role of cumulative inflammation in the development of non-fatal CVD. However, the contributing mechanisms remain unclear. The effect of systemic anti-inflammatory therapy for psoriasis and PsA on the future risk of CVD also needs to be determined. Given the limited cases, we did not have enough power to evaluate the association between psoriasis and risk of stroke. Pending further investigation, physicians treating individuals who develop psoriasis at a younger age, those with long-standing psoriasis, and those with psoriasis plus psoriatic arthritis should consider addressing modifiable CVD risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's already known about this topic?

- Psoriasis has been linked to cardiovascular co-morbidities in previous cross-sectional and case control studies.
- Evidence regarding the association between psoriasis and incident cardiovascular disease (CVD) is limited and conflicting.

What does this study add?

- We found an association between psoriasis and risk of incident non-fatal CVD disease based on prospectively screened large number of participants in Nurses' Health Study II.
- The risk of incident CVD was particularly high for those with longer duration of psoriasis and concomitant psoriatic arthritis.

Table 1

Characteristics of the study population by psoriasis status, Nurse's Health Study II, 1991-2009 *

Characteristics	Psoriasis	
	No	Yes
Age, median (IQR), year	44 (10.0)	45 (10.0)
Race (white, %)	95.3	96.4
Body mass index, kg/m^2, median (IQR)	24.7 (7.1)	25.8 (8.7)
Alcohol intake, g/d, median (IQR)	1.2 (4.8)	1.2 (4.9)
Physical activity, metabolic equivalent hours/wk, median (IQR)	12.4 (22.4)	10.5 (19.7)
Current smoking (%)	9.2	13.2
Family history of cardiovascular disease † (%)	47.6	51.9
Postmenopausal hormone (%)	14.1	16.4
Oral contraceptives use (%)	84.2	84.9
Hypertension (%)	14.4	19.0
Hypercholesterolemia ‡ (%)	25.1	31.6
Aspirin use § (%)	28.8	31.8
Multi-vitamin use (%)	47.0	46.5

* Values are medians (interquartile range, IQR) or percentages.

† The parents' or siblings' lifetime diagnosis of MI or stroke.

‡ Physician-diagnosed elevated cholesterol.

§ Regularly use of aspirin or aspirin-containing products.

Table 2

Age- and multivariate-adjusted hazard ratios (HRs) for the association between psoriasis and non-fatal CVD *

	Cases †	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR ‡ (95% CI)
Non-fatal CVD				
No psoriasis	688	1,677,052	1.00	1.00
Psoriasis	25	32,017	1.82 (1.22-2.72)	1.55 (1.04-2.31)
Non-fatal MI				
No psoriasis	344	1,677,379	1.00	1.00
Psoriasis	15	32,029	2.17 (1.29-3.64)	1.70 (1.01-2.86)
Non-fatal Stroke				
No psoriasis	347	1,677,377	1.00	1.00
Psoriasis	11	32,031	1.60 (0.88-2.92)	1.45 (0.80-2.65)

*Specifically MI and stroke.

†Four Non-fatal MI cases occurred in participants diagnosed with non-fatal stroke.

‡Simultaneously adjusted for age, body mass index (underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, and obesity ≥40 kg/m^2), smoking status (never, past, current smoking with 1-14, 15-24 or ≥25 cigarettes/day), alcohol intake (no, <5.0, 5.0-9.9 or ≥10.0 g/d), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or ≥27.0 metabolic equivalent hours/wk), race (Caucasian, Asian, Hispanic or African American), family history of stroke/MI (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), current aspirin use (yes or no), multi-vitamin use (yes or no), postmenopausal hormone use (premenopause, never, current or past users), oral contraceptives use (never, past or current users).

Table 3

Age- and multivariate-adjusted HRs for the association between confirmed psoriasis and non-fatal CVD

	Cases *	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR † (95% CI)
Non-fatal CVD				
No psoriasis	694	1,690,318	1.00	1.00
psoriasis	19	18,750	2.41 (1.53-3.80)	2.06 (1.31-3.26)
Non-fatal MI				
No psoriasis	346	1,690,650	1.00	1.00
psoriasis	13	18,758	3.28 (1.88-5.70)	2.63 (1.51-4.59)
Non-fatal Stroke				
No psoriasis	351	1,690,645	1.00	1.00
psoriasis	7	18,763	1.77 (0.84-3.73)	1.61 (0.76-3.42)

*Four Non-fatal MI cases occurred in participants diagnosed with non-fatal stroke.

†Simultaneously adjusted for age, body mass index (underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, and obesity ≥40 kg/m^2), smoking status (never, past, current smoking with 1-14, 15-24 or ≥25 cigarettes/day), alcohol intake (no, <5.0, 5.0-9.9 or ≥10.0 g/d), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or ≥27.0 metabolic equivalent hours/wk), race (Caucasian, Asian, Hispanic or African American), family history of stroke/MI (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), current aspirin use (yes or no), multi-vitamin use (yes or no), postmenopausal hormone use (premenopause, never, current or past users) , oral contraceptives use (never, past or current users).

Table 4

Age- and multivariate-adjusted HRs for the association between psoriasis/psoriatic arthritis and non-fatal CVD

	Cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR * (95% CI)
Non-fatal CVD				
No psoriasis	688	1,677,052	1.00	1.00
Only Psoriasis	15	27,804	1.27 (0.76-2.11)	1.13 (0.68-1.89)
Psoriatic arthritis/psoriasis	10	4,213	5.32 (2.85-9.94)	3.47 (1.85-6.51)
P_{trend}			<0.001	0.002
Non-fatal MI				
No psoriasis	344	1,677,379	1.00	1.00
Only Psoriasis	8	27,813	1.34 (0.66-2.70)	1.12 (0.56-2.27)
Psoriatic arthritis/psoriasis	7	4,216	7.40 (3.50-15.66)	4.18 (1.96-8.90)
P_{trend}			<0.001	0.003
Non-fatal Stroke				
No psoriasis	347	1,677,377	1.00	1.00
Only Psoriasis	8	27,811	1.35 (0.67-2.73)	1.27 (0.63-2.56)
Psoriatic arthritis/psoriasis	3	4,220	3.18 (1.02-9.91)	2.40 (0.77-7.51)
P_{trend}			0.05	0.13

* Simultaneously adjusted for age, body mass index (underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, and obesity ≥40 kg/m^2), smoking status (never, past, current smoking with 1-14, 15-24 or ≥25 cigarettes/day), alcohol intake (no, <5.0, 5.0-9.9 or ≥10.0 g/d), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or ≥27.0 metabolic equivalent hours/wk), race (Caucasian, Asian, Hispanic or African American), family history of stroke/MI (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), current aspirin use (yes or no), multi-vitamin use (yes or no), postmenopausal hormone use (premenopause, never, current or past users) , oral contraceptives use (never, past or current users).

Table 5

The association between psoriasis diagnosis age or duration time and risk of incident non-fatal CVD

	Cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted HR * (95% CI)
Psoriasis diagnosis age				
No psoriasis	678	1,677,047	1.00	1.00
Diagnosis age <40 years	4	3,198	3.98 (1.48-10.70)	3.26 (1.21-8.75)
Diagnosis age ≥40 years	5	4,747	2.03 (0.84-4.91)	1.60 (0.66-3.88)
Psoriasis duration time †				
No psoriasis	678	1,677,047	1.00	1.00
Psoriasis <9 years	5	5,542	2.02 (0.84-4.89)	1.64 (0.68-3.96)
Psoriasis ≥9 years	4	2,404	4.04 (1.51-10.83)	3.09 (1.15-8.29)

*Simultaneously adjusted for age, body mass index (underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, and obesity ≥40 kg/m^2), smoking status (never, past, current smoking with 1-14, 15-24 or ≥25 cigarettes/day), alcohol intake (no, <5.0, 5.0-9.9 or ≥10.0 g/d), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9 or ≥27.0 metabolic equivalent hours/wk), race (Caucasian, Asian, Hispanic or African American), family history of stroke/MI (yes or no), hypertension (yes or no), hypercholesterolemia (yes or no), current aspirin use (yes or no), multi-vitamin use (yes or no), postmenopausal hormone use (premenopause, never, current or past users) , oral contraceptives use (never, past or current users).

†Psoriasis duration time is defined as the time from diagnosis date of psoriasis to diagnosis date of non-fatal CVD, death, or end of the follow up, whichever comes first.