Association between baseline insulin resistance and psoriasis incidence: the Women’s Health Initiative

Alfred A. Chan1 · Houmin Li2 · Wendy Li3 · Kathy Pan4 · Jennifer K. Yee5,6 · Rowan T. Chlebowski4 · Delphine J. Lee1,3,6

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Abstract
Small-scale studies offer conflicting evidence regarding the relationship/association between psoriasis and insulin resistance by HOMA-IR (homeostasis model assessment of insulin resistance). The purpose of this study was to assess the association between baseline HOMA-IR and psoriasis incidence in a large-scale longitudinal cohort of postmenopausal women. The analysis included 21,789 postmenopausal women from the Women’s Health Initiative. Psoriasis diagnosis was defined by fee-for-service Medicare ICD-9-CM codes assigned by dermatologists or rheumatologists, and a 2-year lookback period to exclude prevalent cases. Baseline HOMA-IR was calculated using the updated HOMA2 model. Hazard rates from the Cox regression models were stratified by age (10-year intervals), on WHI component (Clinical Trial or Observational Study), and on randomization status within each of the WHI clinical trials. The complete model also adjusted for ethnicity, waist–hip-ratio, and smoking and alcohol habits. Among participants free of psoriasis at entry, those with high baseline HOMA-IR (≥ 2) compared to low (< 1.4) had significantly higher risk for psoriasis over 21-year cumulative follow-up (HR: 1.39, 95% CI 1.08–1.79, \( P \)-trend: 0.011). In postmenopausal women, higher baseline HOMA-IR levels were significantly associated with higher incidence of psoriasis over 21-year cumulative follow-up. Results from this time-to-event analysis indicate that insulin resistance can precede and is associated with an increased risk of psoriasis. Study is limited by Medicare diagnostic code accuracy and cohort age.

Keywords Psoriasis · Insulin resistance

Introduction
Psoriasis is a chronic inflammatory skin disease that affects about 2–4% of the U.S. population. Psoriasis can occur at any age, but peaks between age 20 and 30 years and between 50 and 60 years [1]. In postmenopausal women, the fall in estrogen concentration has been attributed to exacerbation of psoriasis [2]. According to a survey initiated by the National Psoriasis Foundation, 94% of patients reported that psoriasis interferes with their quality of life on a daily basis [3]. Although psoriasis has been traditionally regarded as a disease limited to the skin, it is now well known that it has important health implications beyond the skin [4].

Psoriasis is associated with significant comorbidities including type 2 diabetes [5]. The current evidence hints at a complex relationship between psoriasis and insulin resistance. Small case–control studies (\( n < 200 \) participants) have attempted to characterize the relationship between psoriasis and insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR),
a reliable and validated surrogate marker of insulin resistance [6–8]. However, the results have been conflicting. For example, Dhara et al. reported significantly higher HOMA-IR in psoriasis patients compared to age and sex-matched controls [9]. While Pereira et al. found that psoriasis patients are more than twice as likely to exhibit impaired glucose metabolism than controls, HOMA-IR did not significantly differ between the two groups in those with normal glucose tolerance [10]. Gyldenløve reported a significant association between psoriasis and insulin resistance when assessing with the hyperinsulinemic euglycemic clamp (HEC), but not with HOMA-IR [11].

We propose to better characterize the relationship between psoriasis and insulin resistance (via HOMA-IR) in a large cohort of postmenopausal women. Previous case–control studies have reported increased incidence of diabetes in psoriasis patients [12, 13]. Our study instead aims to explore the reverse: whether a pre-diabetic condition such as high baseline insulin resistance is a predictor of psoriasis. To our knowledge, this is the first study using a large-scale longitudinal cohort to investigate the association between baseline insulin resistance and psoriasis incidence in postmenopausal women.

Patients and methods

Study population

The Women’s Health Initiative (WHI) recruited postmenopausal women ages 50–79 years from across 40 US clinical centers between 1993 and 1998. This includes a “Clinical Trial” cohort (n = 68,132) with the following components: Estrogen-alone trial, Estrogen-plus-Progestin trial, Dietary Modification trial, and Calcium and Vitamin D trial. Each randomized controlled trial has its own exclusionary criteria involving safety, adherence, and retention concerns. Women ineligible or unwilling to join the clinical trials were invited to join the “Observational Study” cohort (n = 93,676). Detailed eligibility criteria and recruitment methods have been previously published [14]. Human subjects review committees at all participating sites approved WHI protocols and participants provided written informed consent.

Of the starting 161,808 postmenopausal women, 31,897 participants had at least one blood draw at enrollment measuring both insulin and glucose for HOMA-IR calculations. Of those, 23,093 women were linked to Medicare fee-for-service Parts A and B (FFS A + B). The final analytic cohort (n = 21,789) excluded 1,304 women who had prevalent cases of psoriasis or were not followed long enough for a 2-year lookback period.

Data collection

At baseline, information on demographics, medical history, and lifestyle behaviors (such as smoking, alcohol, and exercise habits) were obtained through a self-administered questionnaire. Data on lifetime hormone use were obtained by a trained interviewer, assisted by charts displaying colored photographs of various hormone preparations. Trained staff also obtained anthropometric measurements such as height, weight, and waist and hip circumferences. The total Metabolic Equivalent of Task (MET-hours per week) was calculated by multiplying the MET levels for activity by the hours exercised per week and summing the values for all activities.

Psoriasis outcome ascertainment

We classified subjects with psoriasis as previously described [15]. Briefly, psoriasis was defined by fee-for-service Medicare claims using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 696.0 (psoriatic arthropathy) and 696.1 (other psoriasis). To increase the validity of identifying individuals with psoriatic disease, the designation was limited to ICD-9-CM codes given by a dermatologist or rheumatologist. In a study of a managed care patient population in Northern California, psoriasis ICD-9-CM codes reported specifically by a dermatologist have a positive predictive value of 89% (95% CI, 79–95%) [16]. In addition, a 2-year lookback or washout period was implemented so as to not misclassify prevalent psoriasis cases as incidence [15].

Determination of HOMA-IR

Baseline blood draws (Year 0) were excluded if they were drawn after less than 12 h of fasting. Glucose was analyzed using the hexokinase method. Fasting insulin was analyzed by the following methods and detection systems: BMD ES3000 Immunoassay System, Roche 2010 Electrochemiluminescence, Radioimmunoassay (linco Research, St. Louis, MO), and Sandwich Immunoassay (Roche Diagnostics). The analytes were similarly distributed across the various testing methods; much of the differences could be attributed to the demographics selected for the ancillary studies (Figure S1). Insulin resistance was calculated using the HOMA2 version 2.2.3, which is an updated HOMA computer model with nonlinear solutions that account for both circulating proinsulin and variations in hepatic and peripheral glucose resistance; acceptable steady-state
input values were 20 to 400 pmol/L for insulin and 3.0 to 25.0 mmol/L for glucose [17]. Degree of insulin resistance was categorized as defined by previous studies: Low (HOMA-IR < 1.4), Moderate (1.4 ≤ HOMA-IR < 2.0), and High (HOMA-IR ≥ 2.0) [18–20].

**Statistical analysis**

For primary analyses, we used time-to-event Cox proportional hazards regressions to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to study the association between baseline HOMA-IR and psoriasis incidence over the cumulative 21-year follow-up. Participants entered the risk set upon completion of the 2-year lookback period and a delayed-entry was applied for those who entered the risk set after WHI randomization. Event times were censored at the date of first psoriasis diagnosis, death or date of last follow-up through June 2017, whichever came first.

Hazard rates during follow-up were stratified on age (10-year intervals), on WHI component (Clinical Trial or Observational Study), and on randomization status within each of the WHI clinical trials (Diet Modification, Hormone Therapy, Calcium and Vitamin-D Trial). In addition, the following baseline characteristics were included in the Cox regression model to control for potential confounding effects for psoriasis based on previous literature and based on our univariable analyses: ethnicity (Caucasian, Asian, African-American, Hispanic, Other/Unspecified), continuous waist–hip-ratios, smoking (non-smoker, past-smoker, current-smoker), and alcohol habits (non-drinker, past-drinker, current drinker) [21, 22] (Table 2). Separate models with and without adjustment for these covariates were developed and compared. The proportional hazards assumption was tested with Schoenfeld residuals, and no violation of the proportionality assumption was found. In secondary analyses, we tested for interaction between baseline HOMA-IR and smoking habit on psoriasis.

**Results**

HOMA-IR showed a weak positive correlation with baseline BMI (R = 0.46) and WHR (R = 0.34). Figure S2 shows a subgroup of women who were obese (BMI > 30 kg/m² or WHR > 0.85), but had low insulin resistance and vice versa. Baseline characteristics by HOMA-IR are described in Table 1. Women with high HOMA-IR (≥ 2.0) were more likely to be randomized into the WHI Dietary Modification trial, but less likely to the Estrogen-plus-Progestin trial. Those with high HOMA-IR were also more likely to be younger (50–59 years), African-American, obese, prior alcohol drinkers, prior smokers, with prior hysterectomy, with fewer years of education, or fewer hours of physical activity. They were more likely to have a history of diabetes, hypertension, cardiovascular disease, stroke, liver disease, or rheumatoid arthritis. On the other hand, low HOMA-IR was associated with non-melanoma skin cancer and with the use of estrogen or estrogen-plus-progestin at baseline.

Psoriasis incidence rate was 2.36 cases per 1000 persons per year over the median cumulative follow-up of 9.5 years (interquartile range, 4.5–14.7 years). The majority of the study population was Caucasian (58.6%) or African-American (28.0%) and between 60–69 years old (47.1%). Baseline characteristics by psoriasis incidence are described in Table 2. The average age at first incidence of psoriasis was 74.6 years, occurring on average 8.3 years into the study enrollment.

The multivariable analysis adjusts for ethnicity, continuous waist–hip-ratio, smoking and alcohol habits, and was stratified on age (10-year interval), on WHI components (Clinical Trial or Observational Study), and on randomization status within each of the WHI clinical trials (Diet Modification, Hormone Therapy, Calcium and Vitamin-D Trial). Comparing psoriasis risk in HOMA-IR high (≥ 2.0) versus low (< 1.4), the estimated hazard ratio was 1.39 (95% CI 1.08–1.79, P-trend: 0.011) (Fig. 1). Spline-based partial hazard estimates for psoriasis was mostly linear for continuous values of HOMA-IR (P-value Linear: 0.016) (Fig. 2).

In analyses stratified by smoking (a major confounder for psoriasis), no interaction between smoking and HOMA-IR was detected (P-interaction = 0.472). The Kaplan–Meier curve (cumulative hazard over time) shows that among non-smoking women, the risk for psoriasis was steadily and consistently higher in women with high HOMA-IR (≥ 2.0) compared to low (< 1.4) over the 21-year cumulative follow-up period (Fig. 3).

In sensitivity analyses excluding women with potentially confounding factors [such as baseline-treated diabetes (n = 1968), a history of hypertension (n = 8996), cardiovascular disease (n = 3586), rheumatoid arthritis (n = 1291), or non-melanoma skin cancer (n = 1645)], higher insulin resistance remained significantly associated with greater psoriasis incidence.

**Discussion**

Higher baseline insulin resistance assessed by the updated HOMA2 version 2.2.3 was significantly associated with greater incidence of psoriasis in postmenopausal women. Therefore, while other epidemiological studies suggest that psoriasis precedes type II diabetes [12, 13], the risk of psoriasis itself may be attributed to a pre-diabetic condition, with high insulin resistance assessed using HOMA-IR. While the exact mechanisms remain unclear, several theories...
Table 1 Baseline characteristics by HOMA-IR

| Clinical trials                      | Low HOMA-IR n (%) | Moderate HOMA-IR n (%) | High HOMA-IR n (%) | P value |
|--------------------------------------|-------------------|-----------------------|--------------------|---------|
| Estrogen-Alone Trial                 |                   |                       |                    |         |
| Not randomized                       | 7832 (66.4%)      | 1977 (16.8%)          | 1990 (16.9%)       | < 0.001 |
| Placebo                              | 1277 (59.9%)      | 424 (19.9%)           | 430 (20.2%)        |         |
| Treated                              | 1263 (61.4%)      | 367 (17.9%)           | 426 (20.7%)        |         |
| Estrogen + Progestin Trial           |                   |                       |                    |         |
| Not randomized                       | 7832 (66.4%)      | 1977 (16.8%)          | 1990 (16.9%)       | < 0.001 |
| Placebo                              | 2052 (72.3%)      | 446 (15.7%)           | 342 (12.0%)        |         |
| Treated                              | 2060 (69.5%)      | 487 (16.4%)           | 416 (14.0%)        |         |
| Calcium Vitamin D Trial              |                   |                       |                    | 0.496   |
| Not randomized                       | 9579 (66.6%)      | 2400 (16.7%)          | 2399 (16.7%)       |         |
| Placebo                              | 2439 (65.9%)      | 649 (17.5%)           | 612 (16.5%)        |         |
| Treated                              | 2466 (66.5%)      | 652 (17.6%)           | 593 (16.0%)        |         |
| Dietary Modification Trial           |                   |                       |                    | < 0.001 |
| Not randomized                       | 10,834 (69.2%)    | 2465 (15.7%)          | 2367 (15.1%)       |         |
| Placebo                              | 1506 (60.8%)      | 503 (20.3%)           | 466 (18.8%)        |         |
| Treated                              | 2144 (58.8%)      | 733 (20.1%)           | 771 (21.1%)        |         |
| Demographics                         |                   |                       |                    |         |
| Age                                  |                   |                       |                    | < 0.001 |
| 50–59                                | 3601 (62.8%)      | 1027 (17.9%)          | 1105 (19.3%)       |         |
| 60–69                                | 6707 (65.4%)      | 1765 (17.2%)          | 1783 (17.4%)       |         |
| 70–79                                | 4176 (72.0%)      | 909 (15.7%)           | 716 (12.3%)        |         |
| Ethnicity                            |                   |                       |                    | < 0.001 |
| Caucasian                            | 9007 (70.6%)      | 1929 (15.1%)          | 1820 (14.3%)       |         |
| Asian                                | 299 (67.5%)       | 82 (18.5%)            | 62 (14.0%)         |         |
| African-American                     | 3573 (58.5%)      | 1263 (20.7%)          | 1270 (20.8%)       |         |
| Hispanic                             | 1341 (66.6%)      | 330 (16.4%)           | 343 (17.0%)        |         |
| Other/unspecified                    | 254 (55.7%)       | 95 (20.8%)            | 107 (23.5%)        |         |
| Education                            |                   |                       |                    | < 0.001 |
| Less than high school                | 4987 (60.7%)      | 1576 (19.2%)          | 1651 (20.1%)       |         |
| College                              | 5437 (67.9%)      | 1308 (16.3%)          | 1257 (15.7%)       |         |
| Higher                               | 3963 (72.8%)      | 805 (14.8%)           | 673 (12.4%)        |         |
| Type of Job                          |                   |                       |                    | < 0.001 |
| Managerial/professional              | 5435 (70.1%)      | 1201 (15.5%)          | 1118 (14.4%)       |         |
| Technical/sales/admin                | 3749 (65.1%)      | 1055 (18.3%)          | 958 (16.6%)        |         |
| Service/labor                        | 2576 (62.1%)      | 761 (18.3%)           | 812 (19.6%)        |         |
| Homemaker only                       | 1412 (66.3%)      | 354 (16.6%)           | 364 (17.1%)        |         |
| Lifestyle Habits                     |                   |                       |                    |         |
| Alcohol                              |                   |                       |                    | < 0.001 |
| Never                                | 1837 (61.0%)      | 541 (18.0%)           | 632 (21.0%)        |         |
| Past drinker                         | 2795 (56.6%)      | 1021 (20.7%)          | 1119 (22.7%)       |         |
| Current drinker                      | 9721 (71.3%)      | 2093 (15.4%)          | 1814 (13.3%)       |         |
| Smoking                              |                   |                       |                    | 0.006   |
| Never                                | 7554 (67.1%)      | 1919 (17.0%)          | 1792 (15.9%)       |         |
| Past smoker                          | 5562 (65.2%)      | 1476 (17.3%)          | 1487 (17.4%)       |         |
| Current smoker                       | 1166 (68.6%)      | 259 (15.2%)           | 274 (16.1%)        |         |
| Recreation Physical Activity         |                   |                       |                    | < 0.001 |
| (MET-hour)                           | ≥0 to < 2         | 848 (62.6%)           | 225 (16.6%)        |         |
Table 1 (continued)

| Low HOMA-IR n (%) | Moderate HOMA-IR n (%) | High HOMA-IR n (%) | P value |
|-------------------|------------------------|--------------------|---------|
| ≥ 2 to < 8        | 702 (59.8%)            | 223 (19.0%)        | 249 (21.2%) |
| ≥ 8 to < 18       | 733 (67.6%)            | 187 (17.3%)        | 164 (15.1%) |
| ≥ 18              | 3017 (76.0%)           | 509 (12.8%)        | 444 (11.2%) |

Anthropometric Measures

Baseline Body Mass Index (kg/m²)

| Normal (18.5–24.9) | 4379 (91.7%) | 288 (6.0%) | 108 (2.3%) | < 0.001 |
| Overweight (25.0–29.9) | 5618 (75.1%) | 1126 (15.1%) | 735 (9.8%) |
| Obese (≥ 30.0)      | 3847 (44.5%) | 2166 (25.1%) | 2628 (30.4%) |

Baseline Waist to Hip Ratio

| Normal (< 0.800) | 6869 (84.1%) | 798 (9.8%) | 498 (6.1%) | < 0.001 |
| Overweight (0.800–0.849) | 3825 (66.9%) | 1068 (18.7%) | 825 (14.4%) |
| Obese (≥ 0.850) | 3574 (47.1%) | 1792 (23.6%) | 2223 (29.3%) |

Hormone-Related Factors

Estrogen-alone

| Never | 9915 (66.1%) | 2541 (16.9%) | 2540 (16.9%) | < 0.001 |
| Past  | 2264 (64.0%) | 658 (18.6%) | 615 (17.4%) |
| Current | 2295 (70.8%) | 502 (15.5%) | 445 (13.7%) |

Estrogen plus Progestin

| Never | 11,966 (64.8%) | 3251 (17.6%) | 3250 (17.6%) | < 0.001 |
| Past  | 1051 (71.8%) | 215 (14.7%) | 198 (13.5%) |
| Current | 1461 (78.9%) | 235 (12.7%) | 156 (8.4%) |

Menstrual Cycle Regularity

| No | 990 (62.5%) | 272 (17.2%) | 321 (20.3%) | < 0.001 |
| Yes | 12,069 (66.9%) | 3068 (17.0%) | 2898 (16.1%) |
| Sometimes irregular | 1306 (65.4%) | 335 (16.8%) | 355 (17.8%) |

Age at Menopause

| 45 or younger | 4021 (62.6%) | 1154 (18.0%) | 1252 (19.5%) | < 0.001 |
| 46 to 49 | 4419 (69.4%) | 1001 (15.7%) | 948 (14.9%) |
| 50 to 51 | 1837 (70.0%) | 432 (16.5%) | 356 (13.6%) |
| 52 or older | 3067 (68.7%) | 743 (16.6%) | 655 (14.7%) |

Parity

| Never pregnant | 1403 (65.5%) | 371 (17.3%) | 367 (17.1%) | < 0.001 |
| 1 | 3279 (68.6%) | 794 (16.6%) | 709 (14.8%) |
| 2 | 3339 (68.3%) | 806 (16.5%) | 746 (15.3%) |
| 3 | 2182 (65.3%) | 575 (17.2%) | 586 (17.5%) |
| 4 | 2439 (60.9%) | 746 (18.6%) | 823 (20.5%) |
| 5 | 1737 (70.7%) | 376 (15.3%) | 344 (14.0%) |

Hysterectomy

| No | 8367 (69.9%) | 1906 (15.9%) | 1695 (14.2%) | < 0.001 |
| Yes | 6112 (62.3%) | 1793 (18.3%) | 1908 (19.4%) |

Medical History

Diabetes

| No | 13,825 (69.8%) | 3280 (16.6%) | 2698 (13.6%) | < 0.001 |
| Yes | 650 (33.0%) | 419 (21.3%) | 899 (45.7%) |

Hypertension

| No | 9365 (74.5%) | 1787 (14.2%) | 1422 (11.3%) | < 0.001 |
| Yes | 4990 (55.5%) | 1882 (20.9%) | 2124 (23.6%) | < 0.001 |
have been proposed for the pathophysiologic link between psoriasis and insulin resistance. This may be in part due to shared genetic regions of susceptibility between psoriasis and diabetes [23].

While the exact mechanisms that link psoriasis and insulin resistance have not been described, immune dysregulation has been reported to play a key role in both conditions [24]. T-helper cell 1 (Th1) signaling pathway have been implicated in both psoriasis and insulin resistance. A shift in the macrophage population towards more pro-inflammatory M1 than anti-inflammatory M2 has been implicated in both psoriasis and insulin resistance. A shift in the macrophage population towards more pro-inflammatory M1 than anti-inflammatory M2 has been implicated in both conditions [25]. Cytokine production through promotion of NF-κB (nuclear factor kappa light chain enhancer of activated B cells) transcription factor signaling, which may also contribute to macrophage activation, has also been implicated in both conditions [26, 27]. Overproduction of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin (IL)-1β is associated with insulin resistance [28–31]. IL-1β blocks insulin-dependent differentiation of keratinocytes and drives keratinocyte proliferation, both of which are hallmarks of psoriasis pathogenesis [32]. TNFα is also directly implicated in psoriasis pathogenesis and TNFα inhibitors are recommended as a monotherapy treatment option for adults with moderate-to-severe psoriasis [4]. These findings, combined with results from the time-to-event analysis, support the notion that insulin resistance is associated with an increased risk of psoriasis and can precede skin pathology.

Previous studies have also identified a possible relationship between psoriasis and metabolic syndrome, which is associated with insulin resistance and psoriasis severity. For example, patients with metabolic syndrome had significantly higher Psoriasis Area Severity Index (PASI) scores compared to those without metabolic syndrome. Furthermore, in patients without metabolic syndrome, HOMA-IR significantly correlated with PASI score [33]. This is also consistent with a large meta-analysis of observational studies in which patients with more severe psoriasis had greater odds of metabolic syndrome [12]. Our findings suggest that insulin resistance might be explored as an additional therapeutic target in psoriasis patients, especially in those with concomitant diabetes.

Anti-diabetic agents have anti-inflammatory properties in the setting of insulin resistance, obesity, and heart disease [34]. Optimistic reports (case reports, case series, and small clinical trials) suggest thiazolidinediones (TZDs) may provide clinical benefits for psoriasis through a decrease of cytokine production including TNFα; however, TZDs have not been consistently shown to improve disease severity [35]. Metformin may promote macrophage

### Table 1 (continued)

|                                | Low HOMA-IR n (%) | Moderate HOMA-IR n (%) | High HOMA-IR n (%) | P value |
|--------------------------------|-------------------|-----------------------|--------------------|---------|
|                                | No                | Yes                   | No                 | Yes     | |
| Stroke                         | 11,382 (67.7%)    | 2179 (60.8%)          | 2810 (16.7%)       | 667 (18.6%) | 2617 (15.6%) | 740 (20.6%) | < 0.001 |
| Liver Disease Ever             | 14,316 (66.7%)    | 164 (49.8%)           | 3628 (16.9%)       | 73 (22.2%) | 3512 (16.4%) | 92 (28.0%) | 0.008 |
| Bleeding Problems Ever         | 14,187 (66.6%)    | 296 (60.4%)           | 3610 (17.0%)       | 91 (18.6%) | 3500 (16.4%) | 103 (21.0%) | 0.504 |
| History Skin Cancer            | 14,142 (66.5%)    | 330 (64.5%)           | 3611 (17.0%)       | 88 (17.2%) | 3509 (16.5%) | 94 (18.4%) | < 0.001 |
| Rheumatoid Arthritis Ever      | 13,229 (65.8%)    | 1230 (74.8%)          | 3474 (17.3%)       | 226 (13.7%) | 3412 (17.0%) | 189 (11.5%) | 0.010 |
| Other/do not know              | 5874 (64.2%)      | 778 (60.3%)           | 1638 (17.9%)       | 242 (18.7%) | 1634 (17.9%) | 271 (21.0%) | |
|                                |                    |                       |                    |         |         |         |         |

The time-to-event analytic cohort consisted of 21,789 postmenopausal women. The table shows their baseline demographics, personal habits, and medical history by baseline HOMA-IR. The degree of insulin resistance was categorized as defined by previous studies: Low (HOMA-IR < 1.4), Moderate (1.4 ≤ HOMA-IR < 2.0), and High (HOMA-IR ≥ 2.0) [18–20]. Differences in baseline characteristics among HOMA-IR categories were assessed using chi-square tests.

CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent of task; HOMA-IR, homeostasis model assessment for insulin resistance.
Table 2  The distribution and risk of psoriasis by baseline demographic, personal habits, and medical history

| Clinical Trials                          | No psoriasis | Psoriasis | HR (95% CI) | P value |
|------------------------------------------|--------------|-----------|-------------|---------|
| **Estrogen-Alone Trial**                 |              |           |             |         |
| Not randomized                          | 11,549 (97.9%) | 250 (2.1%) | —           |         |
| Placebo                                 | 2002 (97.4%)  | 54 (2.6%)  | Reference   | 0.601   |
| Treated                                 | 2081 (97.7%)  | 50 (2.3%)  | 0.92 (0.63, 1.35) | 0.965   |
| **Estrogen + Progestin Trial**           |              |           |             |         |
| Not randomized                          | 11,549 (97.9%) | 250 (2.1%) | —           |         |
| Placebo                                 | 2764 (97.3%)  | 76 (2.7%)  | Reference   | 0.904   |
| Treated                                 | 2901 (97.9%)  | 62 (2.1%)  | 0.79 (0.56, 1.10) | 0.165   |
| **Calcium Vitamin D Trial**              |              |           |             |         |
| Not randomized                          | 14,046 (97.7%) | 332 (2.3%) | —           |         |
| Placebo                                 | 3625 (98.0%)  | 75 (2.0%)  | Reference   |         |
| Treated                                 | 3626 (97.7%)  | 85 (2.3%)  | 1.12 (0.82, 1.53) | 0.473   |
| **Dietary Modification Trial**           |              |           |             |         |
| Not randomized                          | 15,301 (97.7%) | 365 (2.3%) | —           |         |
| Placebo                                 | 2416 (97.6%)  | 59 (2.4%)  | Reference   |         |
| Treated                                 | 3580 (98.1%)  | 68 (1.9%)  | 0.79 (0.56, 1.12) | 0.190   |
| **Demographics**                         |              |           |             |         |
| Age                                      |              |           |             |         |
| 50–59                                    | 5668 (98.9%)  | 65 (1.1%)  | Reference   |         |
| 60–69                                    | 9972 (97.2%)  | 283 (2.8%) | 1.18 (0.90, 1.56) | 0.234   |
| 70–79                                    | 5657 (97.5%)  | 144 (2.5%) | 0.84 (0.62, 1.13) | 0.253   |
| Ethnicity                                |              |           |             |         |
| Caucasian                                | 12,399 (97.2%) | 357 (2.8%) | Reference   |         |
| Asian                                    | 434 (98.0%)   | 9 (2.0%)   | 0.83 (0.43, 1.61) | 0.579   |
| African-American                        | 6021 (98.6%)  | 85 (1.4%)  | 0.67 (0.53, 0.85) | 0.001   |
| Hispanic                                 | 1980 (98.3%)  | 34 (1.7%)  | 0.93 (0.65, 1.32) | 0.681   |
| Other/unspecified                        | 449 (98.5%)   | 7 (1.5%)   | 0.76 (0.36, 1.60) | 0.466   |
| Education                                |              |           |             |         |
| Less than high school                    | 8048 (98.0%)  | 166 (2.0%) | Reference   |         |
| College                                  | 7818 (97.7%)  | 184 (2.3%) | 1.11 (0.90, 1.36) | 0.346   |
| Higher                                   | 5304 (97.5%)  | 137 (2.5%) | 1.17 (0.93, 1.46) | 0.178   |
| Type of Job                              |              |           |             |         |
| Managerial/professional                  | 7567 (97.6%)  | 187 (2.4%) | Reference   |         |
| Technical/sales/admin                    | 5648 (98.0%)  | 114 (2.0%) | 0.84 (0.67, 1.06) | 0.152   |
| Service/labor                           | 4059 (97.8%)  | 90 (2.2%)  | 0.96 (0.75, 1.24) | 0.772   |
| Homemaker only                           | 2076 (97.5%)  | 54 (2.5%)  | 1.02 (0.75, 1.38) | 0.910   |
| Lifestyle Habits                         |              |           |             |         |
| Alcohol                                  |              |           |             |         |
| Never                                   | 2963 (98.4%)  | 47 (1.6%)  | Reference   |         |
| Past drinker                            | 4829 (97.9%)  | 106 (2.1%) | 1.45 (1.03, 2.04) | 0.034   |
| Current drinker                         | 13,294 (97.5%) | 334 (2.5%) | 1.51 (1.12, 2.05) | 0.008   |
| Smoking                                  |              |           |             |         |
| Never                                   | 11,057 (98.2%) | 208 (1.8%) | Reference   |         |
| Past smoker                             | 8294 (97.3%)  | 231 (2.7%) | 1.52 (1.26, 1.83) | < 0.001 |
| Current smoker                          | 1653 (97.3%)  | 46 (2.7%)  | 1.89 (1.38, 2.61) | < 0.001 |
| Recreation Physical Activity (MET-hour)  |              |           |             |         |
| ≥ 0 to < 2                               | 1310 (96.8%)  | 44 (3.2%)  | Reference   |         |
| ≥ 2 to < 8                               | 1147 (97.7%)  | 27 (2.3%)  | 0.70 (0.44, 1.14) | 0.150   |
| Table 2 (continued) | No psoriasis | Psoriasis | HR | P value |
|----------------------|--------------|-----------|----|---------|
|                       | n (%) | n (%) | (95% CI) |         |
| ≥ 8 to < 18           | 1064 (98.2%) | 20 (1.8%) | 0.55 (0.32, 0.93) | 0.026 |
| ≥ 18                 | 3878 (97.7%) | 92 (2.3%) | 0.66 (0.46, 0.94) | 0.021 |
| **Anthropometric Measures** | | |         |         |
| **Baseline Body Mass Index (kg/m²)** | | |         |         |
| Normal (18.5–24.9)    | 4663 (97.7%) | 112 (2.3%) | Reference |         |
| Overweight (25.0–29.9) | 7321 (97.9%) | 158 (2.1%) | 0.94 (0.74, 1.20) | 0.606 |
| Obese (≥ 30.0)        | 8437 (97.6%) | 204 (2.4%) | 1.13 (0.90, 1.43) | 0.288 |
| **Baseline Waist to Hip Ratio** | | |         |         |
| Normal (<0.800)       | 7998 (98.0%) | 167 (2.0%) | Reference |         |
| Overweight (0.800–0.849) | 5592 (97.8%) | 126 (2.2%) | 1.09 (0.87, 1.38) | 0.458 |
| Obese (≥ 0.850)       | 7395 (97.4%) | 194 (2.6%) | 1.28 (1.04, 1.57) | 0.020 |
| **Hormone-Related Factors** | | |         |         |
| **Estrogen-alone**     | | |         |         |
| Never                 | 14,676 (97.9%) | 320 (2.1%) | Reference |         |
| Past                  | 3443 (97.3%) | 94 (2.7%) | 1.16 (0.92, 1.46) | 0.200 |
| Current               | 3164 (97.6%) | 78 (2.4%) | 1.26 (0.98, 1.61) | 0.068 |
| **Estrogen plus Progesterin** | | |         |         |
| Never                 | 18,036 (97.7%) | 431 (2.3%) | Reference |         |
| Past                  | 1433 (97.9%) | 31 (2.1%) | 0.96 (0.67, 1.38) | 0.828 |
| Current               | 1822 (98.4%) | 30 (1.6%) | 0.82 (0.56, 1.18) | 0.285 |
| **Menstrual Cycle Regularity** | | |         |         |
| No                    | 1542 (97.4%) | 41 (2.6%) | Reference |         |
| Yes                   | 17,623 (97.7%) | 412 (2.3%) | 0.85 (0.61, 1.17) | 0.308 |
| Sometimes irregular   | 1959 (98.1%) | 37 (1.9%) | 0.70 (0.45, 1.09) | 0.116 |
| **Age at Menopause**  | | |         |         |
| 45 or younger         | 6289 (97.9%) | 138 (2.1%) | Reference |         |
| 46 to 49              | 6229 (97.8%) | 139 (2.2%) | 1.01 (0.80, 1.28) | 0.930 |
| 50 to 51              | 2562 (97.6%) | 63 (2.4%) | 1.07 (0.79, 1.44) | 0.666 |
| 52 or older           | 4358 (97.6%) | 107 (2.4%) | 0.99 (0.77, 1.28) | 0.959 |
| **Parity**            | | |         |         |
| Never pregnant        | 2099 (98.0%) | 42 (2.0%) | Reference |         |
| 1                     | 4656 (97.4%) | 126 (2.6%) | 1.29 (0.91, 1.83) | 0.152 |
| 2                     | 4783 (97.8%) | 108 (2.2%) | 1.04 (0.73, 1.49) | 0.830 |
| 3                     | 3262 (97.6%) | 81 (2.4%) | 1.12 (0.77, 1.63) | 0.542 |
| 4                     | 3932 (98.1%) | 76 (1.9%) | 0.91 (0.62, 1.32) | 0.616 |
| 5                     | 2403 (97.8%) | 54 (2.2%) | 1.05 (0.70, 1.57) | 0.827 |
| **Hysterectomy**      | | |         |         |
| No                    | 11,714 (97.9%) | 254 (2.1%) | Reference |         |
| Yes                   | 9575 (97.6%) | 238 (2.4%) | 1.20 (1.00, 1.43) | 0.046 |
| **Medical History**   | | |         |         |
| **Diabetes**          | | |         |         |
| No                    | 19,354 (97.7%) | 449 (2.3%) | Reference |         |
| Yes                   | 1925 (97.8%) | 43 (2.2%) | 1.05 (0.77, 1.43) | 0.773 |
| **Hypertension**      | | |         |         |
| No                    | 12,279 (97.7%) | 295 (2.3%) | Reference |         |
| Yes                   | 8801 (97.8%) | 195 (2.2%) | 0.90 (0.75, 1.08) | 0.274 |
| **Cardiovascular Disease** | | |         |         |
| No                    | 16,446 (97.8%) | 363 (2.2%) | Reference |         |
| Yes                   | 3492 (97.4%) | 94 (2.6%) | 1.14 (0.91, 1.43) | 0.246 |
activation toward the M1 phenotype through the AMPK/NFκB pathway [36], but other data suggest it could decrease inflammatory cytokines [37]. Human cohort data demonstrated no effect of metformin on morbidity and mortality in psoriasis patients with type 2 diabetes [38].

### Strengths and limitations

While the accuracy of ICD-9-CM diagnostic codes has a positive predictive value of 89% (95% CI 79–95%) in the Northern California population, a limitation of our study is the use of ICD-9-CM diagnostic codes from Medicare.
claims reports to identify psoriasis cases [16]. Although hyperinsulinemic euglycemic clamp (HEC) is considered the gold standard for evaluating insulin sensitivity, estimates derived from HOMA-IR strongly correlate with HEC [6–8, 39]. Lastly, our cohort is limited to postmenopausal women, therefore, limiting the generalizability of these findings.

Compared to previous studies (case–control studies with \( n \) < 200), a key strength of our analysis is the use of a large study cohort, which provides for a more stable and robust multivariable model that accounts for key confounders for psoriasis such as obesity and smoking habits. More importantly, our analysis takes into consideration the time variable and indicates the temporal sequence between exposure and outcome compared to previous case–control studies.

Furthermore, most of the previous studies on HOMA-IR used a simple mathematical approximation while we used the updated HOMA2 version 2.2.3 [17]. Whereas BMI and WHR are subject to change in aging women, insulin resistance by HOMA-IR provides a metabolic functional measurement independent of anatomic measurements.

**Conclusion**

Psoriasis is a systemic inflammatory skin disease associated with significant comorbidities. In postmenopausal women, higher baseline insulin resistance assessed by HOMA-IR was significantly associated with an increased risk of psoriasis during a cumulative 21-year follow-up. While previous studies suggested that insulin resistance is a sequela of psoriasis, results from this time-to-event analysis indicate that insulin resistance can precede and is associated with an increased risk of psoriasis. Findings may warrant implementing lifestyle changes such as diet and exercise to reduce insulin resistance, which may ultimately improve or reduce the risk of psoriasis. Further research is warranted to investigate the underlying pathophysiology linking psoriasis and insulin resistance as well as the potential role of hypoglycemic agents in psoriasis management.

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Author contributions AAC was involved in the data acquisition, analysis, and interpretation. HL, RTC, and DJL conceived the idea and initiated the analysis plan for the current study. AAC, HL, W.L., and DJL were involved in drafting the manuscript. RTC, JKY, and KP revised the manuscript critically for important intellectual content. All the authors approved the final version of the manuscript to be submitted for publication. DJL is the guarantor of this work and, as such, had access to data in the study and takes responsibility for integrity of the data and accuracy of the data analysis.

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Declarations

Conflict of interest Rowan Chlebowski is a consultant for Novartis, AstraZeneca, Genentech, Amgen, Immunomedics and received honorarium from Novartis and AstraZeneca. Delphine J. Lee is a consultant for Abeona Therapeutics.

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