# **Materials and Methods**

## Data source

The National Health Insurance Research Database (NHIRD) contains comprehensive information about the insured individuals, including demographic data and health care claims data. Before the data were released to the researchers, the identification numbers of the participants were encrypted to protect individual privacy. The NHIRD data have been used widely in epidemiological studies [21-27]. The diagnostic codes used were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2018-07-016AC).

## Study population, exposure, and outcome

### *Analysis 1: Psoriasis as a risk factor of AD*

A bidirectional cohort study design was used to investigate the longitudinal association between psoriasis and AD (**Figure 1**). In analysis 1, we identified patients with psoriasis from the NHIRD between January 1, 1998, and December 31, 2009. The diagnosis of psoriasis was established according to the ICD-9-CM codes 696.0 and 696.1. Patients were considered to have psoriasis only if the diagnosis was established by dermatologists and the condition was observed at ≥3 outpatient visits. The psoriasis identification algorithm was validated by Lee et al. with a positive predictive value of 98.5% [28].

The primary outcome assessed was new-onset AD, which was identified by the ICD-9-CM code 691. Diagnoses of AD were made at least three times by dermatologists during the observation period. To identify incident AD, we excluded patients with a previous AD diagnosis, invalid insurance status, unknown sex status, or unknown covariates.

For each patient with psoriasis, four matched controls were selected from the Longitudinal Health Insurance Database (LHID), which provides longitudinally linked anonymized data of enrollees randomly sampled from the registry for beneficiaries of the NHIRD. These controls were matched for age, sex, monthly premium, residence, and comorbidities. Monthly premium was classified as 0–500, 501–800, and ≥801 US dollars. Residence was classified into five levels of urbanization, with level 1 indicating the most urbanized area and level 5 the least urbanized area. Monthly premium and urbanization levels were used to represent socioeconomic status.

The index date for the psoriasis group was the date when psoriasis was diagnosed for the first time, whereas the index date for the control was the psoriasis-diagnosed date of the matched patient with psoriasis. All individuals were followed from the index date until a diagnosis of AD, the date of withdrawal from the insurance program, or December 31, 2011, whichever occurred first. To eliminate the effects of biologic therapy on the incidence of AD, we performed a sensitivity analysis, whereby psoriasis patients with prior use of biologic therapy were excluded.

### Analysis 2: AD as a risk factor for psoriasis

The cohort in analysis 2 included patients with AD from the NHIRD between January 1, 1998, and December 31, 2009. The primary outcome assessed was new-onset psoriasis. Similarly, to identify incident psoriasis, we excluded patients with a previous psoriasis diagnosis, invalid insurance status, unknown sex status, or unknown covariates. For each patient with AD, four controls were selected from the LHID after matching for age, sex, monthly premium, residence, and comorbidities.

The index date for the AD group was the date when AD was diagnosed for the first time, whereas the index date for the control was the AD-diagnosed date of the matched patient with AD. All individuals were followed from the index date until a diagnosis of psoriasis, the date of withdrawal from the insurance program, or December 31, 2011, whichever occurred first.

## Comorbidities

The comorbidities considered in this study included allergic conjunctivitis (ICD-9-CM codes 372.05, 372.10, and 372.14), allergic rhinitis (ICD-9-CM code 477), asthma (ICD-9-CM code 493), cancer (ICD-9-CM codes 140–208), thyroid diseases (ICD-9-CM codes 240–246), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401–405), and autoimmune disease (ICD-9-CM codes 340, 358, 443.1, 446.0, 446.1, 446.2, 446.4, 446.5, 446.7, 555, 556.0–556.6, 556.8, 556.9, 710.0, 710.1, 710.2, 710.3, 710.4, and 714). An individual was considered to have comorbidity only if the condition was recorded at ≥3 outpatient visits. Cancers and severe systemic autoimmune diseases were identified in the database of Catastrophic Illness Patients [29]. In Taiwan, the diagnostic information of severe systemic autoimmune diseases and cancers is sent to the insurance administration for review by commissioned expert panels to confirm the diagnosis. After the confirmation of diagnosis, patients are entitled to waive medical co-payment. All information of patients with cancers and severe systemic autoimmune diseases is included in the Catastrophic Illness Patients database.

## Statistical analysis

For between-group comparisons, t-test or Wilcoxon rank sum test was used for continuous variables and Pearson’s test was used for categorical variables. A Cox proportional hazards regression model with adjusted for the potential confounders (including age, sex, monthly premium, residence, and comorbidities) was used to assess the bidirectional association between psoriasis and AD. The adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) indicate the strength and direction of these associations. Two-sided *P* <0.05 was considered to indicate statistical significance. Data analyses were performed using Statistical Analysis System (SAS) software (version 9.4, SAS Institute, Cary, NC, USA).