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ORIGINAL RESEARCH ARTICLE

Association Between Inflammatory Skin Disease and Cardiovascular and Cerebrovascular Co-Morbidities in US Adults: Analysis of Nationwide Inpatient Sample Data

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Abstract

Background Psoriasis, atopic dermatitis or eczema (AD-E), pemphigus, bullous pemphigoid (BP), and hidradenitis are chronic inflammatory skin disorders associated with systemic immune activation, considerable symptom burden, stigma, functional disturbances, and mental health symptoms. All of these might increase cardiovascular risk.

Objective The objective of this study was to determine whether these inflammatory skin diseases are associated with increased cardiovascular/cerebrovascular risk and/or disease.

Methods We analyzed data from the 2002–2012 National Inpatient Sample, including a representative 20% sample of all US hospitalizations ($n = 72{,}108{,}077$ adults).

Results In multivariate logistic regression models with propensity score matching, patients hospitalized with versus without a diagnosis the inflammatory skin diseases examined had higher odds of obesity (odds ratio [95% confidence interval] for pemphigus: 1.16 [1.05–1.29]; BP 1.14 [1.06–1.23]; AD-E: 1.82 [1.79–1.86]; psoriasis: 2.36 [2.32–2.41]; hidradenitis: 2.79 [2.59–3.01]). Inflammatory skin disease was also associated with significantly higher odds of different cardiovascular risk factors, including hypertension (pemphigus: 1.39 [1.31–1.48]; BP 1.96 [1.88–2.05]; AD-E: 1.19 [1.17–1.21]; psoriasis: 1.61 [1.59–1.64]), and diabetes mellitus with complications (pemphigus: 1.34 [1.18–1.52]; BP: 2.06 [1.90–2.24]; AD-E: 1.13 [1.10–1.17]; psoriasis: 1.39 [1.35–1.44]), as well as vascular, cardiovascular, and cerebrovascular disease, including peripheral vascular disease (pemphigus: 1.14 [1.00–1.30]; BP: 1.83 [1.69–1.98]; AD-E: 1.18 [1.14–1.22]; psoriasis: 1.32 [1.28–1.35]), peripheral and visceral atherosclerosis (BP: 1.67 [1.53–1.81]; AD-E: 1.16 [1.12–1.20]; psoriasis: 1.27 [1.24–1.30]), pulmonary circulation disorders (pemphigus: 1.67 [1.39–2.01]; BP: 2.17 [1.92–2.45]; AD-E: 1.39 [1.33–1.45]; psoriasis: 1.37 [1.31–1.43]), congestive heart failure (pemphigus: 1.75 [1.60–1.90]; BP: 2.82 [2.68–2.98]; AD-E: 1.10 [1.07–1.13]; psoriasis: 1.05 [1.02–1.07]), history of transient ischemic attack (pemphigus: 1.36 [1.14–1.62]; BP: 2.03 [1.83–2.26]; AD-E: 1.19 [1.15–1.23]; psoriasis: 1.31 [1.26–1.36]), and cerebrovascular disease. In stratified analyses, multiple inflammatory skin diseases were associated with significantly higher rates of obesity, hypertension, and/or diabetes in patients aged <50 years and females.

Conclusions Psoriasis, pemphigus, BP, AD-E, and hidradenitis were all associated with increased cardiovascular and cerebrovascular risk, especially at younger age.

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Key Points

While cardiovascular disease has been associated with psoriasis, an association of other inflammatory skin diseases and cardiovascular risk is unclear.

The present study found that pemphigus, bullous pemphigoid, atopic dermatitis, hidradenitis, and psoriasis were all associated with increased cardiovascular and cerebrovascular risk.

Particularly high rates of obesity, hypertension, and/or diabetes mellitus were observed in patients with multiple inflammatory skin diseases who were younger and female.

1 Introduction

Chronic inflammatory skin disorders, including psoriasis [1], atopic dermatitis (AD) [2], pemphigus [3], bullous pemphigoid (BP) [4], and hidradenitis [5], are associated with a significant health burden, quality-of-life (QOL) impairment, and co-morbid health conditions. In particular, psoriasis has been consistently found to be associated with increased cardiovascular risk factors and events [6]. These associations have been posited to be specific to psoriasis and related to increased circulating tumor necrosis factor (TNF)-α levels [7]. Cardiovascular risk may be attributable to chronic inflammation, and immune cells play a critical role in the pathogenesis of atherosclerotic lesions [8]. However, recent studies have suggested that other inflammatory skin diseases are also associated with increased cardiovascular risk, including AD [9–12], pemphigus [13], BP [14–16], and hidradenitis [17]. Yet each of these disorders has distinct mechanisms and common inflammatory pathways are not well-established.

On the other hand, each of the abovementioned inflammatory skin diseases are chronic disorders associated with a considerable symptom burden, stigma, functional disturbances, QOL impairment, and mental health symptoms [18–22]. These harmful sequela of chronic disease by themselves may increase cardiovascular risk in affected individuals. We hypothesized that increased cardiovascular and cerebrovascular morbidity occurs in multiple chronic inflammatory skin diseases. In the present study, we examine the associations of various inflammatory skin diseases—i.e., pemphigus, BP, AD, psoriasis, and hidradenitis—with cardiovascular and/or cerebrovascular risk factors and disease in a nationwide hospital cohort of adults.

2 Methods

2.1 Data Source

The 2002–2012 Nationwide Inpatient Sample (NIS) provided by the Healthcare Cost and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality (AHRQ) was analyzed [23]. Each year of the NIS contains an ~20% stratified representative sample of all inpatient hospitalizations in the USA. Sample weights were created by HCUP, which factored in the sampling design of hospitals in the USA. These sample weights are needed to provide representative estimates of hospital discharges across the whole country. All data were de-identified and no attempts were made to identify any of the individuals in the database. All parties with access to the HCUP were compliant to HCUP's formal data use agreement. The study was approved by the institutional review board at Northwestern University (Chicago, IL, USA).

2.2 Identification of Inflammatory Skin Disease and Co-Morbidities

The databases were searched for a primary and/or secondary diagnosis of pemphigus, BP, AD or eczema (ADE), psoriasis, and hidradenitis using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes [24]. The NIS lists one primary diagnosis and up to 24 secondary diagnoses. Per HCUP inpatient database standards, the first listed diagnosis (DX1) is the principal diagnosis, i.e., the primary reason for hospitalization. The primary diagnosis was defined in NIS as the condition chiefly responsible for admission to the hospital for care. Previous studies validated the use of ICD-9-CM codes 694.4 (pemphigus) [25], 694.5 (BP) [25], 691.8 (AD), and 692.9 (eczema) [26], 696.1 (psoriasis) [27, 28], and 705.83 (hidradenitis) [29] in the outpatient and/or inpatient setting. The control group included all hospitalizations without any inflammatory skin disease, yielding a representative cohort of US hospitalizations.

A co-morbidity was considered present with either a primary or secondary diagnosis of the disease. Some co-morbidities were pre-coded according to Association for Healthcare Research and Quality (AHRQ) co-morbidity measures and through the NIS Clinical Classification Software (CCS). Co-morbidities pre-coded by the AHRQ also utilized Diagnosis-Related Groups (DRGs) and thus would capture a higher frequency of the co-morbidities than use of *ICD-9-CM* codes alone; therefore, comparing frequencies for co-morbidities coded by the AHRQ with those using only *ICD-9-CM* codes may not be possible.

Table 1 Association between pemphigus and cardiovascular/cerebrovascular co-morbidities in US adults

Co-morbidity	No ISD	Pemphigus				
	Percentage [95% CI]	Percentage [95% CI]	Crude OR [95% CI]	*P*-value	Propensity OR	*P*-value
Hypertension	42.61 [42.27–42.95]	50.77 [49.23–52.31]	**1.39 [1.31–1.48]**	<0.0001	**1.27 [1.19–1.37]**	<0.0001
Diabetes, uncomplicated	16.61 [16.46–16.77]	25.01 [23.75–26.27]	**1.68 [1.57–1.79]**	<0.0001	**1.57 [1.45–1.70]**	<0.0001
Diabetes with chronic complication	3.64 [3.57–3.70]	4.82 [4.22–5.41]	**1.34 [1.18–1.52]**	<0.0001	**1.28 [1.11–1.47]**	0.0007
Type 2 diabetes mellitus	1.12 [1.10–1.14]	1.49 [1.18–1.80]	**1.33 [1.08–1.64]**	0.0082	**1.32 [1.05–1.67]**	0.0181
Obesity	7.42 [7.28–7.57]	8.53 [7.71–9.35]	**1.16 [1.05–1.29]**	0.0044	1.10 [0.98–1.23]	0.1094
Coronary artery disease	20.76 [20.46–21.07]	19.28 [18.09–20.46]	**0.91 [0.85–0.98]**	0.0149	**0.81 [0.74–0.88]**	<0.0001
Congestive heart failure	7.60 [7.49–7.71]	12.55 [11.60–13.51]	**1.75 [1.60–1.90]**	<0.0001	**1.60 [1.46–1.77]**	<0.0001
Peripheral vascular disease	4.71 [4.63–4.80]	5.34 [4.68–6.00]	**1.14 [1.00–1.30]**	0.0444	1.04 [0.90–1.20]	0.5623
History of myocardial infarction	4.24 [4.15–4.33]	3.77 [3.23–4.30]	0.88 [0.77–1.02]	0.095	**0.77 [0.65–0.91]**	0.0025
Peripheral and visceral atherosclerosis	4.15 [4.08–4.23]	4.22 [3.63–4.82]	1.02 [0.88–1.18]	0.8165	0.93 [0.80–1.10]	0.4094
Myocardial infarction	3.04 [2.98–3.11]	2.91 [2.47–3.36]	0.96 [0.82–1.12]	0.5793	0.90 [0.76–1.08]	0.2707
Pulmonary circulation disorders	1.24 [1.21–1.27]	2.05 [1.68–2.42]	**1.67 [1.39–2.01]**	<0.0001	**1.52 [1.24–1.87]**	<0.0001
Coronary artery occlusion	1.22 [1.20–1.23]	1.07 [0.81–1.32]	0.88 [0.69–1.12]	0.2893	0.82 [0.62–1.08]	0.1589
Pulmonary hypertension	0.04 [0.04–0.04]	0.07 [0.00–0.13]	1.61 [0.60–4.27]	0.344	1.94 [0.73–5.15]	0.1862
Cerebrovascular accident	2.23 [2.20–2.26]	1.76 [1.43–2.09]	**0.79 [0.65–0.95]**	0.0135	**0.76 [0.61–0.94]**	0.012
History of transient ischemic attack	1.97 [1.90–2.03]	2.65 [2.18–3.12]	**1.36 [1.14–1.62]**	0.0007	**1.28 [1.06–1.54]**	0.0094
Late effects of cerebrovascular disease	2.04 [2.00–2.07]	3.50 [2.97–4.03]	**1.74 [1.49–2.04]**	<0.0001	**1.78 [1.51–2.11]**	<0.0001
Ill-defined cerebrovascular disease	1.25 [1.22–1.29]	0.73 [0.50–0.96]	**0.58 [0.42–0.79]**	0.0007	**0.45 [0.31–0.66]**	<0.0001
Other cerebrovascular disease	0.53 [0.52–0.55]	0.86 [0.61–1.11]	**1.62 [1.20–2.17]**	0.0014	**1.63 [1.18–2.25]**	0.0032

Bolded odds ratios represent significance at $P < 0.05$

CI confidence interval, *ISD* inflammatory skin disease, *OR* odds ratio

2.3 Data Processing and Statistical Methods

All data analyses and statistical processes were performed using SAS® version 9.4 (SAS Institute, Cary, NC, USA). Analyses of survey responses were performed using SURVEY procedures. Analysis were performed in adults (≥18 years). All statistical models employed SURVEY procedures, including discharge trend weights, sample strata accounting for each hospital's census region or division, ownership/control, location/teaching, and number of beds that were provided by NIS, and clustering by individual hospital. These models allow for representative weighted estimates of frequency and prevalence of hospital discharges across the USA. Complete case analysis was performed.

Prevalences of co-morbidities and 95% confidence intervals (CIs) were estimated. Stratified analyses were also performed by age (<50, ≥50 years), sex (male, female), race/ethnicity (white, non-white). Rao-Scott Chi square tests were used to compare prevalence estimates between subgroups. Survey-weighted binary logistic regression models were constructed to determine the association of each inflammatory skin disease with various co-morbidities. Propensity score matching models were constructed that controlled for age, sex, race/ethnicity, mean annual household income, insurance status, number of chronic conditions, and hospital region. *P*-values ≤0.05 were considered significant.

3 Results

3.1 Study Population

Overall, there were 72,651,487 adult discharges captured in the NIS between the years 2002 and 2012. There were 6339 admissions for pemphigus (weighted frequency: 30,208), 13,342 for BP (weighted frequency: 63,898), 164,868 for AD-E (weighted frequency: 789,488), 185,803 for psoriasis (weighted frequency: 891,240), and 6872 for hidradenitis (weighted frequency: 32,695).

3.2 Cardiovascular Risk Factors

In bivariate analyses, patients hospitalized with versus without a primary or secondary diagnosis of any of the five inflammatory skin disease examined had significantly

Table 2 Association between bullous pemphigoid and cardiovascular/cerebrovascular comorbidities in US adults

Co-morbidity	No ISD	Bullous pemphigoid				
	Percentage [95% CI]	Percentage [95% CI]	Crude OR [95% CI]	*P*-value	Propensity OR	*P*-value
Hypertension	42.61 [42.27–42.95]	59.32 [58.30–0.34]	**1.96 [1.88–2.05]**	<0.0001	**1.80 [1.71–1.90]**	<0.0001
Diabetes, uncomplicated	16.61 [16.46–16.77]	24.97 [24.04–25.90]	**1.67 [1.59–1.76]**	<0.0001	**1.53 [1.44–1.62]**	<0.0001
Diabetes with chronic complication	3.64 [3.57–3.70]	7.22 [6.64–7.80]	**2.06 [1.90–2.24]**	<0.0001	**1.90 [1.73–2.09]**	<0.0001
Type 2 diabetes mellitus	1.12 [1.10–1.14]	1.71 [1.48–1.95]	**1.53 [1.33–1.76]**	<0.0001	**1.45 [1.24–1.69]**	<0.0001
Obesity	7.42 [7.28–7.57]	8.37 [7.77–8.97]	**1.14 [1.06–1.23]**	0.0007	1.01 [0.93–1.10]	0.8704
Coronary artery disease	20.76 [20.46–21.07]	24.79 [23.83–25.76]	**1.26 [1.19–1.33]**	<0.0001	**1.17 [1.10–1.24]**	<0.0001
Congestive heart failure	7.60 [7.49–7.71]	18.83 [18.01–19.64]	**2.82 [2.68–2.98]**	<0.0001	**2.58 [2.42–2.74]**	<0.0001
Peripheral vascular disease	4.71 [4.63–4.80]	8.29 [7.68–8.89]	**1.83 [1.69–1.98]**	<0.0001	**1.68 [1.54–1.83]**	<0.0001
History of myocardial infarction	4.24 [4.15–4.33]	4.82 [4.36–5.29]	**1.15 [1.04–1.26]**	0.0071	1.08 [0.97–1.21]	0.1827
Peripheral and visceral atherosclerosis	4.15 [4.08–4.23]	6.74 [6.20–7.27]	**1.67 [1.53–1.81]**	<0.0001	**1.59 [1.45–1.74]**	<0.0001
Myocardial infarction	3.04 [2.98–3.11]	3.20 [2.89–3.52]	1.05 [0.95–1.17]	0.3072	0.98 [0.87–1.10]	0.7453
Pulmonary circulation disorders	1.24 [1.21–1.27]	2.64 [2.32–2.97]	**2.17 [1.92–2.45]**	<0.0001	**1.92 [1.69–2.19]**	<0.0001
Coronary artery occlusion	1.22 [1.20–1.23]	1.41 [1.20–1.62]	**1.16 [1.00–1.35]**	0.0492	1.11 [0.93–1.32]	0.2421
Pulmonary hypertension	0.04 [0.04–0.04]	0.03 [0.00–0.06]	0.72 [0.27–1.92]	0.5129	0.67 [0.22–2.07]	0.4878
Cerebrovascular accident	2.23 [2.20–2.26]	2.32 [2.05–2.59]	1.04 [0.93–1.17]	0.5003	0.97 [0.84–1.11]	0.6308
History of transient ischemic attack	1.97 [1.90–2.03]	3.91 [3.51–4.32]	**2.03 [1.83–2.26]**	<0.0001	**1.85 [1.66–2.07]**	<0.0001
Late effects of cerebrovascular disease	2.04 [2.00–2.07]	6.86 [6.32–7.41]	**3.54 [3.26–3.86]**	<0.0001	**3.35 [3.05–3.68]**	<0.0001
Ill-defined cerebrovascular disease	1.25 [1.22–1.29]	1.13 [0.92–1.33]	0.90 [0.75–1.08]	0.2388	0.83 [0.67–1.03]	0.0834
Other cerebrovascular disease	0.53 [0.52–0.55]	1.28 [1.07–1.49]	**2.42 [2.06–2.86]**	<0.0001	**2.18 [1.81–2.63]**	<0.0001

Bolded odds ratios represent significance at $P < 0.05$

CI confidence interval, *ISD* inflammatory skin disease, *OR* odds ratio

higher odds of obesity (odds ratio [95% CI] for pemphigus: 1.16 [1.05–1.29]; BP 1.14 [1.06–1.23]; AD-E: 1.82 [1.79–1.86]; psoriasis: 2.36 [2.32–2.41]; hidradenitis: 2.79 [2.59–3.01]) (Tables 1-5). Inflammatory skin disease was also associated with significantly higher odds of different cardiovascular risk factors, including hypertension (pemphigus: 1.39 [1.31–1.48]; BP 1.96 [1.88–2.05]; AD-E: 1.19 [1.17–1.21]; psoriasis: 1.61 [1.59–1.64]), diabetes without complications (pemphigus: 1.68 [1.57–1.79]; BP: 1.67 [1.59–1.76]; psoriasis 1.51 [1.49–1.54]; hidradenitis 1.30 [1.22–1.39]), diabetes with chronic complications (pemphigus: 1.34 [1.18–1.52]; BP: 2.06 [1.90–2.24]; AD-E: 1.13 [1.10–1.17]; psoriasis: 1.39 [1.35–1.44]), particularly type 2 diabetes (pemphigus: 1.33 [1.08–1.64]; BP: 1.53 [1.34–1.76]; psoriasis: 1.22 [1.17–1.28]). All of these associations remained significant in propensity regression models.

3.3 Associations of Cardiovascular Risk Factors in Inflammatory Skin Disease

In stratified analyses by age, there were significantly higher rates of obesity in patients aged <50 years (10.4-18.5% vs. 7.0%) with versus without inflammatory skin disease and in AD-E (12.6%), psoriasis (15.7%), and hidradenitis (17.5%) versus controls (7.7%) in patients aged ≥50 years ($P < 0.0001$). There were also higher rates of hypertension in patients aged <50 years (22.5–31.1% vs. 16.2%) with versus without inflammatory skin disease and in BP (60.7%), AD-E (60.0%), and psoriasis (63.4%) vs. controls (59.1%) in patients aged >50 years ($P < 0.0001$). Similarly, there were higher rates of uncomplicated diabetes in patients aged <50 years with any inflammatory skin disease (8.4–16.7% vs. 6.6%; $P < 0.0001$), and all inflammatory skin disorders at age ≥50 years (25.6–25.7% vs. 22.9%; $P < 0.0001$) except AD-E (21.1%).

In stratified analyses by sex, there were higher rates of obesity in males with AD-E (10.4%), psoriasis (13.5%) and hidradenitis (13.0%), but not pemphigus (6.6%) or BP (5.9%) compared with controls (6.8%) and females in all inflammatory disorders versus controls (9.9–22.3% vs. 7.8%) ($P < 0.0001$ for both). In contrast, there were higher rates of hypertension only in females with psoriasis (54.6%), AD-E (46.4%), BP (60.4%), and pemphigus (52.7%) versus controls (39.0%), and males with psoriasis (54.4%) and BP (57.8%) versus controls (48.3%), but

Table 3 Association between atopic dermatitis or eczema and cardiovascular/cerebrovascular co-morbidities in US adults

Co-morbidity	No ISD	Atopic dermatitis/eczema				
	Percentage [95% CI]	Percentage [95% CI]	Crude OR [95% CI]	*P*-value	Propensity OR	*P*-value
Hypertension	42.61 [42.27–42.95]	46.89 [46.43–47.35]	**1.19 [1.17–1.21]**	<0.0001	**1.05 [1.03–1.07]**	<0.0001
Diabetes, uncomplicated	16.61 [16.46–16.77]	16.69 [16.42–16.96]	1.01 [0.99–1.02]	0.5028	**0.90 [0.89–0.92]**	<0.0001
Diabetes with chronic complication	3.64 [3.57–3.70]	4.10 [3.94–4.26]	**1.13 [1.10–1.17]**	<0.0001	1.02 [0.98–1.06]	0.2935
Type 2 diabetes mellitus	1.12 [1.10–1.14]	1.11 [1.05–1.17]	0.99 [0.94–1.04]	0.612	**0.88 [0.83–0.93]**	<0.0001
Obesity	7.42 [7.28–7.57]	12.75 [12.44–13.06]	**1.82 [1.79–1.86]**	<0.0001	**1.61 [1.58–1.65]**	<0.0001
Coronary artery disease	20.76 [20.46–21.07]	16.51 [16.16–16.85]	**0.75 [0.74–0.77]**	<0.0001	**0.67 [0.66–0.69]**	<0.0001
Congestive heart failure	7.60 [7.49–7.71]	8.29 [8.07–8.51]	**1.10 [1.07–1.13]**	<0.0001	**1.03 [1.01–1.06]**	0.0229
Peripheral vascular disease	4.71 [4.63–4.80]	5.51 [5.32–5.69]	**1.18 [1.14–1.22]**	<0.0001	**1.07 [1.04–1.11]**	<0.0001
History of myocardial infarction	4.24 [4.15–4.33]	3.42 [3.30–3.55]	**0.80 [0.78–0.83]**	<0.0001	**0.73 [0.70–0.75]**	<0.0001
Peripheral and visceral atherosclerosis	4.15 [4.08–4.23]	4.79 [4.62–4.95]	**1.16 [1.12–1.20]**	<0.0001	**1.07 [1.03–1.11]**	0.0002
Myocardial infarction	3.04 [2.98–3.11]	1.71 [1.63–1.79]	**0.56 [0.53–0.58]**	<0.0001	**0.52 [0.49–0.55]**	<0.0001
Pulmonary circulation disorders	1.24 [1.21–1.27]	1.71 [1.63–1.80]	**1.39 [1.33–1.45]**	<0.0001	**1.24 [1.18–1.31]**	<0.0001
Coronary artery occlusion	1.22 [1.20–1.23]	0.91 [0.86–0.96]	**0.75 [0.71–0.79]**	<0.0001	**0.70 [0.66–0.74]**	<0.0001
Pulmonary hypertension	0.04 [0.04–0.04]	0.06 [0.04–0.07]	**1.38 [1.12–1.70]**	0.003	1.23 [0.96–1.58]	0.1099
Cerebrovascular accident	2.23 [2.20–2.26]	1.66 [1.59–1.73]	**0.74 [0.71–0.77]**	<0.0001	**0.71 [0.67–0.74]**	<0.0001
History of transient ischemic attack	1.97 [1.90–2.03]	2.33 [2.22–2.43]	**1.19 [1.15–1.23]**	<0.0001	1.04 [1.00–1.08]	0.0552
Late effects of cerebrovascular disease	2.04 [2.00–2.07]	2.49 [2.39–2.59]	**1.23 [1.18–1.28]**	<0.0001	**1.15 [1.10–1.20]**	<0.0001
Ill-defined cerebrovascular disease	1.25 [1.22–1.29]	0.98 [0.92–1.03]	**0.78 [0.74–0.82]**	<0.0001	**0.71 [0.67–0.76]**	<0.0001
Other cerebrovascular disease	0.53 [0.52–0.55]	0.67 [0.62–0.71]	**1.25 [1.18–1.33]**	<0.0001	**1.19 [1.10–1.27]**	<0.0001

Bolded odds ratios represent significance at $P < 0.05$

CI confidence interval, *ISD* inflammatory skin disease, *OR* odds ratio

lower rates of hypertension in both males and females with hidradenitis (32.2% and 30.0%) ($P < 0.0001$). However, there were higher rates of uncomplicated diabetes only in females with all inflammatory disorders versus controls (16.6–25.8% vs. 14.8%), and males with psoriasis (22.5%), BP (25.5%), and pemphigus (23.9%) versus controls (19.4%).

In stratified analyses by race/ethnicity, there were significantly higher rates of obesity in both whites (8.7–19.3% vs. 7.6%) and non-whites (9.2–18.0% vs. 8.0%) with versus without inflammatory skin disease ($P < 0.0001$ for both). In contrast, there were higher rates of hypertension only in whites and non-whites with psoriasis (55.0% and 55.3%), AD-E (49.2% and 43.9%), BP (59.5% and 63.7%), and pemphigus (52.3% and 49.6%) versus controls (44.8% and 40.4%), but lower rates of hypertension in both whites and non-whites with hidradenitis (32.2% and 31.0%) ($P < 0.0001$ for both). Last, higher rates of uncomplicated diabetes were found in whites and non-whites with hidradenitis (23.8% and 19.7%), psoriasis (22.4% and 27.2%), BP (23.3% and 31.8%), and pemphigus (22.9% and 30.4%) versus controls (16.2% and 18.4%).

3.4 Vascular, Cardiovascular, and Cerebrovascular Disease

In bivariate analyses, inflammatory skin disease was also associated with significantly higher odds of vascular, cardiovascular, and cerebrovascular disease, including peripheral vascular disease (pemphigus: 1.14 [1.00–1.30]; BP: 1.83 [1.69–1.98]; AD-E: 1.18 [1.14–1.22]; psoriasis: 1.32 [1.28–1.35]), peripheral and visceral atherosclerosis (BP: 1.67 [1.53–1.81]; AD-E: 1.16 [1.12–1.20]; psoriasis: 1.27 [1.24–1.30]), pulmonary circulation disorders (pemphigus: 1.67 [1.39–2.01]; BP: 2.17 [1.92–2.45]; AD-E: 1.39 [1.33–1.45]; psoriasis: 1.37 [1.31–1.43]), congestive heart failure (pemphigus: 1.75 [1.60–1.90]; BP: 2.82 [2.68–2.98]; AD-E: 1.10 [1.07–1.13]; psoriasis: 1.05 [1.02–1.07]), history of transient ischemic attack (pemphigus: 1.36 [1.14–1.62]; BP: 2.03 [1.83–2.26]; AD-E: 1.19 [1.15–1.23]; psoriasis: 1.31 [1.26–1.36]), late effects of cerebrovascular disease (pemphigus: 1.74 [1.49–2.04]; BP: 3.54 [3.26–3.86]; AD-E: 1.23 [1.18–1.28), and other cerebrovascular disease (pemphigus: 1.62 [1.20–2.17]; BP 2.42 [2.06–2.86]; AD-E: 1.25 [1.18–1.33]) (Tables 1-5).

Table 4 Association between psoriasis and cardiovascular/cerebrovascular co-morbidities in US adults

Co-morbidity	No ISD	Psoriasis				
	Percentage [95% CI]	Percentage [95% CI]	Crude OR [95% CI]	*P*-value	Propensity OR	*P*-value
Hypertension	42.61 [42.27–42.95]	54.48 [54.07–54.89]	**1.61 [1.59–1.64]**	<0.0001	**1.23 [1.21–1.25]**	<0.0001
Diabetes, uncomplicated	16.61 [16.46–16.77]	23.13 [22.80–23.46]	**1.51 [1.49–1.54]**	<0.0001	**1.20 [1.18–1.22]**	<0.0001
Diabetes with chronic complication	3.64 [3.57–3.70]	4.99 [4.79–5.20]	**1.39 [1.35–1.44]**	<0.0001	**1.05 [1.01–1.09]**	0.0081
Type 2 diabetes mellitus	1.12 [1.10–1.14]	1.37 [1.31–1.43]	**1.22 [1.17–1.28]**	<0.0001	0.99 [0.95–1.04]	0.7366
Obesity	7.42 [7.28–7.57]	15.92 [15.58–16.27]	**2.36 [2.32–2.41]**	<0.0001	**1.77 [1.74–1.81]**	<0.0001
Coronary artery disease	20.76 [20.46–21.07]	22.76 [22.37–23.16]	**1.13 [1.10–1.15]**	<0.0001	**0.86 [0.85–0.88]**	<0.0001
Congestive heart failure	7.60 [7.49–7.71]	7.94 [7.74–8.14]	**1.05 [1.02–1.07]**	0.0001	**0.88 [0.86–0.90]**	<0.0001
Peripheral vascular disease	4.71 [4.63–4.80]	6.11 [5.92–6.29]	**1.32 [1.28–1.35]**	<0.0001	1.03 [1.00–1.06]	0.0837
History of myocardial infarction	4.24 [4.15–4.33]	5.35 [5.18–5.53]	**1.28 [1.24–1.32]**	<0.0001	**0.96 [0.93–0.99]**	0.0087
Peripheral and visceral atherosclerosis	4.15 [4.08–4.23]	5.21 [5.05–5.37]	**1.27 [1.24–1.30]**	<0.0001	1.01 [0.98–1.04]	0.5374
Myocardial infarction	3.04 [2.98–3.11]	2.94 [2.83–3.05]	**0.96 [0.93–1.00]**	0.0273	**0.77 [0.74–0.80]**	<0.0001
Pulmonary circulation disorders	1.24 [1.21–1.27]	1.69 [1.61–1.76]	**1.37 [1.31–1.43]**	<0.0001	**1.06 [1.01–1.11]**	0.0134
Coronary artery occlusion	1.22 [1.20–1.23]	1.14 [1.08–1.19]	**0.94 [0.89–0.98]**	0.0051	**0.77 [0.74–0.82]**	<0.0001
Pulmonary hypertension	0.04 [0.04–0.04]	0.05 [0.04–0.07]	**1.33 [1.08–1.63]**	0.0072	0.98 [0.76–1.25]	0.8389
Cerebrovascular accident	2.23 [2.20–2.26]	2.05 [1.98–2.13]	**0.92 [0.89–0.95]**	<0.0001	**0.77 [0.74–0.80]**	<0.0001
History of transient ischemic attack	1.97 [1.90–2.03]	2.55 [2.44–2.67]	**1.31 [1.26–1.36]**	<0.0001	1.04 [1.00–1.08]	0.0703
Late effects of cerebrovascular disease	2.04 [2.00–2.07]	1.99 [1.90–2.08]	0.98 [0.94–1.02]	0.2674	**0.79 [0.76–0.83]**	<0.0001
Ill-defined cerebrovascular disease	1.25 [1.22–1.29]	1.55 [1.48–1.63]	**1.24 [1.19–1.30]**	<0.0001	1.05 [1.00–1.10]	0.0702
Other cerebrovascular disease	0.53 [0.52–0.55]	0.54 [0.50–0.58]	1.01 [0.94–1.09]	0.7646	**0.84 [0.77–0.91]**	<0.0001

Bolded odds ratios represent significance at $P < 0.05$

CI confidence interval, *ISD* inflammatory skin disease, *OR* odds ratio

Most of these associations remained significant in propensity regression models.

4 Discussion

In the present study, there was increased cardiovascular and cerebrovascular risk across multiple inflammatory skin diseases, including psoriasis, pemphigus, BP, AD-E, and hidradenitis. In particular, obesity, hypertension, diabetes, peripheral vascular disease, cerebrovascular disease, coronary artery disease, and congestive heart failure were associated with multiple inflammatory skin diseases. Most of these associations remained significant in multivariable models and in stratified analyses by age, sex, and race/ethnicity. Patients with versus without inflammatory skin disease had higher rates of obesity, hypertension, and/or diabetes at younger age (<50 years) and higher rates among certain inflammatory skin conditions in sex and race stratified groups. Together, the results suggest there may be common risk factors and/or mechanisms for increased cardiovascular and cerebrovascular risk across multiple inflammatory skin disorders (Table 6).

These findings are consistent with previous studies that found increased cardiovascular risk and/or disease in psoriasis [6], AD-E [9–12], pemphigus [13], BP [14–16], and hidradenitis [17]. A meta-analysis of 75 studies, including 503,686 persons with psoriasis and 29,686,694 controls, found that psoriasis was associated with increased odds of cardiovascular disease overall, particularly ischemic heart disease, peripheral vascular disease, atherosclerosis, diabetes, hypertension, dyslipidemia, obesity, and metabolic syndrome [6]. Similarly, several population-based studies demonstrated increased odds of general and central obesity, and of high blood pressure in children with moderate–severe AD [9], and increased obesity, hypertension, diabetes, and other cardiovascular risk factors [10], as well as coronary artery disease, heart attack, congestive heart failure, stroke, and peripheral vascular disease [11] in adults with AD. Moreover, a meta-analysis of 30 studies found that AD was associated with increased odds of overweight and/or obesity in both children and adults in the USA and Asia, but not Europe [12]. A retrospective study of 147 Brazilian patients with pemphigus vulgaris or foliaceus found they had higher blood pressure and higher rates of diabetes, obesity, hypertriglyceridemia, and cardiovascular events [13]. Several

Table 5 Association between hidradenitis and cardiovascular/cerebrovascular co-morbidities in US adults

Co-morbidity	No ISD	Hidradenitis				
	Percentage [95% CI]	Percentage [95% CI]	Crude OR [95% CI]	*P*-value	Propensity OR	*P*-value
Hypertension	42.61 [42.27–42.95]	30.86 [29.44–32.29]	**0.60 [0.56–0.64]**	<0.0001	**0.67 [0.63–0.72]**	<0.0001
Diabetes, uncomplicated	16.61 [16.46–16.77]	20.57 [19.45–21.68]	**1.30 [1.22–1.39]**	<0.0001	**1.47 [1.36–1.59]**	<0.0001
Diabetes with chronic complication	3.64 [3.57–3.70]	3.27 [2.80–3.74]	0.90 [0.77–1.04]	0.141	1.04 [0.88–1.23]	0.6451
Type 2 diabetes mellitus	1.12 [1.10–1.14]	0				
Obesity	7.42 [7.28–7.57]	18.26 [17.09–19.44]	**2.79 [2.59–3.01]**	<0.0001	**3.18 [2.93–3.45]**	<0.0001
Coronary artery disease	20.76 [20.46–21.07]	4.81 [4.20–5.41]	**0.20 [0.17–0.22]**	<0.0001	**0.23 [0.20–0.27]**	<0.0001
Congestive heart failure	7.60 [7.49–7.71]	2.78 [2.35–3.21]	**0.35 [0.30–0.41]**	<0.0001	**0.40 [0.33–0.48]**	<0.0001
Peripheral vascular disease	4.71 [4.63–4.80]	1.10 [0.85–1.36]	**0.23 [0.18–0.29]**	<0.0001	**0.27 [0.21–0.35]**	<0.0001
History of myocardial infarction	4.24 [4.15–4.33]	1.32 [1.04–1.60]	**0.30 [0.25–0.38]**	<0.0001	**0.36 [0.28–0.45]**	<0.0001
Peripheral and visceral atherosclerosis	4.15 [4.08–4.23]	0.98 [0.73–1.22]	**0.23 [0.18–0.30]**	<0.0001	**0.28 [0.21–0.36]**	<0.0001
Myocardial infarction	3.04 [2.98–3.11]	0.09 [0.02–0.16]	**0.03 [0.01–0.06]**	<0.0001	**0.04 [0.02–0.09]**	<0.0001
Pulmonary circulation disorders	1.24 [1.21–1.27]	0.52 [0.34–0.71]	**0.42 [0.29–0.60]**	<0.0001	**0.41 [0.28–0.61]**	<0.0001
Coronary artery occlusion	1.22 [1.20–1.23]	0.02 [0.00–0.05]	**0.02 [0.00–0.08]**	<0.0001	**0.02 [0.00–0.12]**	<0.0001
Pulmonary hypertension	0.04 [0.04–0.04]	0				
Cerebrovascular accident	2.23 [2.20–2.26]	0.03 [0.00–0.07]	**0.02 [0.01–0.05]**	<0.0001	**0.02 [0.01–0.08]**	<0.0001
History of transient ischemic attack	1.97 [1.90–2.03]	0.77 [0.56–0.98]	**0.39 [0.30–0.51]**	<0.0001	**0.42 [0.31–0.56]**	<0.0001
Late effects of cerebrovascular disease	2.04 [2.00–2.07]	0.59 [0.39–0.78]	**0.28 [0.20–0.40]**	<0.0001	**0.31 [0.21–0.47]**	<0.0001
Ill-defined cerebrovascular disease	1.25 [1.22–1.29]	0.07 [0.01–0.13]	**0.06 [0.03–0.14]**	<0.0001	**0.07 [0.03–0.18]**	<0.0001
Other cerebrovascular disease	0.53 [0.52–0.55]	0.06 [0.00–0.11]	**0.11 [0.04–0.28]**	<0.0001	**0.12 [0.04–0.37]**	0.0002

Bolded odds ratios represent significance at $P < 0.05$

CI confidence interval, *ISD* inflammatory skin disease, *OR* odds ratio

Table 6 Summary of co-morbid health conditions with significant positive association with inflammatory skin disease

Co-morbidity	Pemphigus	Bullous pemphigoid	Atopic dermatitis	Psoriasis	Hidradenitis
Hypertension	X*	X*	X*	X*	
Diabetes, uncomplicated	X*	X*		X*	X*
Diabetes with chronic complication	X*	X*	X	X*	
Type 2 diabetes mellitus	X*	X*		X	
Obesity	X	X	X*	X*	X*
Coronary artery disease		X*		X	
Congestive heart failure	X*	X*	X*	X	
Peripheral vascular disease	X	X*	X*	X	
History of myocardial infarction		X		X	
Peripheral and visceral atherosclerosis		X*	X*	X	
Myocardial infarction					
Pulmonary circulation disorders	X*	X*	X*	X	
Coronary artery occlusion		X			
Pulmonary hypertension			X	X	
Cerebrovascular accident					
History of transient ischemic attack	X*	X*	X*	X	
Late effects of cerebrovascular disease	X*	X*	X*		
Ill-defined cerebrovascular disease				X	
Other cerebrovascular disease	X*	X*	X*		

X indicates significance within bivariate models, *X** indicates significance within bivariate and multivariate propensity score models

retrospective studies found cardiovascular co-morbidities were common in patients with BP [14–16]. A systematic review and meta-analysis of nine studies, including 6174 patients with hidradenitis and 24,993 controls, found that hidradenitis was associated with increased odds of general and central obesity, active and history of smoking,

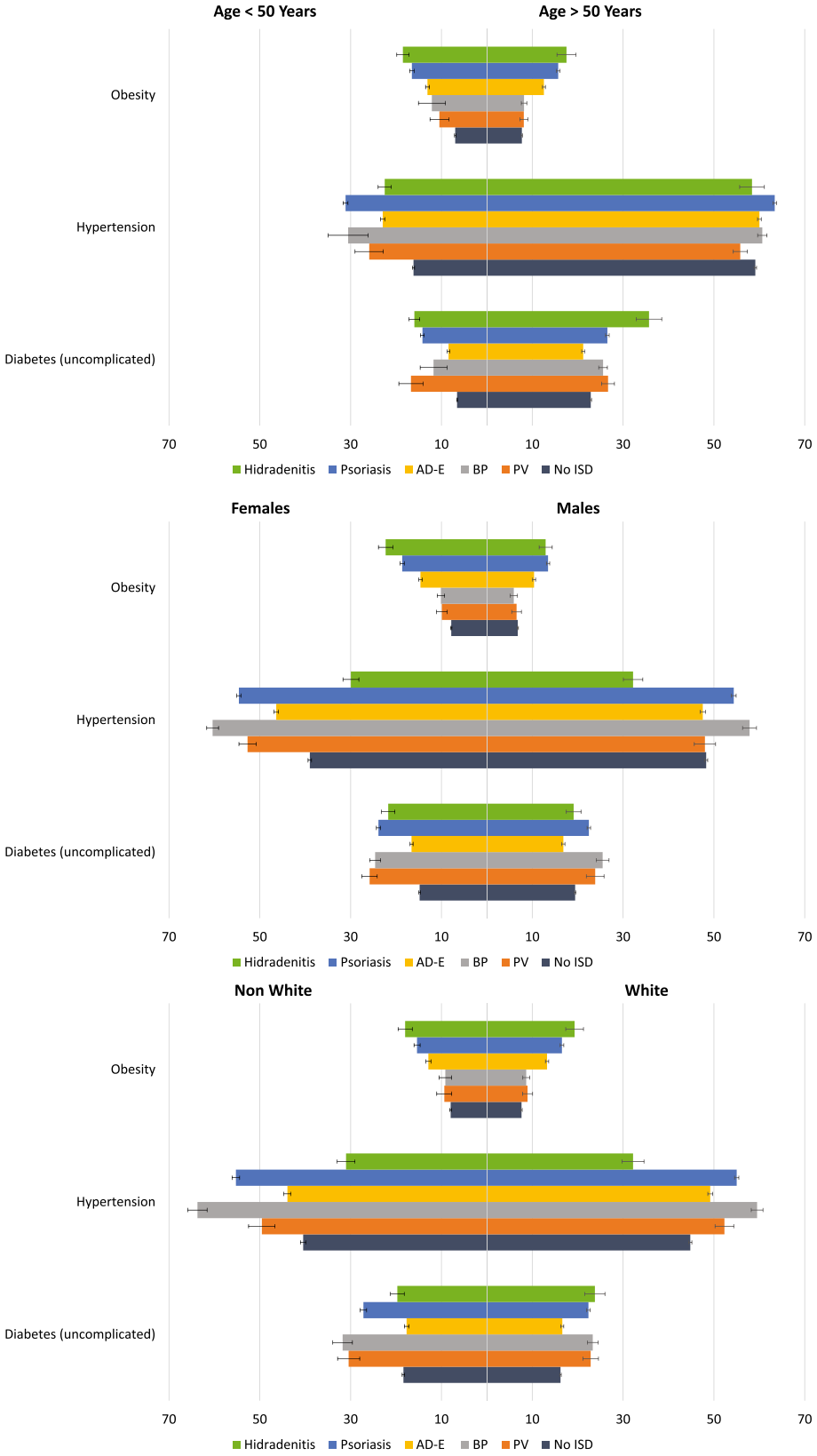

Fig. 1 Rate of co-morbidity for each inflammatory skin disease controlling for age, sex, and race. There was a significant difference in rates for all co-morbidities between inflammatory disorders ($P < 0.0001$) when controlling for age, sex, and race. *AD-E* atopic dermatitis or eczema, *BP* bullous pemphigoid, *ISD* inflammatory skin disease, *PV* pemphigus vulgaris

hypertriglyceridemia, low high-density lipoprotein, diabetes, and metabolic syndrome [17]. In addition, the results of the present study suggest that BP has the highest odds of hypertension, diabetes, and cardiovascular disease compared with the other inflammatory skin disorders, even after controlling for age and other sociodemographics, whereas hidradenitis was associated with the highest odds of obesity. Together, the results suggest that there may be distinct profiles of cardiovascular and cerebrovascular co-morbidities associated with each of these inflammatory skin diseases.

Notably, obesity, hypertension, and diabetes were significantly more likely to occur for all inflammatory skin disorders in patients aged <50 years, but were only significant for some inflammatory disorders and cardiovascular co-morbidities at age ≥50 years. This suggests that inflammatory skin diseases are early-life risk factors for cardiovascular disease. Nevertheless, older age is a strong risk factor for cardiovascular disease. Thus, as patients age, the risk of cardiovascular disease increases in all groups, including those without inflammatory skin disease (Fig. 1).

Several mechanisms have been proposed for the associations between different inflammatory skin diseases and cardiovascular risk. Increased circulating levels of TNF-α, interleukin (IL)-17, and IL-22 are thought to play a role in increased cardiovascular risk in psoriasis [30, 31]. IL-17 and IL-22 have also been found to be upregulated in tissue and/or serum of patients AD [32, 33], pemphigus vulgaris [34], BP [35], and hidradenitis [36]. TNF-α has been found to be upregulated in psoriasis [37], hidradenitis [38], pemphigus, and pemphigoid [39–41] but not AD [42]. Thus, long-term systemic activation of different inflammatory pathways may contribute to cardiovascular risk differentially across a gamut of inflammatory skin diseases. Nevertheless, each of these inflammatory diseases share a common theme of being chronic diseases with considerable symptom burden, and impact on function and QOL [18–22, 43]. Moreover, psoriasis [44], AD [45], and hidradenitis [46] were associated with higher rates of smoking but not pemphigus [47–49]. Similarly, psoriasis [50–52] and AD [10, 53–55] are associated with decreased physical activity and more sedentary behavior. Many of these poor health behaviors are not specific to inflammatory skin disease but also occur in any chronic debilitating disorder. Of note, these findings may also occur in other inflammatory skin diseases not examined in this study. The mechanisms of association between inflammatory skin disease and cardiovascular risk is likely multifactorial, secondary to the long-term effects of both inflammatory and behavioral factors.

Strengths of this study include an analysis of a nationally representative sample of all-payer data over a period of 11 years with >72 million records. Limitations include underreporting of cardiovascular co-morbidities within the dataset. All entries within this database were single inpatient admissions rather than complete health records for individual patients. Thus, past cardiovascular co-morbidities might not have been recorded for those admitted. In addition, there may have been an underreporting of dermatologic co-morbidities when patients were admitted for acute co-morbidities such as myocardial infarction (MI). This likely explains why there are significant associations with chronic diagnosis codes, such as history of MI, but inverse associations with MI itself. Disease severity was not documented for each disorder. We a priori decided to examine these five inflammatory skin diseases because of their debilitating nature and considerable inpatient burden [3–5, 56, 57]. Future studies are needed to assess if cardiovascular co-morbidity rates differ consistently by disease severity across all inflammatory skin disorders.

5 Conclusions

Psoriasis, pemphigus, BP, AD-E, and hidradenitis were all associated with increased cardiovascular and cerebrovascular risk, especially at younger age. Future research is needed to determine the optimal strategies for reducing cardiovascular risk in these disorders.

Author contributions J.I. Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. J.I. Silverberg was involved in the study concept and design; and obtained the funding. J.I. Silverberg and M. Kwa were responsible for the acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and statistical analysis.

Compliance with Ethical Standards

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Conflict of interest J.I. Silverberg and M. Kwa have no relevant conflicts of interest to declare.

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