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Association between climate, pollution and hospitalization for pemphigus in the USA

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Summary

Background. Little is known about the impact of ultraviolet exposure, climate factors and pollutants on pemphigus.

Aim. To determine whether these factors are associated with pemphigus exacerbation resulting in hospitalization.

Methods. The analysis used data from the 2002–2012 National Inpatient Sample in the USA, including 68 476 920 children and adults, and measurements of relative humidity (%), ultraviolet (UV) index, outdoor air temperature and particulate matter of ≤ 2.5 or ≤ 10 μm (PM2.5 and PM10).

Results. Higher rates of admission primarily for pemphigus occurred during the summer and autumn months (June–November), with the highest admission rates in July and October (both 19.7 per million). There was significant statewide variation of the prevalence of hospitalization for pemphigus, with apparent hotspots located in the southwest and northeast states. Hospitalization for a primary diagnosis of pemphigus vs. other diagnosis was associated with significantly lower humidity [mean (95% confidence interval): 64.8% (63.2–66.4%) vs. 66.4% (65.6–67.3%); analysis of variance, $P < 0.01$) and higher temperature [58.7 (57.1–60.2) vs. 56.3 (55.8–56.7)°F, $P = 0.001$], UV index [6.0 (5.7–6.2) vs. 5.7 (5.6–5.7), $P = 0.02$], PM2.5 [12.9 (12.0–13.7) vs. 11.8 (11.5–12.0) mg/m^3, $P < 0.001$] and PM10 [26.2 (24.5–27.9) vs. 23.1 (22.6–23.6) mg/m^3, $P < 0.001$]. All associations remained significant in multilevel regression models that controlled for age, sex and race/ethnicity, except for ultraviolet index, which was associated with pemphigus hospitalization only for Hispanic patients [odds ratio (95% CI) for quartile 4: 2.07 (1.02–4.21)].

Conclusion. Increasing temperature, UV exposure and small particle air pollution are associated with increased hospitalization for pemphigus. Patients with pemphigus may benefit from avoidance of these potential environmental triggers.

Introduction

Pemphigus is a chronic debilitating autoimmune disorder, manifesting as acantholytic blisters of the skin and/or mucous membranes. Severe disease is associated with intense pain, oesophageal involvement leading to difficulty in eating,[1] increased opportunistic infection,[2] medication-related complications and/or comorbid autoimmune disorders,[3] all of which increase risk of hospitalization. The severe and debilitating nature and the lack of safe and effective therapeutic options emphasize the importance of identifying modifiable risk factors for disease onset and/or exacerbation.

Dynamic climate factors such as ultraviolet (UV) radiation, humidity, temperature and particulate matter (PM) may play an important role in driving disease activity in pemphigus. There are several case reports and

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series of UV-induced pemphigus foliaceus, vulgaris and erythematosus.[4–7] However, it is unclear whether UV exposure is a clinically relevant trigger of disease exacerbation in the broader US population. While climate factors have been shown to play a role in other inflammatory skin disorders such as atopic dermatitis,[8] their role in pemphigus has not previously been examined. Moreover, although there is no direct evidence of an association between PM and pemphigus, PM has been shown to cause severe oxidative stress and inflammatory response, thereby accelerating skin ageing.[9,10] We hypothesized that climate, UV index and PM level are associated with higher risk of pemphigus. In this study, we examined the association of climate factors and pollutants with rates of hospitalization for pemphigus in the USA.

Methods

Approval by the Northwestern University institutional review board was waived, as this was a data study. Patient consent was not required all data were de-identified.

Data source

The 2002–2012 National Inpatient Sample (NIS) provided by the Healthcare Cost and Utilization Project (HCUP) was analysed. Each year of NIS contains an approximately 20% stratified representative sample of all hospitalizations in the USA. Sample weights were created by NIS that factored the sampling design of hospitals in the USA; these sample weights were 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 were compliant with HCUP's formal data use agreement.

Pemphigus definition and climate measurement

Pemphigus was identified using the *International Classification of Disease*, ninth edition, clinical modification (ICD-9-CM) codes (see Supporting Information Methods). Daily levels of relative outdoor humidity, temperature (1179 measurement stations), UV index (58 stations in major cities across all 50 states), PM ≤ 2.5 mg/m^3 (PM2.5) and ≤ 10 (PM10) mg/m^3 (> 3000 measurement stations across all 50 states) for 2002–2012 were obtained from the Environmental Protection Agency.

Statistical analysis

Details of data processing and statistical analyses are presented in Supporting Information Methods.

Results

Population characteristics

In total, there were 68 476 920 discharges captured in the NIS between the years 2002 and 2012, excluding patients with live birth or pregnancy. There were 1185 and 5179 unweighted admissions with a primary and secondary diagnosis of pemphigus, and 5647 and 24 681 weighted admissions, respectively. The top 20 primary diagnoses for inpatients with a diagnosis of pemphigus are presented in Table S1. Patients with a secondary diagnosis of pemphigus (mean ± SE 71.0 ± 0.3 years) were significantly older than those with a primary diagnosis of pemphigus (57.8 ± 1.0 years) and those without a diagnosis of pemphigus(57.20 ±0.2 years). Inpatients with a primary diagnosis of pemphigus were 42.2% male and 45.1% white, and the prevalence varied significantly by race ($P < 0.001$). Higher rates of admission primarily for pemphigus occurred during the summer and autumn months (June–November) (Fig. 1a); the highest admission rates were in July and October (both 19.7 per million). Adults admitted with a primary diagnosis of pemphigus vs. those without pemphigus had a higher prevalence of any skin infection (18.9% vs. 4.3%; $P < 0.001$). These patterns were similar between study years.

Geographical variation

Prevalence of hospitalization was higher in the northeast and west than the south and midwest regions (Fig. 1b). Inpatients with a primary diagnosis of pemphigus were more likely to be living in the northeast [OR (95% CI): 1.88 (1.35–2.62)] and west [2.01 (1.51–2.66)] compared with midwest regions. Moreover, there was significant statewide variation of the prevalence of hospitalization for pemphigus, with apparent hotspots located in the southwest and northeast. California (prevalence: 21.6 per million), New Mexico (21.2 per million) and Texas (16.2 per million) were the southwestern states with the highest prevalence, whereas New Jersey (27.5 permillion) and New York (20.8 per million) were the northeastern states with the highest prevalence (Fig. 2).

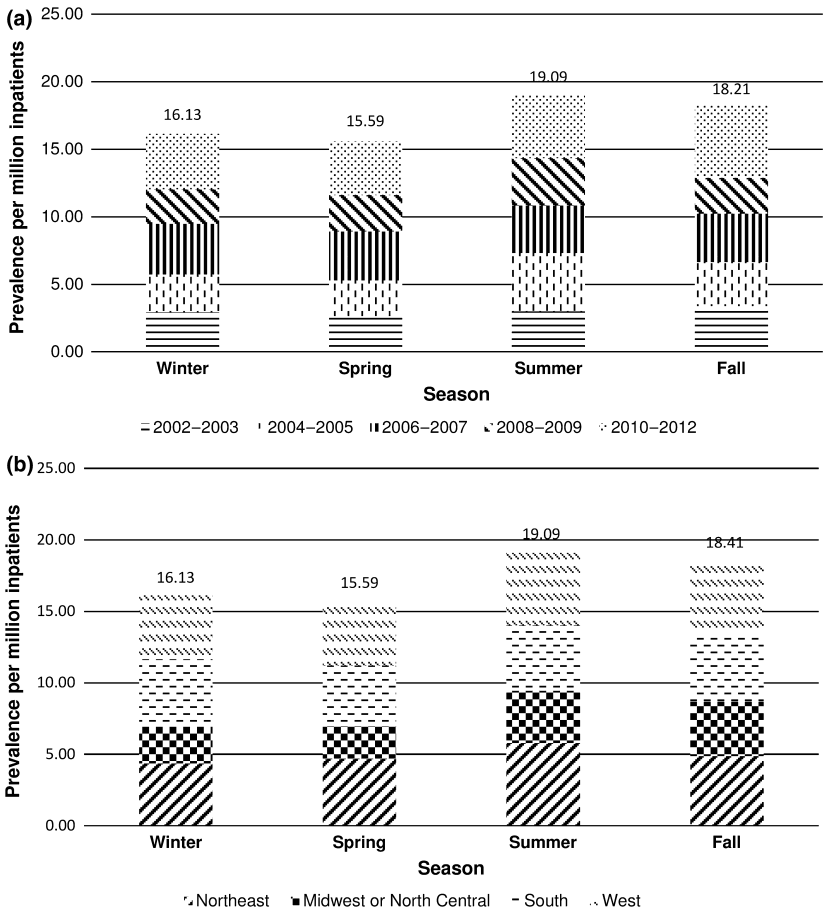

Figure 1 Prevalence of pemphigus hospitalization by seasons grouped by (a) year and (b) hospital region. (a) Prevalence of hospitalization for pemphigus per million hospitalized adults with a primary diagnosis of pemphigus in (a) the periods 2002–2003, 2004–2005, 2006–2007, 2008–2009 and 2010–2012, and (b) the northeast, midwest or north central, south, and west hospital regions.

Climate variables and small particle air pollution

There were 38 223 366 admission records with available hospital zip and/or state Federal Information Processing Standard (FIPS) codes and at least one environmental value during each month of admission. Kernel density plots for mean annual outdoor relative humidity, temperature, UV index, PM2.5 and PM10 were plotted for hospitalizations with or without a diagnosis of pemphigus (Fig. S1, Fig. S2). For patients admitted with a primary diagnosis of pemphigus compared with those without pemphigus, mean (95% CI) humidity was significantly lower [64.8% (63.2–66.4%) vs. 66.4% (65.6–67.3%), $P < 0.01$], whereas temperature [58.7 (57.1–60.2) vs. 56.3 (55.8–56.7) °F, $P = 0.001$], UV index [6.0 (5.7–6.2) vs. 5.7 (5.6–5.7), $P = 0.02$], PM2.5 [12.9 (12.0–13.7) vs.11.8 (11.5–12.0) mg/m^3, $P < 0.001$] and PM10 [26.2 (24.5–27.9) vs. 23.1 (22.6–23.6) mg/m^3, $P < 0.001$] were all significantly higher. There were no significant differences in environmental factors between those with a secondary diagnosis of pemphigus vs. no pemphigus ($P \geq 0.09$).

Similarly, hospitalization for pemphigus was inversely associated with lower temperature [OR (95% CI) for quartile 1 (Q1) 0.65 (0.48–0.87)] and higher relative humidity [Q3: 0.63 (0.45–0.90), Q4: 0.63 (0.43–0.91); ≥ 70%: 0.60 (0.46–0.79)], but positively associated with higher UV index [Q2: 1.32 (1.04–1.69); Q4: 1.39 (1.12–2.79); ≥ 11: 1.78 (1.12–2.84)], PM2.5 [Q4: 1.70 (1.18–2.45); ≥ 15 mg/m^3: 1.50 (1.11–2.01)] and PM10 [Q3: 1.46 (1.06–2.01); Q4: 1.99 (1.42–2.79); ≥ 30 mg/m^3: 1.65 (1.25–2.17); ≥ 50 mg/m^3: 2.21 (1.27–3.87)] (Table 1).

As population characteristics often vary by state and region, we constructed multilevel models that adjusted for sex, race/ethnicity and age. The associations with hospitalization for pemphigus remained significant for hospital region [adjusted OR (95% CI): northeast: 2.26 (1.59–

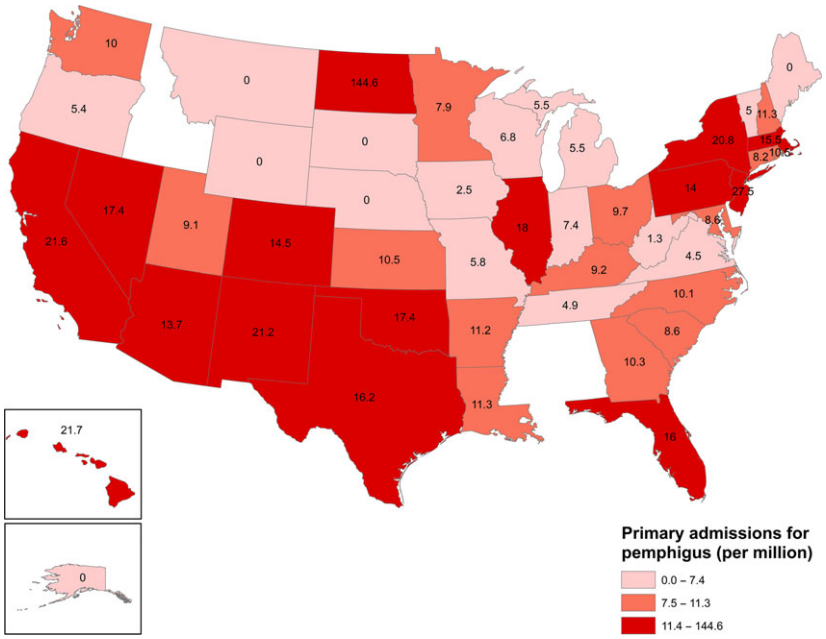

Figure 2 Statewide variation in the prevalence of pemphigus hospitalization in the USA. Pemphigus hospitalization rates were divided into tertiles and colour-coded. Light pink indicates tertile 1; orange-pink, tertile 2; red, tertile 3.

3.20); south: 1.43 (1.03–1.98); west 2.38 (1.76–3.21)], temperature [Q1: 0.65 (0.46–0.91)], humidity [Q3: 0.65 (0.44–0.96); ≥ 70%: 0.66 (0.50–0.87)] and higher levels of PM10 [Q3 1.48 (1.06–2.08), Q4 1.83 (1.28–2.61), > 30 mg/m^3 1.47 (1.10–1.98), > 50 mg/m^3 1.84 (1.01–3.36)] and PM2.5 [> 15 mg/m^3 1.42 (1.04–1.94)] ($P < 0.05$ for all). However, the association between pemphigus and UV index did not remain significant in multivariate analyses. Therefore, we stratified analyses to determine which demographic factors were confounders. Higher UV index was associated with increased hospitalization for pemphigus only for Hispanic inpatients [Q4: 2.07 (1.02–4.21)] but not patients categorized as white, black or multiracial/other ($P \geq 0.13$) (Table 2).

Similar results were found in multivariable models that controlled for the diagnosis of any skin infections and in models of environmental variables averaged over all available study years (n = 37 620 890 based on zip codes and 643 134 based on state FIP codes) (Tables S2 and S3).

Discussion

In the present study, we found significant seasonal differences in hospitalization rates for pemphigus, with highest rates in the summer and autumn months. Moreover, there were two apparent hotspots of hospitalization for pemphigus, namely in the southwestern and northeastern states. Hospitalization primarily for pemphigus was associated with significantly higher mean and quartile monthly temperature and UV index and lower relative humidity individually, and with higher UV index and temperature in combination. In addition, hospitalization for pemphigus was associated with higher levels of PM2.5 and PM10 individually, and PM10 in combination with high temperature and UV index. These associations remained significant in models that controlled for race/ethnicity, age, sex, insurance status and admissions occurring at weekends for temperature, humidity, PM2.5 and PM10. However, the association between UV index and hospitalization for pemphigus was only significant in patients of Hispanic/Latino descent. By contrast, there were no associations of climate factors and pollutants with secondary admission of patients with pemphigus for other reasons. Together, the results suggest potentially harmful effects on pemphigus of hot and sunny climates and of small particle air pollution.

The association between UV exposure and hospitalization for pemphigus is consistent with previous reports of UV-induced pemphigus.[4–7] Small case reports and series have suggested that multiple subtypes of pemphigus, including vulgaris, foliaceus and erythematosus, may be triggered by UV phototherapy in patients being treated for other inflammatory dermatoses.[4,5] A study of 55 Israeli patients with

Table 1 Climate associations of hospitalization for pemphigus

	Primary diagnosis of pemphigus									
	No		Yes				Model 1		Model 2	
Variable	Raw frequency	Weighted prevalence (95% CI)	Raw frequency	Weighted prevalence (95% CI)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)†	*P*	Adjusted OR (95% CI)‡	*P*
Hospital region										
Northeast	13524045	20.21 (18.94–21.48)	308	26.37 (20.63–32.11)	1.88 (1.35–2.62)	< 0.001*	2.26 (1.59–3.20)	< 0.001*	1.89 (1.36–2.64)	< 0.001*
Midwest	15652985	23.32 (22.12–24.51)	189	16.14 (12.65–19.64)	1 (ref)	–	1 (ref)	–	1 (ref)	–
South	26593541	38.52 (36.88–40.51)	394	32.55 (26.68–38.42)	1.22 (0.90–1.66)	0.21	1.43 (1.03–1.98)	0.03*	1.20 (0.88–1.64)	0.24
West	12311286	17.96 (16.84–19.07)	294	24.94 (20.53–29.35)	2.01 (1.51–2.66)	< 0.001*	2.38 (1.76–3.21)	< 0.001*	1.97 (1.48–2.61)	< 0.001*
Temperature (°F), quartile										
First	5853322	25.22 (24.18–26.26)	93	19.42 (15.14–23.70)	0.65 (0.48–0.87)	< 0.01*	0.65 (0.46–0.91)	0.01*	0.64 (0.48–0.87)	< 0.01*
Second	5851573	24.90 (24.31–25.48)	136	27.63 (23.59–31.68)	0.93 (0.73–1.18)	0.54	0.93 (0.72–1.20)	0.58	0.93 (0.73–1.17)	0.53
Third	5847797	24.98 (24.16–25.79)	113	23.22 (18.69–27.75)	0.78 (0.58–1.04)	0.09	0.75 (0.54–1.03)	0.07	0.78 (0.58–1.04)	0.09
Fourth	5838996	24.91 (23.87–25.94)	144	29.73 (25.09–34.37)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Relative humidity (%), quartile										
First	4730153	24.86 (22.59–27.13)	125	29.23 (23.45–35.01)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	4684338	24.85 (23.51–26.20)	142	33.54 (28.28–38.80)	1.15 (0.88–1.50)	0.32	1.04 (0.77–1.40)	0.81	1.16 (0.89–1.52)	0.27
Third	4754503	25.15 (23.87–26.42)	81	18.74 (14.47–23.01)	0.63 (0.45–0.90)	< 0.01*	0.65 (0.44–0.96)	0.03*	0.65 (0.46–0.91)	0.01*
Fourth	4732449	25.14 (23.33–26.95)	78	18.49 (12.98–24.00)	0.63 (0.43–0.91)	0.01*	0.71 (0.50–1.01)	0.06	0.64 (0.44–0.93)	0.02*
> 70	8136041	45.16 (40.85–45.46)	134	31.45 (25.01–37.90)	0.60 (0.46–0.79)	< 0.001*	0.66 (0.50–0.87)	< 0.01*	0.61 (0.47–0.80)	< 0.001*
< 70	10765402	56.84 (54.54–59.15)	292	68.55 (62.10–74.99)	1 (ref)	–	1 (ref)	–	1 (ref)	–
PM10 (μ/m^2), 25 °C, quartile										
First	5443410	24.93 (23.35–26.50)	76	17.31 (13.20–21.43)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	5357845	24.65 (23.60–25.70)	94	22.28 (17.89–26.66)	1.30 (0.95–1.78)	0.1	1.27 (0.90–1.78)	0.17	1.29 (0.94–1.77)	0.11
Third	5549774	25.36 (24.23–26.50)	109	25.76 (20.65–30.88)	1.46 (1.06–2.01)	0.02*	1.48 (1.06–2.08)	0.02*	1.47 (1.07–2.02)	0.02*
Fourth	5509923	25.06 (22.96–27.16)	151	34.65 (28.08–41.22)	1.99 (1.42–2.79)	< 0.001*	1.83 (1.28–2.61)	< 0.001*	1.98 (1.41–2.76)	< 0.001*
> 30	4229934	19.20 (17.34–21.07)	122	28.12 (22.12–34.12)	1.646 (1.25–2.17)	< 0.001*	1.47 (1.10–1.98)	0.01*	1.63 (1.24–2.15)	< 0.001*
< 30	17631018	80.80 (78.93–82.66)	308	71.88 (65.88–77.88)	1 (ref)	–	1 (ref)	–	1 (ref)	–
> 50	490993	2.19 (1.67–2.72)	21	4.73 (1.93–7.53)	2.21 (1.27–3.87)	< 0.01*	1.84 (1.01–3.36)	< 0.05*	2.18 (1.25–3.82)	< 0.01*
< 50	21369959	97.81 (97.29–98.33)	409	95.27 (92.47–98.07)	1 (ref)	–	1 (ref)	–	1 (ref)	–
PM2.5 AQI & speciation mass (μ/m^2), LC, quartile										
First	5444343	25.10 (23.27–26.93)	75	19.33 (14.27–24.38)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	5410981	25.02 (23.99–26.04)	87	22.00 (17.35–26.65)	1.14 (0.80–1.63)	0.46	0.99 (0.67–1.46)	0.96	1.15 (0.81–1.63)	0.45
Third	5421141	24.98 (23.96–26.01)	101	26.01 (21.35–30.68)	1.35 (0.97–1.88)	0.07	1.21 (0.83–1.76)	0.32	1.36 (0.98–1.89)	0.07
Fourth	5453189	24.90 (23.13–26.67)	129	32.66 (26.06–39.26)	1.70 (1.18–2.45)	< 0.01*	1.47 (0.99–2.19)	0.06	1.71 (1.19–2.46)	< 0.01*
> 15	4751108	21.70 (20.04–23.36)	116	29.32 (22.54–36.11)	1.50 (1.11–2.01)	< 0.01*	1.42 (1.04–1.94)	0.03*	1.50 (1.11–2.01)	< 0.01*
< 15	16978546	78.30 (76.64–79.96)	276	70.68 (63.89–77.46)	1 (ref)	–	1 (ref)	–	1 (ref)	–
UV index, quartile										
First	9025167	25.18 (24.59–25.77)	141	20.68 (17.08–24.29)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	8996090	24.92 (24.61–25.24)	186	27.07 (23.62–30.51)	1.32 (1.04–1.69)	0.03*	1.23 (0.93–1.62)	0.14	1.32 (1.03–1.69)	0.03*

Table 1. continued

Variable	Primary diagnosis of pemphigus										
	No		Yes					Model 1		Model 2	
	Raw frequency	Weighted prevalence (95% CI)	Raw frequency	Weighted prevalence (95% CI)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)†	*P*	Adjusted OR (95% CI)‡	*P*
Third	8999284	25.06 (24.72–25.41)	164	23.86 (20.32–27.39)	1.16 (0.90–1.50)	0.26	1.06 (0.79–1.42)	0.72	1.17 (0.91–1.51)	0.23
Fourth	8969859	24.83 (24.19–25.47)	195	28.39 (24.57–32.21)	1.39 (1.08–1.79)	0.01*	1.29 (0.99–1.68)	0.06	1.39 (1.09–1.79)	< 0.01*
> 11	752327	2.06 (1.78–2.34)	25	3.62 (1.90–5.33)	1.78 (1.12–2.84)	0.02*	1.51 (0.94–2.45)	0.09	1.74 (1.09–2.77)	0.02*
< 11	35238073	97.94 (97.66–98.22)	661	96.38 (94.67–98.10)	1 (ref)	–	1 (ref)	–	1 (ref)	–

AQI, Air Quality Index; LC, local conditions PM205, ≤ 2.5 or ≤ 10 lm; UV, ultraviolet. *Significant at $P < 0.05$; †multivariate logistic regression models adjusted for age (continuous), sex(male/female), race/ethnicity (white/other), insurance status (yes/no) and weekend admission (yes/no); ‡multivariate logistic regression models adjusted for any skin infection (yes/no).

pemphigus found that 18% had been continually exposed to UV radiation 5 years prior to disease onset.[11] A prospective study found that UVB exposure of nonlesional skin induced acantholysis in 15 of 21 patients with fogo sevalgem and 6 of 8 with pemphigus.[7] There is considerable geographical variation in the epidemiology of pemphigus, with the highest incidence occurring in countries with intense heat and UV exposure during summer, including Greece, Iran, Israel and Tunisia.[12] The present study suggests that UV exposure contributes toward pemphigus flares, resulting in hospitalization, especially of Hispanic/Latino patients. We recommend that patients with known or a high risk of pemphigus should be counselled on appropriate sun-protection and sun-avoidance measures to minimize exogenous triggering of their disease.

There also appear to be other climate factors and pollutants contributing toward pemphigus flares, including increased temperature, PM2.5 and PM10 levels, and low humidity. Some of these effects may be related to co-occurrence with higher UV index. However, unlike UV index, which was associated with pemphigus only in Hispanic/Latino patients, the associations of temperature, humidity, PM2.5 and PM10 with pemphigus remained significant in all racial/ethnic groups in our study. Thus, these factors may play a role in pemphigus independently of UV exposure. Patients with pemphigus may benefit from increasing their indoor relative humidity and minimizing exposure to high temperature, UV and pollutants.

Higher humidity may improve skin barrier function by preventing transepidermal water loss and epidermal proliferation, and by altering distribution of lamellar bodies within the stratum granulosum and comeum.[13] Lower temperature may result in decreased skin moisture evaporation and metabolic activities, which may strengthen the skin barrier. PM induces oxidative stress via production of reactive oxygen species and secretion of pro-inflammatory cytokines, including tumour necrosis factor-α, interleukin (IL)-1α and IL-8, which may lead to degradation of collagen and acceleration of skin ageing.[9,10] These factors have previously been shown to be associated with atopic dermatitis, another inflammatory skin disorder,[8,14] although it is unclear if these environmental exposures impact pemphigus via similar mechanisms. However, it is possible that climate and pollution factors could be influencing pemphigus hospitalization directly via increased autoimmunity or indirectly via increased skin infections or other indirect effects. However, skin infections do not appear to be a major confounder, as the associations between pemphigus and

Table 2 UV index associations of hospitalization for pemphigus in different racial/ethnic groups

	Primary diagnosis of pemphigus									
	No		Yes				Model 1		Model 2	
UV index	Raw frequency	Weighted prevalence (95% CI)	Raw frequency	Weighted prevalence (95% CI)	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)†	*P*	Adjusted OR (95% CI)‡	*P*
White, quartile										
First	4989538	24.74 (24.10–25.38)	66	23.65 (18.50–28.80)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	5037163	24.79 (24.42–25.15)	77	27.26 (22.16–32.37)	1.15 (0.83–1.61)	0.41	1.15 (0.83–1.61)	0.40	1.15 (0.83–1.61)	0.41
Third	5040024	24.95 (24.55–25.34)	59	21.05 (15.86–26.23)	0.88 (0.61–1.28)	0.51	0.89 (0.61–1.28)	0.52	0.89 (0.62–1.29)	0.54
Fourth	5192476	25.52 (24.84–26.20)	79	28.04 (22.91–33.17)	1.15 (0.83–1.60)	0.41	1.15 (0.83–1.60)	0.41	1.15 (0.83–1.60)	0.40
Black, quartile										
First	927396	25.13 (24.39–25.88)	19	21.14 (12.26–30.02)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	878428	23.61 (23.09–24.12)	20	21.72 (14.21–29.24)	1.09 (0.63–1.90)	0.75	1.10 (0.63–1.91)	0.73	1.09 (0.63–1.90)	0.75
Third	902968	24.42 (23.80–25.04)	31	33.32 (22.92–43.73)	1.62 (0.86–3.05)	0.13	1.62 (0.86–3.05)	0.13	1.64 (0.87–3.07)	0.13
Fourth	998118	26.84 (26.02–27.66)	23	23.82 (14.66–32.97)	1.06 (0.54–2.06)	0.88	1.06 (0.54–2.08)	0.87	1.06 (0.54–2.07)	0.87
Hispanic, quartile										
First	513002	17.83 (16.21–19.44)	15	11.08 (4.49–17.67)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	772160	26.48 (25.56–27.27)	41	29.85 (22.24–37.46)	1.81 (0.93–3.52)	0.08	1.77 (0.92–3.43)	0.09	1.79 (0.92–3.46)	0.09
Third	700995	24.18 (23.56–24.79)	25	18.47 (12.33–24.61)	1.23 (0.59–2.58)	0.59	1.21 (0.58–2.53)	0.62	1.25 (0.59–2.62)	0.56
Fourth	919246	31.52 (30.15–32.89)	55	40.60 (30.97–50.23)	2.07 (1.02–4.21)	0.04*	2.01 (1.00–4.04)	0.05	2.09 (1.03–4.25)	0.04*
Multiracial/other, quartile										
First	374651	22.71 (21.32–24.11)	15	24.73 (13.52–35.94)	1 (ref)	–	1 (ref)	–	1 (ref)	–
Second	413102	24.72 (23.88–25.55)	14	23.09 (10.55–35.64)	0.86 (0.37–1.97)	0.72	0.84 (0.37–1.90)	0.68	0.86 (0.37–1.96)	0.71
Third	399270	24.14 (23.55–24.73)	14	22.95 (11.07–34.83)	0.87 (0.38–2.03)	0.75	0.86 (0.38–1.97)	0.72	0.88 (0.38–2.03)	0.76
Fourth	472014	28.43 (27.38–29.48)	18	29.23 (17.40–41.07)	0.95 (0.55–1.63)	0.84	0.92 (0.54–1.57)	0.76	0.95 (0.55–1.63)	0.84

UV, ultraviolet. *Significant at $P < 0.05$; †multivariate logistic regression models adjusted for age (continuous), sex(male, female), race/ethnicity (white, other), insurance status (yes, no) and weekend admission (yes, no); ‡multivariate logistic regression models adjusted for any skin infection (yes, no).

environmental variables remained significant in multivariable models that controlled for diagnosis of skin infections. Future prospective studies are warranted to elucidate both the direct and indirect mechanisms of these environmental exposures in pemphigus.

Strengths and limitations

The strengths of this study include the large number of patients with pemphigus with a wide range of ages, racial/ethnic and socioeconomic backgrounds, and representative hospitals across the entire USA. By contrast, previous studies of pemphigus or other blistering skin diseases on environmental factors were often limited to more homogenous patient populations, small sample sizes or regional hospitals, which lacked variety and generalization in climate conditions. We previously validated the ICD-9-CM code for pemphigus and found it to have excellent specificity and positive predictive value in the inpatient setting.[15]

However, there are several limitations to the study as well. Month of admission was available in NIS, but not the exact date of admission. Thus, environmental factors were limited to mean levels from the admission month, which might differ somewhat from exposures during the week preceding admission. To protect the identity of patients, month of admission and/or hospital geographical information were missing for many patients, thus, analysis of environmental factors was only possible for 55% of the cohort. Moreover, there were also missing values for some the climate factors and/or pollutants for specific years and months. To address this, monthly climate values were also determined by averaging values across all available years between 2002 and 2012. These analyses showed similar results compared with values from the specific month of admission. We were also unable to distinguish between different subsets of pemphigus, such as pemphigus vulgaris or foliaceus. Finally, the patients analysed represent those in an inpatient setting, which may not necessarily be generalizable to all patients with pemphigus. It is likely that patients admitted primarily for pemphigus have more severe disease and are not representative of the entire spectrum of patients with pemphigus.

Conclusion

This study provides evidence of an association between climate factors and pollution on hospitalization for pemphigus. In particular, higher UV radiation and higher PM2.5 and PM10 levels were associated with higher risk of pemphigus, whereas higher humidity and lower temperature were inversely associated with pemphigus. Future studies are needed to confirm these findings and to understand the mechanisms and clinical relevance of these associations.

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What's already known about this topic?

- Climate factors and pollution are associated with some inflammatory skin disorders, such as atopic dermatitis and psoriasis.
- However, the role of climate factors and pollution on pemphigus has not been well described.

What does this study add?

- The present study revealed novel associations between hospitalization for pemphigus and environmental factors, including higher temperature, ultraviolet index, and PM2.5 and PM10 levels, but lower outdoor relative humidity.
- Patients with or at high risk for pemphigus may benefit from counselling on avoidance of these environmental triggers of their disease.

References

1 Calka O, Akdeniz N, Tuncer I *et al.* Oesophageal involvement during attacks in pemphigus vulgaris patients. *Clin Exp Dermatol* 2006; **31**: 515–19.
2 Leshem YA, Gdalevich M, Ziv M *et al.* Opportunistic infections in patients with pemphigus. *J Am Acad Dermatol* 2014; **71**: 284–92.
3 Parameswaran A, Attwood K, Sato R *et al.* Identification of a new disease cluster of pemphigus vulgaris with autoimmune thyroid disease, rheumatoid arthritis and type I diabetes. *Br J Dermatol* 2015; **172**: 729–38.
4 Sanchez-Palacios C, Chan LS. Development of pemphigus herpetiformis in a patient with psoriasis receiving UV-light treatment. *J Cutan Pathol* 2004; **31**: 346–9.
5 Kano Y, Shimosegawa M, Mizukawa Y *et al.* Pemphigus foliaceus induced by exposure to sunlight. Report of a

case and analysis of photochallenge-induced lesions. *Dermatology* 2000; **201**: 132–8.
6 Igawa K, Matsunaga T, Nishioka K. Involvement of UV-irradiation in pemphigus foliaceus. *J Eur Acad Dermatol Venereol* 2004; **18**: 216–17.
7 Reis VM, Toledo RP, Lopez A *et al.* UVB-induced acantholysis in endemic pemphigus foliaceus (fogo selvagem) and pemphigus vulgaris. *J Am Acad Dermatol* 2000; **42**: 571–6.
8 Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol* 2013; **133**: 1752–9.
9 Vierkotter A, Schikowski T, Ranft U *et al.* Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 2010; **130**: 2719–26.
10 Maier KL, Alessandrini F, Beck-Speier I *et al. Health* effects of ambient particulate matter – biological mechanisms and inflammatory responses to in vitro and in vivo particle exposures. *Inhal Toxicol* 2008; **20**: 319–37.
11 Wohl Y, Brenner S. Pemphigus in Israel – an epidemiologic analysis of cases in search of risk factors. *Isr Med Assoc J* 2003; **5**: 410–12.
12 Alpsoy E, Akman-Karakas A, Uzun S. Geographic variations in epidemiology of two autoimmune bullous diseases: pemphigus and bullous pemphigoid. *Arch Dermatol Res* 2015; **307**: 291–8.
13 Sato J, Denda M, Chang S *et al.* Abrupt decreases in environmental humidity induce abnormalities in permeability barrier homeostasis. *J Invest Dermatol* 2002; **119**: 900–4.
14 Kathuria PS, Silverberg JI. Association between small particle air pollution, climate and childhood eczema prevalence and severity: a US population-based study. *Pediatr Allergy Immunol* 2016; **27**: 478–85.
15 Hsu D, Brieva J, Nardone B *et al.* Validation of database search strategies for the epidemiological study of pemphigus and pemphigoid. *Br J Dermatol* 2016; **174**: 645–8.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Climate variable density plots for the specific month and year of admission for (a) relative outdoor humidity (%), (b) outdoor temperature (deg F), (c) UV index, (d) PM 2.5 (mg/m^3) and (e) PM 10 (mg/m^3).

Figure S2. Climate variable density plots for the month of admission averaged over all available years between 2002 and 2012 for (a) relative outdoor humidity (%), (b) outdoor temperature (deg F), (c) UV index, (d) PM 2.5 (mg/m^3) and (e) PM 10 (mg/m^3).

Table S1. Top 20 primary admission diagnoses for patients with a secondary diagnosis of pemphigus.

Table S2. Climate associations of hospitalization for pemphigus using mean monthly levels of environmental factors using all available values between 2002 and 2012.

Table S3. UV index associations of hospitalization for pemphigus in different racial/ethnic groups using mean monthly levels of environmental factors using all available values between 2002 and 2012.

Table S4. Factor analysis summary statistics.

Appendix S1. Methods and results.