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Increased risk of stroke in contact dermatitis patients

A nationwide population-based retrospective cohort study

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Abstract

Dermatologic diseases are not traditional risk factors of stroke, but recent studies show atopic dermatitis, psoriasis, and bullous skin disease may increase the risk of stroke and other cardiovascular diseases. No previous studies have focused on the association between contact dermatitis and stroke.

We established a cohort comprised of 48,169 contact dermatitis patients newly diagnosed in 2000–2003 and 96,338 randomly selected subjects without the disorder, frequency matched by sex, age, and diagnosis year, as the comparison cohort. None of them had a history of stroke. Stroke incidence was assessed by the end of 2011 for both cohorts.

The incidence stroke was 1.1-fold higher in the contact dermatitis cohort than in the comparison cohort (5.93 vs 5.37 per 1000 person-years, $P < 0.01$). The multivariable Cox method analyzed adjusted hazard ratios (aHRs) were 1.12 (95% confidence interval [CI], 1.05–1.19) for all stroke types and 1.12 (95% CI, 1.05–1.20) for ischemic stroke and 1.11 (95% CI, 0.94–1.30) for hemorrhagic stroke. The age-specific aHR of stroke for contact dermatitis cohort increased with age, from 1.14 (95% CI, 1.03–1.27) for 65 to 74 years; to 1.27 (95% CI, 1.15–1.42) for 75 years and older. The aHR of stroke were 1.16 (95% CI, 1.07–1.27) and 1.09 (95% CI, 1.00–1.18) for men and women, respectively.

This study suggests that patients with contact dermatitis were at a modestly increased risk of stroke, significant for ischemic stroke but not for hemorrhagic stroke. Comorbidity, particularly hypertension, increased the hazard of stroke further.

Abbreviations: ACD = allergic contact dermatitis, aHRs = adjusted hazard ratios, CI = 95% confidence interval, HR = crude hazard ratio, ICD = irritant contact dermatitis, IL-2 = interleukin-2, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHRI = National Health Research Institute, NTD = New Taiwan Dollar, RAS = renin–angiotensin system, Th2 = T helper type 2.

Keywords: contact dermatitis, insurance data, ischemic stroke, stroke

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C-HY and F-CS contributed equally to this study.

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1. Introduction

Stroke is one of the leading causes of deaths in the world and the most frequent cause of permanent disability in Taiwan.[1,2] Contact dermatitis is the main cause of occupational dermatitis because of exposing to irritants (irritant contact dermatitis, ICD) or allergens (allergic contact dermatitis, ACD).[3] Both are induced by repeated skin contact with low-molecular-weight chemicals called xenobiotics or haptens. Although both disorders may have similar clinical and histological presentations, they are with different pathophysiological grounds. ICD is a nonspecific inflammatory dermatitis induced by chemicals with proinflammatory properties, which activate the innate immune system. ACD is a delayed hypersensitivity responding to skin inflammation mediated by hapten-specific T-cells.[4] There is no specific test for the diagnosis of ICD. The patch test is the mainstay of ACD diagnosis with good sensitivity and specificity.[5]

Recent epidemiological studies have implied that atopic dermatitis, psoriasis, and bullous skin disease may increase the risk of stroke and other cardiovascular diseases.[6–11] The contact dermatitis is an inflammation of the skin surface after exposure to an irritant or allergen. Allergens may bind to Langerhans cells and present them to activate T helper type 2 (Th2). Subsequently, pro-inflammatory cytokines and chemokines are produced and persisted during the inflammation process. During acute ischemic stroke, activated T lymphocyte (CD4+ and CD8+ T-cells) may induce brain injury through producing proinflammatory cytokines, including interleukin-2 (IL-2), IL-12, interferon-gamma, and tumor necrosis factor-alpha, which play a role in the pathogenesis of stroke.[12] Another study have revealed that the elevations of proinflammatory cytokines in peripheral blood is associated with long-term functional outcome of stroke.[13] Recent studies showed inflammation may increase the incidence of stroke and involved in the pathogenesis of acute stroke.[14–20] However, the correlation between contact dermatitis and the risk of stroke has not been fully understood yet. This study estimated the risk of stroke among contact dermatitis patients during a 9-year follow-up period (2000–2008) after diagnosis of contact dermatitis, in comparison to a cohort of patients without contact dermatitis during the same period.

2. Methods

2.1. Database

This study used the "Longitudinal Health Insurance Database (LHID)" released by the Taiwan National Health Research Institute (NHRI) in 2009, covering claims data from 1996 to 2008. The LHID contained life-time longitudinal claims data of both outpatient and inpatient cares for 1,000,000 beneficiaries who were randomly sampled from 23.74 million enrollees in the National Health Insurance (NHI) program (http://www.nhi.gov.tw/english/index.aspx). The NHI covers approximately 99% of the population of Taiwan. The sample cohort and all enrollees were similar in distributions of age, sex, and health care costs. The details of the LHID have been described in previous studies.[10] The NHRI converted all personal identification numbers into surrogate numbers before releasing the data file to researchers as a scrambled secondary data file to secure the privacy of insured persons. This study was approved by the Research Ethics Committee at China Medical University and Hospital (CMU-REC-101–012).

2.2. Study samples

Faculty in biostatistics and epidemiology supervised data process, study cohorts establishment, and analysis. We established a contact dermatitis cohort and a comparison cohort from the population selected in LHID. The contact dermatitis cohort was identified from inpatients and patients ambulatory care clinics for the treatment of contact dermatitis (ICD-9-CM code 692) for the first time from 2000 to 2003, 20 years of age and older (Fig. 1). To ensure the validity of the diagnoses, we selected patients who had received at least 3 consensus diagnoses of the disease (n = 50,324). We excluded patients with a previous diagnosis of all types of stroke (ICD-9-CM codes 430 to 438, n = 1268) and those with incomplete demographic information (n = 887), resulting in 48,169 patients in the contact dermatitis cohort. The first medical visit, at which the patient received a diagnosis of contact dermatitis, was set as the index date of diagnosis. The comparison cohort consisting of 96,338 persons were randomly selected from the remaining patients in the LHID, frequency matched by sex, age, and index date. We assigned the first medical visit of the comparison subject between the years 2000 and 2003 as the index date of visit. Subjects with stroke at the baseline were excluded.

2.3. Outcome measures

We started to follow-up a study subject once was identified as an eligible person to be included in the specific study cohort. The person-years of followed-up was measured until the occurrence of stroke (ICD-9-CM codes 430–437) or December 31, 2008, or until censored because of loss to follow-up, death, or withdrawal from the insurance program. The stroke types were classified as hemorrhagic (ICD-9-CM codes 430–432) and ischemic (ICD-9-CM codes 433–437). Furthermore, we selected patients who had undergone brain computed tomography or magnetic resonance imaging and had at least 3 consensus diagnoses of stroke to ensure the validity of stroke diagnoses.

2.4. Data process and analysis

We used desk top computer equipped with SAS statistical package (version 9.1.2; SAS Institute, Inc., Cary, NC) to perform data process, study cohorts establishment and statistical analyses. The scrambled identification numbers were used to link data among claims data records for data analyses. We used Pearson's $\chi 2$ test and the *t*-test to examine the differences in sociodemographic characteristics, including age ($\leq$39, 40–59, 60–79, and $>$80 years), sex, monthly income (less than 15,840 New Taiwan Dollar [NTD], 15,841–25,000 NTD and more than 25,001 NTD), level of urbanization (from level 1 as the most urbanized to level 5 as the least urbanized),[6] and the conventional risk factors for stroke, including hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), coronary heart disease (ICD-9-CM codes 410–414), dyslipidemia (ICD-9-CM code 272), and atrial fibrillation (ICD-9-CM code 4273). We then estimated the 9-year cumulative incidence of stroke using the Kaplan–Meier method, and the difference between 2 cohorts was examined using the Log-rank test. The incidence densities of stroke were calculated for both cohorts. Univariate and multivariate Cox proportional hazards regression models were used to estimate the crude hazard ratio (HR) and adjusted hazard ratio (aHR), respectively, and 95% confidence interval (CI) to assess the stroke hazards relating to contact dermatitis, compared

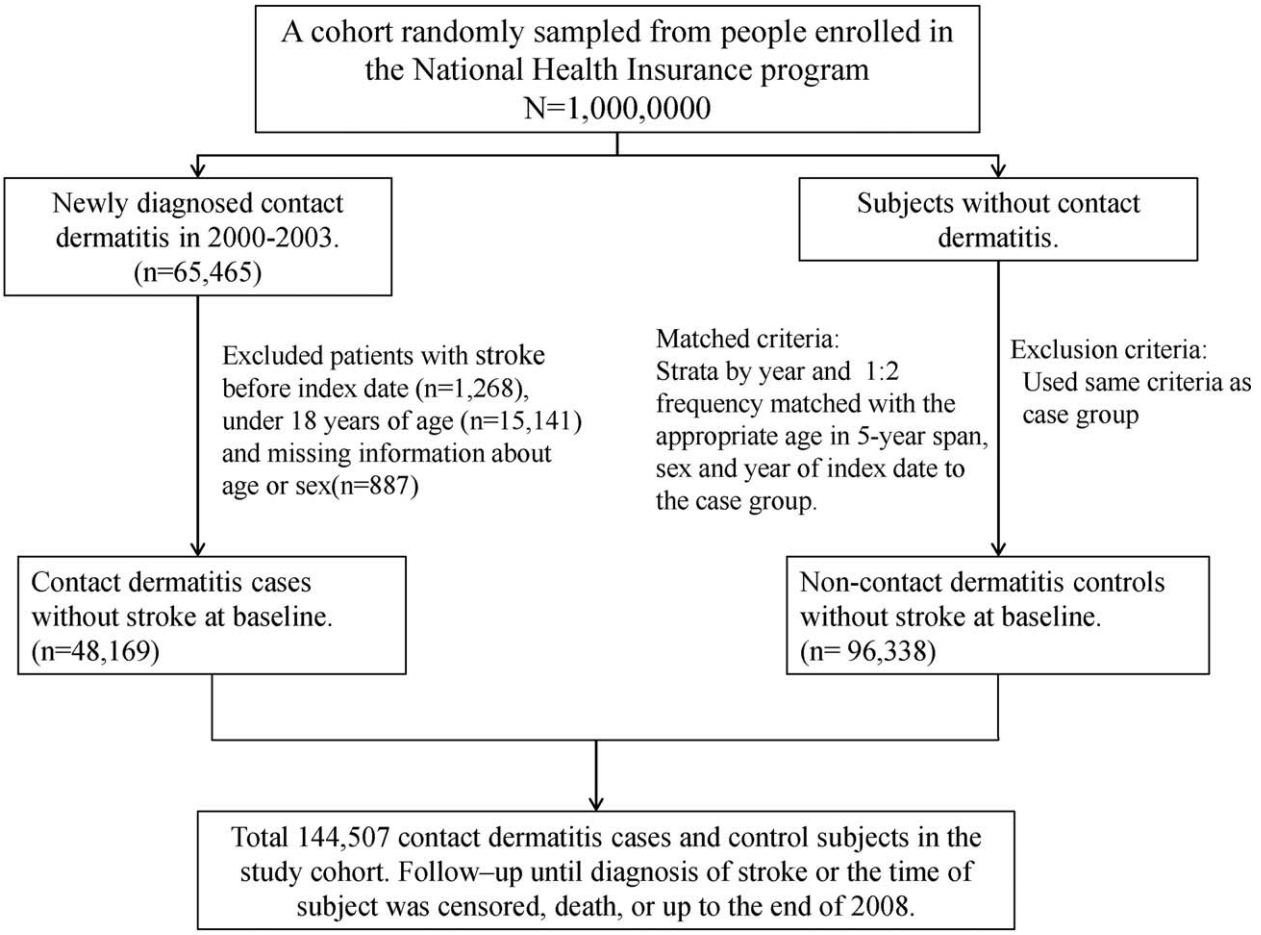

Figure 1. Flow diagram for the study cohorts with and without contact dermatitis.

with the noncontact dermatitis cohort. The multivariate model was simultaneously adjusted for age, sex, monthly income, level of urbanization, and comorbidities including hypertension, diabetes, coronary heart diseases, atrial fibrillation, and dyslipidemia. We further pooled both cohorts to measure whether there were joint effects on the hazards of stroke between contact dermatitis and comorbidities. A 2-tailed P value of < 0.05 was considered statistically significant.

3. Results

Eligible study subjects consisted of 48,169 patients in the contact dermatitis cohort and 96,338 people in the noncontact dermatitis comparison cohort, with similar sex and age distributions (Table 1). The mean age was slightly higher for the contact dermatitis cohort (45.3 vs 45.1 years old). Contact dermatitis patients were more likely to have hypertension (12.8% vs 9.31%), diabetes (8.75% vs 6.03%), coronary heart disease (8.64% vs 5.99%), atrial fibrillation (0.45% vs 0.29%), and dyslipidemia (8.74% vs 6.19%).The mean duration of follow-up was shorter in the contact dermatitis cohort than in the control cohort (5.95 vs 6.15 years, $P < 0.001$) (data not show).

During the 9-year follow-up period, the cumulative incidence of stroke was significantly greater in the contact dermatitis cohort than in the comparisons (Log-rank test $P < 0.001$) (Fig. 2). The overall incidence of stroke were 5.93 and 5.37 per 1000 person-years ($P < 0.01$), respectively, with the crude HR of 1.10 (95% CI, 1.04–1.17) (Table 2). After adjusting for age, sex, monthly income, level of urbanization, and comorbidities including hypertension, diabetes, coronary heart diseases, atrial fibrillation and dyslipidemia, the aHR of stroke for the contact dermatitis cohort compared with the comparison cohort was 1.12 (95% CI, 1.05–1.19). The incidence rates of ischemic stroke were 5.11 and 4.60 per 1000 person-years for the contact dermatitis and comparison cohorts, respectively, with the adjusted HR of 1.12 (95% CI, 1.05–1.20) for the contact dermatitis cohort. The aHR of contact dermatitis for hemorrhagic stroke was 1.11, but was not statistically significant (95% CI, 0.94–1.30). The stroke incidence increased with age in both cohorts, and the contact dermatitis cohort to comparison cohort HR of stroke also increased with age. Men had greater incidence rates of stroke than women in both the contact dermatitis cohort (7.32 vs 4.86 per 1000 person-years) and the comparison cohort (6.86 vs 4.09 per 1000 person-years). Table 3 shows that the aHR of stroke was greater for subjects with hypertension than for subjects with contact dermatitis, with the joint effects increased slightly, to an aHR of 1.33 (95% CI, 1.26–1.41; $P = 0.02$). The joint effects between contact dermatitis and other comorbidities changed minorly, such as with diabetes (adjusted HR = 1.33, 95% CI, 1.25–1.40), coronary heart disease (adjusted HR = 1.32, 95% CI, 1.24–1.39), atrial fibrillation (adjusted HR = 1.31, 95% CI, 1.24–1.39), and dyslipidemia (adjusted HR = 1.32, 95% CI, 1.25–1.40).

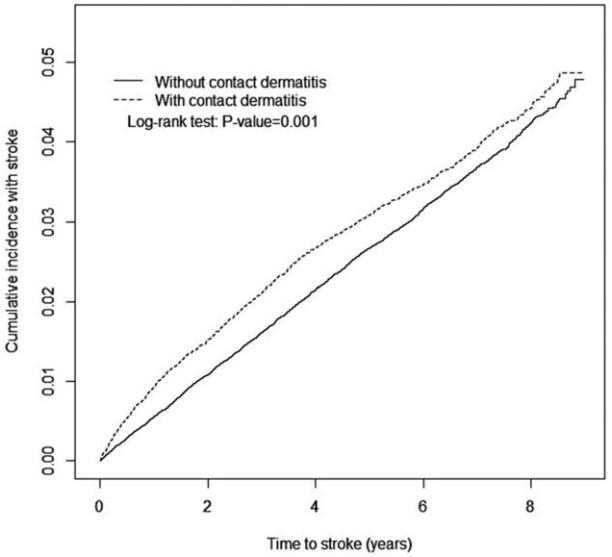

Figure 2. Cumulative incidence of stroke for patients with contact dermatitis (dashed line) and without contact dermatitis (solid line), 2000–2008.

4. Discussion

To the best of our knowledge, this study represents the first attempt to investigate the risk of stroke among patients with contact dermatitis, adjusting for patient demographic characteristics, and comorbid medical disorders.

Among the age- and sex-matched subjects, the likelihood of all strokes was 1.12-fold higher for patients with contact dermatitis during the 9-year follow-up period, after adjusting for other stroke risk factors (Table 2). The risk was significant for both male and female patients, but male patients had a higher risk of developing a subsequent stroke. In addition, the risk of stroke associated with contact dermatitis increased with age and significant in the oldest age group. This may be due to the incidence of stroke increasing with age, and the influence of contact dermatitis on stroke may have been modest. However, the effect of contact dermatitis on stroke seemed to be more obvious in the elderly. The likelihood of ischemic stroke was also 1.12-fold higher among patients with contact dermatitis. There was no significant increase in the risk of hemorrhagic stroke.

Accordingly, our study found a link between contact dermatitis and subsequently all stroke and ischemic stroke, but not hemorrhagic stroke. The actual mechanisms contributing to the association between contact dermatitis and stroke are not known. We hypothesize chronic inflammation may play a role in the pathogenesis to increase the risk of ischemic stroke.[11,20]

Several studies support the associations between chronic inflammation and cardiovascular disease and type 2 diabetes. Most attentions focused on the role of inflammatory cytokines such as interleukins and tumor necrosis factor-α to increase oxidative stress, increase insulin resistance, and oxidize low density lipoproteins.[21,22] These actions, which lead to endothelial dysfunction, are all proatherogenic and may contribute to atherosclerotic plaque vulnerable to rupture and initiate a clinical cardiovascular disease event.[20,23] A recent study showed that

Table 1

Demographic characteristics and conventional risk factors for stroke in patients with contact dermatitis and the comparison cohort, 2000–2003 (n = 144,507).

	Contact dermatitis				
	Yes (N = 48,169)		No (N = 96,338)		
Variables	n	%	n	%	*P*
Age, mean, SD*	45.3 (18.2)		45.1 (18.0)		0.99
≤39	21,573	44.8	43,139	44.8	
40–59	15,707	32.6	31,416	32.6	
60–79	8871	18.4	17,746	18.4	
>80	2018	4.19	4037	4.19	
Gender					
Male	26,524	55.1	53,048	55.1	0.99
Female	21,645	44.9	43,290	44.9	
Comorbidity					
Hypertension	6162	12.8	8968	9.31	<0.0001
Diabetes	4215	8.75	5806	6.03	<0.0001
Coronary heart disease	4163	8.64	5770	5.99	<0.0001
Atrial fibrillation	215	0.45	279	0.29	<0.0001
Dyslipidemia	4210	8.74	5966	6.19	<0.0001
Monthly income, NTD					
≤15,840	16,171	34	33,727	35	<0.0001
15,841–25,000	21,614	44.9	43,809	45.5	
≧25,001	10,384	21.6	18,802	19.5	
Urbanization level					
1 highest	14,010	29.1	29,297	30.4	<0.0001
2	14,288	29.7	27,807	28.9	
3	8671	18	17,878	18.6	
4	6694	13.9	12,555	13	
5 lowest	4506	9.35	8801	9.14	

NTD = New Taiwan Dollar, SD = standard deviation.

P = Chi-square test, a *t*-test.

†The urbanization level was categorized into 5 levels based on population density, with level 1 as the most urbanized and level 5 the least urbanized.

Table 2

Incidence densities of stroke and the contact dermatitis cohort to comparisons cohort hazard ratios of stroke by demographic characteristics.

	Contact dermatitis						Contact dermatitis cohort to comparisons	
	Yes			No				
Variables	Stroke event	PY	Stroke rate[#]	Stroke event	PY	Stroke rate[#]	cHR (95% CI)[*]	aHR (95% CI)[†]
All	1698	286,515	5.93	3183	592,628	5.37	1.10 (1.04, 1.17)[**]	1.12 (1.05, 1.19)[***]
Subtype								
Ischemic	1464	286,515	5.11	2729	592,628	4.6	1.11 (1.04, 1.18)[**]	1.12 (1.05, 1.20)[***]
Hemorrhagic	234	286,515	0.82	454	592,628	0.77	1.06 (0.91, 1.25)	1.11 (0.94, 1.30)
Age, y								
≤64	604	251,643	2.4	1190	507,961	2.34	1.02 (0.93, 1.13)	0.93 (0.84, 1.02)
65–74	539	21,941	24.6	1029	53,050	19.4	1.26 (1.14, 1.40)[***]	1.14 (1.03, 1.27)[*]
>74	555	12,931	42.9	964	31,617	30.5	1.39 (1.25, 1.54)[***]	1.27 (1.15, 1.42)[***]
Gender								
Male	908	124,069	7.32	1795	261,666	6.86	1.16 (1.06, 1.27)[***]	1.16 (1.07, 1.27)[***]
Female	790	162,446	4.86	1388	330,962	4.09	1.07 (0.98, 1.15)	1.09 (1.00, 1.18)[*]

aHR = adjusted hazard ratio, cHR = crude hazard ratio (HR), CI = confidence interval, PY = person-years.

[#] Rate = incidence rate, per 1000 person-years; PY = person-years.

[†] Adjusted HR: multivariable analysis including age, sex, monthly income, level of urbanization and comorbidities of hypertension, diabetes, coronary heart diseases, atrial fibrillation, dyslipidemia.

[*] $P < 0.05$.

[**] $P < 0.01$.

[***] $P < 0.001$.

risks of cardiovascular diseases and type 2 diabetes mellitus increased across a range of organ-specific (include psoriasis and bulous skin disease) and multisystem chronic inflammatory disorders with evidence that risk is associated with severity of inflammation.[11] It strongly supports the hypothesis that any source of chronic inflammation is associated with cardiovascular disease and type 2 diabetes.

Recent studies have shown that atopic dermatitis, psoriasis, and bullous skin disease may increase the risk of stroke and other cardiovascular diseases. The exact underlying mechanism is unknown, although the chronic inflammation has been linked to these cardiovascular events.[6–11] The immune mechanisms of both ICD and ACD are cytokines and chemokines involved, associating with apoptosis and cellular necrosis, and denoting a polymorphic inflammatory reaction. Contact dermatitis may thus cause local and systemic inflammation as well as modification of endothelial function.[4,24–27] We suspect the chronic "inflammation burden" of contact dermatitis can play a role to increase the risk of ischemic stroke, in the same manner as other dermatologic diseases mentioned above. But the exact mechanism needs further investigation. We also found that patients with contact dermatitis were more prevalent with cardiovascular risk factors. This finding has been reported is also seen in previous studies in patients with psoriasis and atopic dermatitis.[28–32] We hypothesize the immune-response raised from these dermatological diseases including contacted dermatitis might also cause the activation of local renin–angiotensin system (RAS) in the skin. And activation of the RAS system was associated with the development of stroke and other cardiovascular disease.[33–35] It is well known that risk factors for stroke include hypertension, diabetes mellitus, high cholesterol, coronary heart disease, atrial fibrillation, and so on. Patients with hypertension are particularly at an elevated risk for stroke. These factors may confound or interact with contact dermatitis for the stroke risk. However, results in Table 3 show that the stroke risk associated with contact dermatitis may be independent of these traditionally recognized risk factors. Hypertension remains the major risk for stroke. The risk of stroke increased slightly for subjects with both hypertension and contact dermatitis. As we know, data regarding cardiovascular risk among patients with contact dermatitis are still lacking. Nevertheless, stroke incidence remained higher in patients with contact dermatitis than those without contact dermatitis after adjusting for these cardiovascular risk factors.

A particular strength of the present study is the use of a population-based dataset, which enables us to trace all cases of contact dermatitis and stroke during the study period. Moreover, the large sample size affords considerable statistical power for detecting real differences between the 2 cohorts. However, this study does have some limitations.

First, patients with contact dermatitis were identified using ICD-9 codes in the claims database; coding errors might be introduced, leading to misclassification such as ICD and ACD. The proportion of ICD and ACD cases were not defined in our study. ICD is a response to irritants inducing localized inflammatory in skin because of direct cytotoxic effect of irritants. Skin lesions in ICD are limited to the contact site. In contrast, ACD is a T-cell-mediated delayed-type hypersensitivity response to repeated skin exposure to contact allergens. Skin lesions in ACD are not limited to the contact site.[4] Therefore, the "inflammation burden" in ACD is more "systemic" than that in ICD. Hence, we suspect the association between ACD and stroke may be relatively stronger than that with ICD, but further studies are needed to verify this hypothesis.

Second, under the NHI program, out-of-pocket co-payments for outpatient care are very low. Nearly all acute stroke patients in Taiwan are admitted to the hospital for several days. Therefore, it was highly unlikely for patients with acute stroke not to seek medical care during this period. However, there are still patients with contact dermatitis who prefer undergoing topical steroid treatment at the local pharmacy due to the convenience, and who have not sought medical help, or have made only 1 or 2 visits to ambulatory care centers. These patients may have been enrolled in the control cohort. If contact dermatitis is a risk factor for stroke, this bias may have mildly

Table 3

Cox proportional hazards regression analysis of the risk of stroke-associated-contact dermatitis with the joint effect of comorbidity.

Variables		N	Event n	Adjusted HR† (95% CI)	P&
Contact dermatitis	Hypertension				0.02
No	No	87,370	1867	1 (Reference)	
No	Yes	8968	1316	1.28 (1.25, 1.31)***	
Yes	No	42,007	844	1.08 (1.07, 1.08)***	
Yes	Yes	6162	854	1.33 (1.26, 1.41)***	
Contact dermatitis	Diabetes				0.86
No	No	90,532	2438	1 (Reference)	
No	Yes	5806	745	1.23 (1.19, 1.26)***	
Yes	No	43,954	1202	1.08 (1.07, 1.08)***	
Yes	Yes	4215	496	1.33 (1.25, 1.40)***	
Contact dermatitis	Coronary heart disease				0.17
No	No	90,568	2449	1 (Reference)	
No	Yes	5770	734	1.17 (1.14, 1.20)***	
Yes	No	44,006	1197	1.08 (1.07, 1.08)***	
Yes	Yes	4163	501	1.32 (1.24, 1.39)***	
Contact dermatitis	Atrial fibrillation				0.24
No	No	96,059	3116	1 (Reference)	
No	Yes	279	67	1.13 (1.10, 1.16)***	
Yes	No	47,954	1662	1.08 (1.07, 1.08)***	
Yes	Yes	215	36	1.31 (1.24, 1.39)***	
Contact dermatitis	Dyslipidemia				0.11
No	No	90,372	2643	1 (Reference)	
No	Yes	5966	540	1.16 (1.13, 1.20)***	
Yes	No	43,959	1352	1.08 (1.07, 1.08)***	
Yes	Yes	4210	346	1.32 (1.25, 1.40)***	

CI = confidence interval, HR = hazard ratio.

† Adjusted HR: adjusted for age and sex.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

& P-value for interaction.

increased the incidence rate of stroke in the comparison cohort. Besides, the diagnosis of "contact dermatitis" may be under-reported in the inpatient databases and this may underestimate the incidence of stroke in the contact dermatitis cohort. So the HR of contact dermatitis for stroke in this study may be relatively underestimated.

Third, residual confounding variables, including obesity, physical activity, smoking, and alcohol use, dietary habits, and family history, are associated with stroke, but were not included in our database. The association between contact dermatitis and these factors is unknown. Further study is suggested to clarify this issue.

Finally, as a further potential limitation, the study population mainly consisted of Taiwanese Chinese; therefore, the results may not be applicable to other ethnic groups.

5. Conclusion

We found that, over a 9-year follow-up period, the risk of both all stroke or ischemic stroke was 1.12-fold higher among patients with contact dermatitis than in the comparison cohort, and that this association was independent of any initial comorbid hypertension, diabetes, coronary heart disease, dyslipidemia, or atrial fibrillation, as well as the monthly income or level of urbanization. Hypertension acts as a significant effect modifier in the synergistic role in our study. Our study is among the first to provide evidence that contact dermatitis, the main cause of occupational dermatitis, may be a modest but significant risk factor for all stroke and ischemic stroke. Further studies should be conducted to determine whether our findings can be replicated and to explore the exact underlying pathomechanisms.

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References

[1] American Heart, Association, Heart Disease, Stroke Statistics-2016 UpdateA Report from the American Heart Association. American Heart Association, Dallas, TX:2016.
[2] Ministry of Health, WelfareCause of Death Statistics in Taiwan. Ministry of Health and Welfare, Executive Yuan, Taiwan:2014.
[3] Coenraads PJ, Goncalo M. Skin diseases with high public health impact. Contact dermatitis. Eur J Dermatol 2007;17:564–5.
[4] Nosbaum A, Vocanson M, Rozieres A, et al. Allergic and irritant contact dermatitis. Eur J Dermatol 2009;19:325–32.
[5] Nethercott JR, Holness DL. Validity of patch test screening trays in the evaluation of patients with allergic contact dermatitis. J Am Acad Dermatol 1989;21:568.
[6] Su VY, Chen TJ, Yeh CM, et al. Atopic dermatitis and risk of ischemic stroke: a nationwide population based study. Ann Med 2014;46:84–9.
[7] Silverberg JI. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. Allergy 2015;70:1300–8.

[8] Xu T, Zhang YH. Association of psoriasis with stroke and myocardial infarction: meta-analysis of cohort studies. Br J Dermatol 2012;167: 1345–50.
[9] Gu WJ, Weng CL, Zhao YT, et al. Psoriasis and risk of cardiovascular disease: a meta-analysis of cohort studies. Int J Cardiol 2013;168: 4992–6.
[10] Chiang CH, Huang CC, Chan WL, et al. Psoriasis and increased risk of ischemic stroke in Taiwan: a nationwide study. J Dermatol 2012;39: 279–81.
[11] Dregan A, Charlton J, Chowienczyk P, et al. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. Circulation 2014;130:837–44.
[12] Arumugam TV, Granger DN, Mattson MP. Stroke and T-cells. Neuromolecular Med 2005;7:229–42.
[13] Vila N, Filella X, Deulofeu R, et al. Cytokine-induced inflammation and long-term stroke functional outcome. J Neurol Sci 1999;162:185–8.
[14] Tuttolomondo A, Di Raimondo D, Pecoraro R, et al. Inflammation in ischemic stroke subtypes. Curr Pharm Des 2012;18:4289–310.
[15] Tuttolomondo A, Pecoraro R, Pinto A. Studies of selective TNF inhibitors in the treatment of brain injury from stroke and trauma: a review of the evidence to date. Drug Des Devel Ther 2014;7:2221–38.
[16] Tuttolomondo A, Pecoraro R, Casuccio A, et al. Peripheral frequency of CD4+ CD28-cells in acute ischemic stroke: relationship with stroke subtype and severity markers. Medicine (Baltimore) 2015;94:e81.
[17] Tuttolomondo A, Pecoraro R, Di Raimondo D, et al. Immune-inflammatory markers and arterial stiffness indexes in subjects with acute ischemic stroke with and without metabolic syndrome. Diabetol Metab Syndr 2014;27:28.
[18] Muir KW, Tyrrell P, Sattar N, et al. Inflammation and ischaemic stroke. Curr Opin Neurol 2007;20:334–42.
[19] McColl BW, Allan SM, Rothwell NJ. Systemic inflammation and stroke: pathology and targets for therapy. Biochem Soc Trans 2007;35(pt 5):1163–5.
[20] McColl BW, Allan SM, Rothwell NJ. Systemic infection, inflammation and acute ischemic stroke. Neuroscience 2009;158:1049–61.
[21] Libby P. Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 2006;83:456S–60S.
[22] Egger G, Dixon J. Inflammatory effects of nutritional stimuli: further support for the need for a big picture approach to tackling obesity and chronic disease. Obes Rev 2010;11:137–49.
[23] Libby P. Inflammation in atherosclerosis. Nature 2002;420:868–74.
[24] Kaur S, Zilmer K, Leping V. Allergic contact dermatitis is associated with significant oxidative stress. Dermatol Res Pract 2014;2014:415638.
[25] Kaur S, Zilmer K, Leping V, et al. Comparative study of systemic inflammatory responses in psoriasis vulgaris and mild to moderate allergic contact dermatitis. Dermatology 2012;225:54–61.
[26] Goebeler M, Gutwald J, Roth J, et al. The severity of irritant contact dermatitis in various strains of mice correlates with endothelial expression of migration inhibitory factor (MIF). Arch Dermatol Res 1991;283:246–50.
[27] Das PK, de Boer OJ, Visser A, et al. Differential expression of ICAM-1, E-selectin and VCAM-1 by endothelial cells in psoriasis and contact dermatitis. Acta Derm Venereol Suppl (Stockh) 1994;186:21–2.
[28] Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. JAMA Dermatol 2013;149:84–91.
[29] Ma C, Harskamp CT, Armstrong EJ, et al. The association between psoriasis and dyslipidemia: a systematic review. Br J Dermatol 2013; 168:486–95.
[30] Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens 2013;31:433–42.
[31] Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes 2012;2:e54.
[32] Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in two US adult population studies. J Allergy Clin Immunol 2015;135:721–8.
[33] Marcheselli S, Micieli G. Renin–angiotensin system and stroke. Neurol Sci 2008;29:277–88.
[34] Steckelings UM, Czarnetzki BM. The renin–angiotensin-system in the skin. Evidence for its presence and possible functional implications. Exp Dermatol 1995;4:329–34.
[35] Paul M, Poyan Mehr A, Kreutz R. Physiology of local renin–angiotensin systems. Physiol Rev 2006;86:747–803.