European Journal of Internal Medicine 59 (2019) 97–103

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Association between heat stroke and ischemic heart disease: A national longitudinal cohort study in Taiwan

Min-Feng Tseng[a,b], Chu-Lin Chou[b,c], Chi-Hsiang Chung[d,e], Wu-Chien Chien[d,*,1], Ying-Kai Chen[a], Hsiu-Chien Yang[a], Pauling Chu[b,f,**,1]

[a] Department of Internal Medicine, Zuoying Branch of Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan
[b] Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[c] Department of Medical Research, Ping-Tung Christian Hospital, Ping-Tung, Taiwan
[d] School of Public Health, National Defense Medical Center, Taipei, Taiwan
[e] Taiwanese Injury Prevention and Safety Promotion Association, Taipei, Taiwan
[f] Center for the Prevention and Treatment of Heat Stroke, Tri-Service General Hospital, Taipei, Taiwan

ARTICLE INFO

Keywords:
Heat stroke
Ischemic heart disease

ABSTRACT

The purpose of this study is to determine the relationship between heat stroke and ischemic heart disease (IHD), in a nationwide population using a longitudinal approach. We retrospectively examined the data from the National Health Insurance Research Database (NHIRD) in Taiwan, for patients examined between 2000 and 2013. In total, 628 patients with a heat stroke episode were enrolled and matched with 1256 patients without any history of a heat stroke episode by propensity score matching at a ratio of 1:2. The mean follow-up years of the heat stroke group was 11.89 years and the mean follow up of the control group was 11.51 years. An association between heat stroke episodes and IHD (log-rank $p < .001$) was found in a univariate cox regression analysis. After multivariate adjustment, age, comorbidities (hypertension, diabetes, stroke), and lower insurance premiums were associated with IHD events in patients who had a heat stroke. IHD was independently associated with heat stroke following cox multivariate regression analysis and patients with a heat stroke episode had a higher incidence of IHD events compared to those without any heat stroke episode ($2598.41/10^5$ person-years vs. $1286.14/10^5$ person-years, adjusted hazard ratio 3.527, 95% CI: 2.078–4.032, $p < .001$). The onset of IHD in patients who suffered a heat stroke was earlier than in those without a heat stroke episode (2.08 ± 3.45 vs. 3.61 ± 3.25 years, $p < .001$). In conclusion, clinicians should be aware about evaluating the IHD risk following a heat stroke episode in a patient.

1. Introduction

Heat injuries include heat stroke, heat syncope, heat cramps, and heat exhaustion, which reportedly caused approximately 70,000 deaths in Europe in 2003 [1]. As the prevalence of hot climates increase, deaths due to heat injuries are expected to rise by up to 2.5 folds in the 2050s, from a current annual death of approximately 2000 in the United States [2]. It has been reported that heat stroke is the most serious form of heat injuries and has a high rate of mortality (approximately 80%); however, it can be reduced to 10% with early diagnosis and immediate cooling [2]. Several risk factors for heat stroke include obesity, poor acclimatization, inadequate hydration, strenuous exercise, and hot and humid climates [3]. Moreover, heat stroke occurs in old persons due to chronic dehydration, underlying comorbidities, and relative deficiencies of the heat shock protein with aging [4,5]. It is important to know how to prevent a heat stroke.

Heat stroke is usually the result of a strenuous activity or prolonged exposure to high temperatures, resulting in the core body temperature rising above 40.0 °C (104.0 °F) and a disturbed sensorium [3]. Several studies have demonstrated the importance of evaluating heat stroke patients for damage to vital organs [6–10]. In a retrospective cohort study, Yang et al. analyzes the data from 117 consecutive patients (86 survivors, 31 nonsurvivors) who has suffered an exertional heat stroke, at 48 Chinese hospitals between April 2003 and July 2015, which demonstrates that recurrent heat strokes could predispose to central nervous system injuries [6]. Heat stroke can cause multiple syndromes

* Corresponding author.
** Corresponding author at: Division of Nephrology, Tri-Service General Hospital, 325 Section 2, Cheng-Kung Road, Neihu District 114, Taipei, Taiwan.
E-mail addresses: chienwu@mail.ndmctsgh.edu.tw (W.-C. Chien), pauling.chu@gmail.com (P. Chu).
[1] Equal contribution.

https://doi.org/10.1016/j.ejim.2018.09.019
Received 3 May 2018; Received in revised form 21 September 2018; Accepted 27 September 2018
Available online 05 October 2018
0953-6205/ © 2018 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

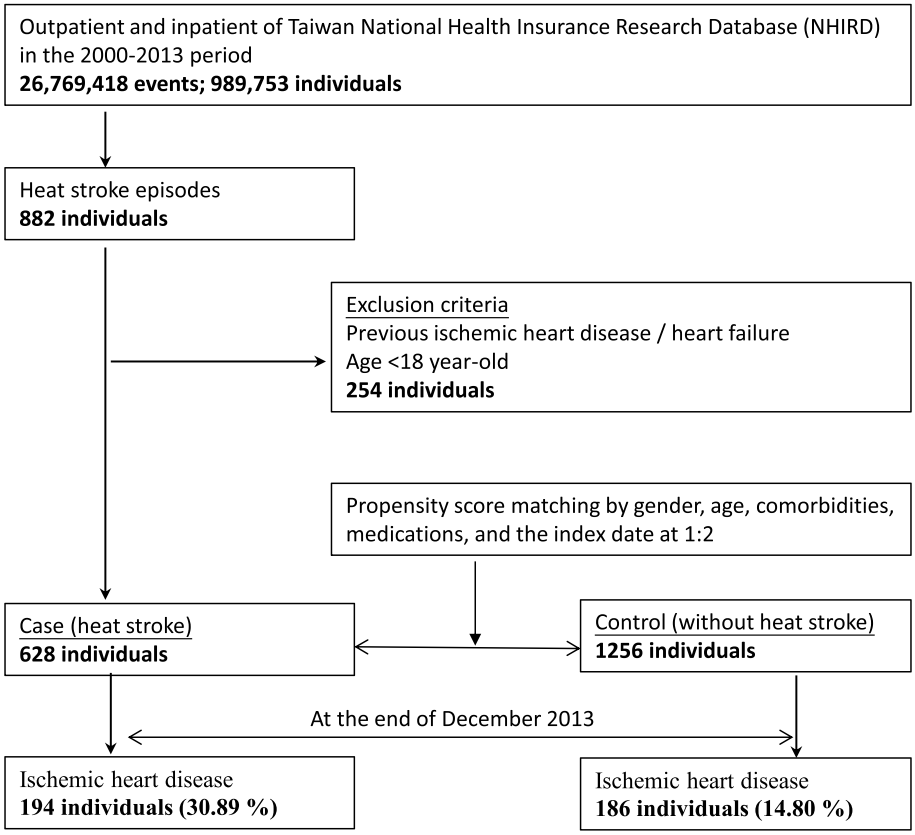

Fig. 1. Cohort assembly of patients with or without heat stroke.

including bowel ischemia, [7] acute liver failure, [8] coagulopathy, [9] impaired renal function with electrolyte disturbances [10] and myocardial damage [11,12].

It is reported that patients who have suffered a heat stroke might have decreased left-ventricular end-diastolic volume, leading to a reduced cardiac stroke volume and decrease in coronary artery perfusion [13], resulting in ischemic heart disease (IHD). Although the underlying mechanisms that lead to the development of IHD in patients suffering from heat stroke remain unclear, the effects of heat stroke on IHD have been reported. Animal studies have shown that microvascular endothelial injury and inflammation play a significant role in the cardiovascular pathogenesis of heat injury [14–16]. Additionally, dehydration due to the heat stroke could be implicated in the IHD process [17].

However, no studies have yet investigated the long-term consequences of heat stroke on ischemic heart disease (IHD) in the general population. We used data from the Taiwan National Health Insurance Research Database (NHIRD) for the period 2000–2013 to evaluate the association between heat stroke episodes and IHD events.

2. Materials and Methods

2.1. Data sources

This nationwide, observational, propensity-score-matched cohort study used data from the Taiwan NHIRD. The Institutional Review Board of the Tri-Service General Hospital (No. 2–105–05-082) approved this study and waived the requirement of informed consent, and we confirmed that all analyses followed the relevant guidelines and regulations. The study enrolled all patients diagnosed with heat stroke (ICD-9-CM 992.0) in Taiwan. In this study, we used data from the NHIRD in Taiwan to investigate the association between heat stroke and IHD events for the period between 2000 and 2013.

The NHIRD contained all registration files and details about the original claims for 1 million beneficiaries of the National Health Insurance database structured for research purposes. The NHIRD contained clinical data for population-based longitudinal cohort studies in Taiwan [18]. NHIRD being one of the highest quality databases worldwide [19], had been widely used for longitudinal cohort studies [20–27]. It contained information regarding the outpatient data, inpatient data, disease profiles, drugs prescribed, intervention procedures, and medical costs for > 99% of the population in Taiwan, covering > 22 million people. The diagnosis codes were based on the 9th revision of the International Classification of Diseases. To protect privacy, the individuals' identities were encrypted within the NHIRD.

2.2. Study design

This study used all the registered information and data of the original claims of 1 million individuals between January 1, 2000, and December 31, 2013, from the NHIRD. Patients diagnosed with heat stroke based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes: (heat stroke, ICD-9-CM 992.0) were included. The diagnosis of heat stroke was a primary diagnosis. The exclusion criteria included patients who had been diagnosed with IHD or heart failure, or < 18 years old during enrollment.

The remaining patients whose follow-up data were available were divided into two groups: patients who had suffered a heat stroke and those with no history of heat stroke (Fig. 1). Patients and controls were enrolled and propensity-score-matched (1:2) by age, sex, index date, comorbidities, and baseline medications. A logistic regression model was used for propensity matching analysis. The index date was defined as the date of onset of heat stroke and the follow-up period was considered from the same date. We assigned a date for the control patients who had not experienced a heat stroke event, as a pseudo-heat-stroke event, which matched the index date of their corresponding study

Table 1
Basic Characteristics of Case Patients with Heat stroke and Matched Control Patients after Propensity Score Matching.

	Total		Heat stroke		Control		*P*
	N = 1884	(%)	*N* = 628	(%)	*N* = 1256	(%)	
Gender							0.999
Male	1221	64.81	407	64.81	814	64.81	
Female	663	35.19	221	35.19	442	35.19	
Age (years)			50.13 ± 19.13		50.75 ± 18.82		0.508
Cormobilities							0.999
Hypertension	288	15.28	96	15.28	192	15.28	
Diabetes	291	15.44	97	15.44	145	15.44	
Hyperlipidemia	63	3.34	21	3.34	42	3.34	
Cerebral stroke	576	30.57	192	30.57	384	30.57	
Medications							
CCB	170	9.02	62	9.87	108	8.60	0.394
β-Blockers	136	7.22	45	7.17	91	7.25	0.907
ACEIs	197	10.46	66	10.51	131	10.43	0.958
ARBs	47	2.49	18	2.87	29	2.31	0.531
Anti-diabetic drugs	154	8.17	53	8.44	101	8.04	0.789
Anti-platelet drug	150	7.96	51	8.12	99	7.88	0.857
Statins	283	15.02	95	15.13	188	14.97	0.946
Climate							< 0.001*
Spring	472	25.05	105	16.72	367	29.22	
Summer	640	33.97	373	59.39	267	21.26	
Autumn	391	20.75	107	17.04	284	22.61	
Winter	381	20.22	43	6.85	338	26.91	
Insured Premium (NT$)							< 0.001*
< 18,000	1842	97.77	606	96.50	1236	98.41	
18,000-34,999	32	1.70	22	3.50	10	0.80	
≧35,000	10	0.53	0	0.00	10	0.80	
Patient Care Quality							< 0.001*
Medical center	482	25.58	126	20.06	356	28.34	
Regional hospital	596	31.63	172	27.39	424	33.76	
Local hospital	806	42.78	330	52.55	476	37.90	
Urbanization Level							< 0.001*
1 (The highest)	589	31.26	158	25.16	431	34.32	
2	819	43.47	289	46.02	530	42.20	
3	111	5.89	32	5.10	79	6.29	
4 (The lowest)	365	19.37	149	23.73	216	17.20	
Area of Taiwan							< 0.001*
Northern area	724	38.43	189	30.10	535	42.60	
Middle area	581	30.84	223	35.51	358	28.50	
Southern area	416	22.08	118	18.79	298	23.73	
Eastern area	148	7.86	87	13.85	61	4.86	
Islands area	15	0.80	11	1.75	4	0.32	

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCB, calcium-channel blocker;
N denotes sample size.
P-value (category variable: Chi-square/Fisher exact test; continue variable: t-test).
* denotes $P < .05$ and was considered statistically significant.

subjects (referred to as the index date). This method minimized the length of time bias in this cohort study.

During the study period, the comorbidities (hypertension, hyperlipidemia, stroke, diabetes mellitus), current medications (calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, anti-platelet agents, anti-diabetics, statins), insurance premium, season, demographic characteristics, the urbanization level of the place of residence, and the level of care were recorded at admission. We also recorded the incidence of IHD events to ensure that the heat stroke preceded the IHD events and to address protopathic bias.

Baseline comorbidities were identified using ICD-9 codes and included diabetes mellitus (250–250.3, 250.7, 250.4–250.6), hypertension (401–405), hyperlipidemia (272.0–272.4), and stroke (430–438). Our IHD patients were monitored starting from the year 2000. The tracking duration, as well as the time from the onset of heat stroke to IHD, was calculated.

2.3. Outcome measures

The outcomes detected were in the primary diagnosis position. The primary outcome was IHD (ICD-9-CM codes: 410–414) after heat stroke, assessed for the period 2000–2013. All the study participants were monitored from the index date until the onset of IHD events (ICD-9-CM codes: 410–414), withdrawal from the NHIRD program, death, or till the end of 2013. The secondary outcome was the duration between the heat stroke episodes and the IHD events in each subgroup.

2.4. Statistical analysis

Through propensity score matching, the two groups were balanced with respect to known confounding factors to ensure comparability during analyses and minimize the bias [28].

Baseline distribution of demographic characteristics and comorbidities were evaluated using the chi-square test for categorical variables and *t*-test for continuous variables. A logistic regression model was used for propensity matching and the ratio of the study subjects and the matched cohort was 1:2 (heat stroke group: control group = 1:2). Multivariate models were simultaneously adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, brain stroke, calcium-channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, antidiabetic

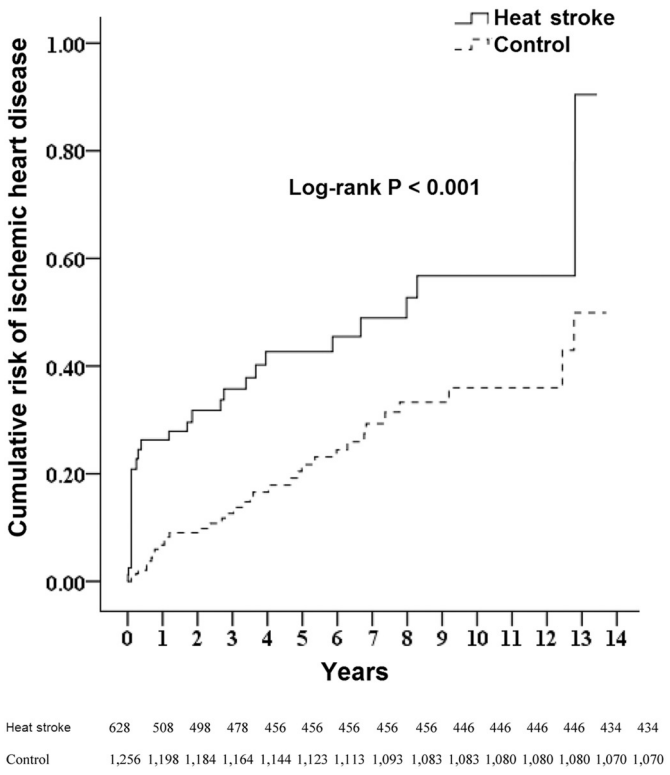

Fig. 2. Kaplan-Meier curve for cumulative risk of ischemic heart disease in patients with and without heat stroke.

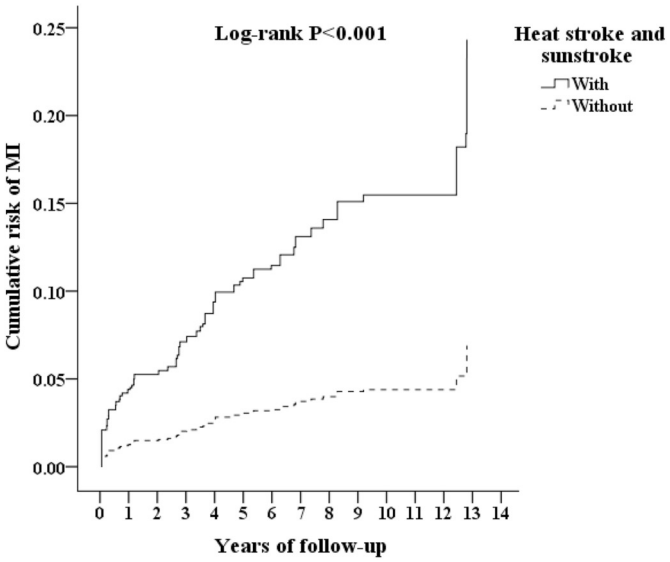

Fig. 3. Kaplan-Meier curve for cumulative risk of ischemic heart disease in patients with and without heat stroke. Patients with previous heart disease or age < 18 years were not excluded.

drugs, and antiplatelet drugs. After stratifying by age, sex, comorbidities, and medications, the relative risk for IHD in the heat stroke group were compared with that in the control group using the Cox model. Cumulative incidence curves of IHD for the two cohorts were assessed using Kaplan-Meier analysis, and the differences between the cohorts were evaluated using the log-rank test. Univariate and multivariate Cox regression analyses were used to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for all outcomes. All variants with a significant difference ($P < .05$) in the univariate analysis were entered into the multivariate model, Kaplan-Meier curves, and log-rank test. Spearman's correlation was used to assess the relationship between the two variables for monotonic relationships. In the outcomes analysis, P values lower than 0.05 were considered as statistically significant. All data analyses were conducted using the SPSS software version 22 (SPSS Inc., Chicago, IL, USA).

3. Results

In this study, a total of 882 individuals diagnosed with heat stroke for the first time were enrolled. Of these, 254 patients were excluded on the basis of exclusion criteria. After propensity score matching by gender, age, index date, comorbidities, and medications, a total of 628 patients and 1256 matched controls were enrolled, as shown in Fig. 1. During the 13 years of follow-up, we identified 194 IHD events (30.89%) in the heat stroke group and 186 (14.80%) IHD events in the control group.

As depicted in Table 1, the baseline characteristics of the patients and controls were comparable with respect to gender, age, insurance premiums (in NT$), hypertension, hyperlipidemia, diabetes mellitus, stroke, and current medications like calcium channel blockers, beta-blockers, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, anti-diabetics, anti-platelet drugs, and statins. Patients with heat stroke, however, were more likely than controls to reside in middle or eastern Taiwan and outlets islands, in an area with a higher urbanization level, and local hospital care.

Fig. 2 showed the Kaplan–Meier curve for cumulative IHD risk stratified by heat stroke with a log-rank test. Heat stroke was associated with a significantly increased risk of IHD events (Log-rank $P < .001$). From the first year of follow-up to the thirteenth year, the incidence of IHD events in the heat stroke group was higher than in the control group. Furthermore, the incidence of IHD events increased dramatically within the first year after heat stroke. If patients with previous heart disease or age < 18 years were not excluded and all of the 882 patients with heat stroke was compared with all control subjects, heat stroke was still associated with a significantly increased risk of IHD events (Log-rank $P < .001$) (Fig. 3).

The adjusted hazards ratio of IHD events in the groups of subjects with heat stroke and matched controls were depicted in Table 2. Patients with heat stroke had a higher rate of IHD events than the control patients had (adjusted HR = 3.527, $P < .001$), during the follow-up period after adjustment by age, gender, insurance premium, comorbidities, current medications including calcium channel blockers, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, antidiabetics, anti-platelet drugs, statins, climate, urbanization level, patient care quality, and the geographical part of Taiwan. The risks of IHD events were associated with those with age > 40 years, some comorbidities (diabetes, hypertension, cerebral stroke, hyperlipidemia, and medications), and low insurance premiums (low socioeconomic status), although $p < .05$ for absence and presence of these comorbidities. There was a correlation between heat stroke episodes and IHD events in the hot climate areas in Taiwan. After analyzing the Spearman's correlation coefficient in subgroup analysis, these covariates (hypertension, diabetes, stroke, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, anti-diabetic drugs, anti-platelet drugs, and statins) were not significantly associated with heat stroke.

The mean follow-up time of the heat stroke group and the control group was 11.89 ± 13.32 and 11.51 ± 12.96 years, respectively (Table 3). The duration between the onset of heat stroke and IHD was 2.08 ± 3.45 years. In contrast, the duration in the matched group was 3.61 ± 3.25 years. The onset of IHD in patients who suffered a heat stroke was earlier than in those without a heat stroke episode.

4. Discussion

This is the first study to examine the long-term consequences of heat

Table 2
Risk of Ischemic Heart Disease among Patients with Heat stroke and Matched Control Patients.

	Heat stroke			Control						
	Event	PYs	Rate (per 105 PYs)	Event	PYs	Rate (per 105 PYs)	Cox regression adjusted HR#	95%CI		P
Ischemic heart disease	194	7466.09	2598.41	186	14,461.88	1286.14	3.527	2.781	4.473	< 0.001*
Gender										
Male	125	5132.06	2435.67	107	8460.87	1264.65	2.895	2.078	4.032	< 0.001*
Female	69	2334.03	2956.26	79	6001.01	1316.45	8.406	4.816	14.671	< 0.001*
Age (year-old)										
18–29	10	603.52	1656.95	0	597.40	0.00	–			–
30–39	0	1106.31	0.00	0	1832.74	0.00	–			–
40–49	21	1452.77	1445.51	36	2234.53	1611.08	7.406	1.944	28.209	0.003*
50-59	47	1879.15	2501.13	32	3464.60	923.63	3.555	1.746	7.236	< 0.001*
60-69	46	1484.69	3098.29	48	2371.14	2024.34	130.929	29.492	581.265	< 0.001*
70-79	47	620.50	7574.54	64	2807.08	2279.95	3.231	1.874	5.568	< 0.001*
≧80	23	319.15	7206.64	6	1154.39	519.76	36.050	0.073	193.425	< 0.001*
Hypertension										
No	121	6850.58	1766.27	129	11,432.92	1128.32	2.712	1.995	3.697	< 0.001*
Yes	73	615.51	11,860.08	57	3028.96	1881.83	7.043	2.698	18.387	< 0.001*
Diabetes										
No	144	6538.99	2202.17	115	12,397.21	927.63	5.332	3.902	7.286	< 0.001*
Yes	50	927.10	5393.16	71	2064.67	3438.81	22.523	9.928	51.098	< 0.001*
Hyperlipidemia										
No	194	7463.94	2599.16	176	13,804.76	1274.92	3.509	2.760	4.462	< 0.001*
Yes	0	2.15	0.00	10	657.12	1521.79	0.000	–	–	0.997
Cerebral stroke										
No	174	7364.84	2362.58	164	12,845.04	1276.76	3.070	2.382	3.957	< 0.001*
Yes	20	101.25	19,753.09	22	1616.84	1360.68	8.064	1.004	15.919	0.046*
CCB										
No	184	6340.43	2902.01	181	12,316.87	1469.53	3.438	2.701	4.377	< 0.001
Yes	10	1125.66	888.37	5	2145.01	233.10	6.612	5.244	8.439	< 0.001
β-Blockers										
No	189	6952.13	2718.59	183	13,760.66	1329.88	3.565	2.811	4.529	< 0.001
Yes	5	513.96	972.84	3	701.22	427.83	3.988	3.124	5.001	< 0.001
ACEIs										
No	182	6367.53	2858.25	175	12,257.92	1427.65	3.425	2.503	4.444	< 0.001
Yes	12	1098.56	1092.34	11	2203.96	499.10	3.811	2.979	4.832	< 0.001
ARBs										
No	194	5923.81	3274.92	186	12,752.22	1458.57	3.527	2.781	4.473	< 0.001
Yes	0	1542.28	0.00	0	1709.66	0.00	–	–	–	–
Anti-diabetic drugs										
No	164	6189.67	2649.58	142	10,436.27	1360.64	3.329	2.602	4.343	< 0.001
Yes	30	1276.42	2350.32	44	4025.61	1093.00	3.703	2.935	4.798	< 0.001
Anti-platelet drug										
No	154	4574.99	3366.13	144	10,436.24	1379.81	4.201	3.025	5.424	< 0.001
Yes	40	2891.10	1383.56	42	4025.64	1043.31	2.308	1.803	3.012	< 0.001
Statins										
No	167	5747.14	2905.79	156	11,476.75	1359.27	3.623	2.871	4.735	< 0.001
Yes	27	1718.95	1570.73	30	2985.13	1004.98	2.422	2.099	3.468	< 0.001
Climate										
Spring	22	1337.53	1644.82	81	3695.17	2192.05	5.721	2.526	10.999	< 0.001*
Summer	103	1142.63	9014.29	25	2751.87	908.47	82.939	43.785	157.107	< 0.001*
Autumn	48	2960.50	1621.35	59	4314.26	1367.56	0.982	0.579	1.665	0.946
Winter	21	2025.43	1036.82	21	3700.58	567.48	1.000	0.378	2.642	0.498
Insured premium§										
< 18,000	194	6757.36	2870.94	186	14,276.52	1302.84	3.527	2.781	4.473	< 0.001*
18,000–34,999	0	708.73	0.00	0	183.60	0.00	–	–	–	–
≧35,000	0	0.00	–	0	1.76	0.00	–	–	–	–
Patient care quality										
Medical center	13	1285.79	1011.05	42	3021.24	1390.16	0.842	0.288	2.460	0.754
Regional hospital	86	3848.74	2234.50	90	7368.36	1221.44	4.327	2.685	6.974	< 0.001*
Local hospital	95	2331.56	4074.53	54	4072.28	1326.04	10.129	5.226	19.632	< 0.001*
Urbanization level										
1 (The highest)	81	1108.31	7308.42	48	4149.67	1156.72	21.839	10.527	45.303	< 0.001*
2	101	4012.32	2517.25	83	7322.65	1133.47	8.313	5.327	12.972	< 0.001*
3	0	674.88	0.00	17	648.46	2621.60	0.000	–	–	0.884
4 (The lowest)	12	1670.58	718.31	38	2341.10	1623.17	0.525	0.266	6.156	0.602
Area of Taiwan										
Northern area	85	1153.22	7110.53	92	5604.17	1641.63	7.562	5.962	9.591	< 0.001*
Middle area	33	3816.02	864.78	34	4313.25	788.27	1.915	1.510	2.430	< 0.001*

(*continued on next page*)

Table 2 (*continued*)

	Heat stroke			Control						
	Event	PYs	Rate (per 105 PYs)	Event	PYs	Rate (per 105 PYs)	Cox regression adjusted HR#	95%CI		P
Southern area	12	1722.18	696.79	20	3428.17	583.40	2.084	1.613	2.667	< 0.001*
Eastern area	67	755.48	8868.53	40	1110.94	3600.55	4.299	3.385	5.496	< 0.001*
Islands area	0	19.19	0.00	0	5.35	0.00	–	–	–	–

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCB, calcium-channel blocker; PYs, person-years; adjusted HR, adjusted hazard ratio, CI, confidence interval.

[#] Adjusted for covariates including age, gender, insurance premium, comorbidities, calcium channel blockers, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, diabetes mellitus medication, anti-platelet drugs, statins, season, location, and urbanization level.

[$] denotes New Taiwan dollar.

* denotes $P < .05$ and was considered statistically significant.

Table 3
Follow-up years Among Heat Stroke Patients and Matched Control Patients.

	Heat stroke				Control				P
	Min	Middle	Max	Mean ± SD	Min	Middle	Max	Mean ± SD	
The cohort study	0.01	5.87	12.97	11.89 ± 13.32	0.01	6.89	13.70	11.51 ± 12.96	0.989
IHD events	0.10	0.25	12.80	2.08 ± 3.45	0.10	3.03	12.77	3.61 ± 3.25	< 0.001*

IHD, Ischemic heart disease, SD, Standard deviation.

* denotes $P < .05$ and was considered statistically significant.

stroke on IHD. The major findings of our study are as follows: (1) Patients suffering for heat stroke are at risk for IHD. (2) There is a positive relationship between IHD events and hot climate in patients with heat stroke episodes, with a higher risk in old age, those with low insurance premiums (low socioeconomic status), and presence of comorbidities (diabetes, hypertension, and stroke). (3) The onset of IHD in patients who suffered a heat stroke is earlier than in those without a heat stroke episode.

In this cohort study, we demonstrate that patients suffering from heat stroke episodes have increased IHD events. Although the underlying mechanisms for the development of IHD in patients suffering from heat stroke remain unclear, some suggested mechanisms are microvascular endothelial injury and inflammation [14–16]. Rasouli et al. also indicates that hemoconcentration, (a decrease in plasma volume) is significantly associated with the prevalence and severity of IHD [17]. These findings suggest a mechanical pathway between heat stroke and myocardial ischemia.

In this study, we observe that advanced age, comorbidities (diabetes, hypertension, and stroke), low insurance premiums (low socioeconomic status), and lower quality of health care are associated with increased IHD events in patients suffering from heat stroke episodes. Aging is associated with attenuated sweating and skin vasodilation, resulting in heat stroke episodes when in a hot climate [29]. Moreover, it is known that the risk of IHD increases substantially with age [30], which is consistent with our result of age affecting IHD events. There are cardiovascular risks factors for heat stroke episodes, such as patients with existing systemic vascular disease [31,32] and diabetes mellitus [33], indicating a probable cardiovascular involvement in the consequences of heat stroke episodes.

Individuals with low insurance premiums have a low socioeconomic status in Taiwan, and these patients were a risk for IHD events in our study. Janati et al. also reports that people from lower socioeconomic status are at a greater risk of IHD events than those from higher socioeconomic status [34]. Our study also discovers that the risk of heat stroke episodes increases noticeably with gradual urbanization. The variation in daily temperature is significantly more in an urban area than in a suburban area [35]. One of the causes for environmental and temperature changes in the urban areas is the urban heat island effect, which occurs when a city experiences much hotter temperatures than the nearby rural areas [36]. Urbanization alters the natural surface and atmospheric circumstances. The biogeochemical effect of urban aerosol or haze pollution contributes to urban heat island in the urban areas than in the surrounding rural areas [37].

The strengths of our study include the use of a national database, a case-control matched index date, and the use of propensity score matching between the study and control groups to ensure comparability during analyses and minimize the bias due to confounding factors. Moreover, this population-based observational study includes adjustments for possible potential risk factors.

Our study has a few limitations. First, we could not assess the severity of IHD because this information is not available from the database. Second, we could not obtain body height, weight, and occupation, information on personal habits, disease severity, or family history due to the privacy policy of NHIRD. Third, the data from 2000 to 2013 is used; hence, the results may not be applicable to more recent data. Fourth, because this is a retrospective study, we may not assure quality control of all data. Fifth, the sample size is not large enough and the effect size is the compelling case. However, since there has been no significant change in the ICD-9 codes, diagnostic criteria of IHD, or the administrative process in the NHIRD since 2013, it is unlikely that the data quality would have changed significantly in years that are more recent. A further study is necessary to evaluate the accuracy of accompanying comorbidity diagnoses among the IHD cases.

5. Conclusions

Our results show the association between heat stroke episodes and increased IHD consequences. The onset of IHD in patients who suffered a heat stroke is earlier than in those without a heat stroke episode. Therefore, being vigilant about the cardiovascular complications in patients with heat stroke is suggested.

Acknowledgment

This work was supported by research grants from the Tri-Service General Hospital (TSGH-C103-122).

Disclosures

None.

References

[1] Robine JM, Cheung SL, Le Roy S, Van Oyen H, Griffiths C, Michel JP, et al. Death toll exceeded 70,000 in europe during the summer of 2003. C R Biol 2008;331:171–8.
[2] Centers for Disease. C, Prevention. Heat–related illnesses and deaths-United States, 1994–1995. MMWR Morb Mortal Wkly Rep 1995;44:465–8.
[3] Leon LR, Bouchama A. Heat stroke. Compr Physiol 2015;5:611–47.
[4] Khosla R, Guntupalli KK. Heat-related illnesses. Crit Care Clin 1999;15:251–63.
[5] Hopp S, Dominici F, Bobb JF. Medical diagnoses of heat wave-related hospital admissions in older adults. Prev Med 2018;110:81–5.
[6] Yang M, Li Z, Zhao Y, Zhou F, Zhang Y, Gao J, et al. Outcome and risk factors associated with extent of central nervous system injury due to exertional heat stroke. Medicine (Baltimore) 2017;96:e8417.
[7] Masood U, Sharma A, Syed W, Manocha D. Bowel ischemia from heat stroke: a rare presentation of an uncommon complication. Case Rep Med 2016;2016:5217690.
[8] Carvalho AS, Rodeia SC, Silvestre J, Povoa P. Exertional heat stroke and acute liver failure: a late dysfunction. BMJ Case Rep 2016;2016.
[9] Ramanathan M, Pedersen M, Ramsey R, Seetharam A. Diagnostic value of coagulation factor and intracranial pressure monitoring in acute liver failure from heat stroke: Case report and review of the literature. Transplant Proc 2015;47:817–9.
[10] Satirapoj B, Kongthaworn S, Choovichian P, Supasyndh O. Electrolyte disturbances and risk factors of acute kidney injury patients receiving dialysis in exertional heat stroke. BMC Nephrol 2016;17:55.
[11] Wakino S, Hori S, Mimura T, Miyatake S, Fujishima S, Aikawa N. A case of severe heat stroke with abnormal cardiac findings. Int Heart J 2005;46:543–50.
[12] Chen WT, Lin CH, Hsieh MH, Huang CY, Yeh JS. Stress-induced cardiomyopathy caused by heat stroke. Ann Emerg Med 2012;60:63–6.
[13] Wilson TE, Brothers RM, Tollund C, Dawson EA, Nissen P, Yoshiga CC, et al. Effect of thermal stress on frank-starling relations in humans. J Physiol 2009;587:3383–92.
[14] Mohanty D, Gomez J, Mustafa KY, Khogali M, Das KC. Pathophysiology of bleeding in heat stress: an experimental study in sheep. Exp Hematol 1997;25:615–9.
[15] Gader AM, Al-Mashhadani SA, Al-Harthy SS. Direct activation of platelets by heat is the possible trigger of the coagulopathy of heat stroke. Br J Haematol 1990;74:86–92.
[16] Roberts GT, Ghebeh H, Chishti MA, Al-Mohanna F, El-Sayed R, Al-Mohanna F, et al. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. Arterioscler Thromb Vasc Biol 2008;28:1130–6.
[17] Rasouli M, Kiasari AM, Arab S. Indicators of dehydration and haemoconcentration are associated with the prevalence and severity of coronary artery disease. Clin Exp Pharmacol Physiol 2008;35:889–94.
[18] Kao CH. Clinical studies stemming from the Taiwan national health insurance database. Eur J Intern Med 2016;31:e8.
[19] Hsing AW, Ioannidis JP. Nationwide population science: Lessons from the Taiwan national health insurance research database. JAMA Intern Med 2015;175:1527–9.
[20] Lin HF, Li YH, Wang CH, Chou CL, Kuo DJ, Fang TC. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. Nephrol Dial Transplant 2012;27:1585–90.
[21] Hung TH, Chou CL, Fang TC. Impact of renal dysfunction in cirrhotic patients with bacterial infections other than spontaneous bacterial peritonitis. Hepatol Res 2014;44:863–70.
[22] Chou CL, Hsieh TC, Wang CH, Hung TH, Lai YH, Chen YY, et al. Long-term outcomes of dialysis patients after coronary revascularization: a population-based cohort study in Taiwan. Arch Med Res 2014;45:188–94.
[23] Wang YC, Hsieh TC, Chou CL, Wu JL, Fang TC. Risks of adverse events following coprescription of statins and calcium channel blockers: a nationwide population-based study. Medicine (Baltimore) 2016;95:e2487.
[24] Hsieh TC, Chou CL, Chen JS, Kuo CH, Wang YC, Lai YH, et al. Risk of mortality and of atherosclerotic events among patients who underwent hemodialysis and subsequently developed retinal vascular occlusion: a taiwanese retrospective cohort study. JAMA Ophthalmol 2016;134:196–203.
[25] Kuo CH, Hsieh TC, Wang CH, Chou CL, Lai YH, Chen YY, et al. Increased risks of mortality and atherosclerotic complications in incident hemodialysis patients subsequently with bone fractures: a nationwide case-matched cohort study. PLoS One 2015;10:e0121705.
[26] Lin HC, Chao PZ, Lee HC. Sudden sensorineural hearing loss increases the risk of stroke: a 5-year follow-up study. Stroke 2008;39:2744–8.
[27] Chien LN, Chou CL, Chen HH, Kao CC, Lin YC, Wu YL, et al. Association between stroke risk and metformin use in hemodialysis patients with diabetes mellitus: a nested case-control study. J Am Heart Assoc 2017;6.
[28] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–83.
[29] Stapleton JM, Fujii N, McGinn R, McDonald K, Kenny GP. Age-related differences in postsynaptic increases in sweating and skin blood flow postexercise. Physiol Rep 2014;2.
[30] Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. Circulation 1999;99:1165–72.
[31] De Blois J, Kjellstrom T, Agewall S, Ezekowitz JA, Armstrong PW, Atar D. The effects of climate change on cardiac health. Cardiology 2015;131:209–17.
[32] Ishigami A, Hajat S, Kovats RS, Bisanti L, Rognoni M, Russo A, et al. An ecological time-series study of heat-related mortality in three european cities. Environ Health 2008;7:5.
[33] Semenza JC, McCullough JE, Flanders WD, McGeehin MA, Lumpkin JR. Excess hospital admissions during the July 1995 heat wave in chicago. Am J Prev Med 1999;16:269–77.
[34] Janati A, Matlabi H, Allahverdipour H, Gholizadeh M, Abdollahi L. Socioeconomic status and coronary heart disease. Health Promot Perspect 2011;1:105–10.
[35] Peng S, Piao S, Ciais P, Friedlingstein P, Ottle C, Breon FM, et al. Surface urban heat island across 419 global big cities. Environ Sci Technol 2012;46:696–703.
[36] Zhou B, Rybski D, Kropp JP. The role of city size and urban form in the surface urban heat island. Sci Rep 2017;7:4791.
[37] Cao C, Lee X, Liu S, Schultz N, Xiao W, Zhang M, et al. Urban heat islands in China enhanced by haze pollution. Nat Commun 2016;7:12509.