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Self-Reported Eczema in Relation with Mortality from Cardiovascular Disease in Japanese: the Japan Collaborative Cohort Study

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Aim: Previous studies suggested a positive association between eczema and cardiovascular disease (CVD), probably through enhanced systemic inflammation. However, several studies reported null findings about eczema and CVD, so the evidence is still controversial.

Methods: We asked 85,099 participants (35,489 men and 49,610 women), aged 40 to 79 years, without a history of CVD or cancer at baseline between 1988 and 1990, to complete a lifestyle questionnaire, including information eczema frequency (seldom, sometimes or often).

Results: During the 6,389,818 person-years of follow-up, there were 1,174 deaths from coronary heart disease (CHD), 979 from heart failure, 366 from cardiac arrhythmia, 2,454 from total stroke, 1,357 from ischemic stroke, 1,013 from hemorrhagic stroke, and 201 from aortic aneurysm or dissection. The multivariable-adjusted model showed that individuals who "sometimes" or "often" had eczema had 0.82 (95%confidence interval (CI): 0.69–0.97) or 1.26 (95%CI: 1.01–1.56) times the risk of mortality from CHD, respectively, compared to those who "seldom" did. Individuals who "often" had 1.30 (95%CI: 1.05–1.61) times the risk of mortality from CHD, compared to those who "seldom or sometimes" did. There was no association of eczema with mortality from other CVD, or no interaction between eczema and sex or age, in relation to any CVD mortality risk.

Conclusions: Self-reported frequent eczema was associated with increased risk of mortality from CHD, but not other major CVD, in a Japanese general population. Since steroid usage was not considered, future studies should include it as a potential confounding factor.

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Key words: Eczema, Cardiovascular disease, Atherosclerosis, CHD, Population-based study

Introduction

Chronic inflammation is an important risk factor for cardiovascular disease (CVD)[1-5]. Chronic inflammatory diseases, such as systemic lupus erythematosus[6], rheumatoid arthritis[7], psoriatic arthritis[8], and inflammatory bowel disease[9, 10], may be associated with an increased risk of CVD.

Eczema, which is also a chronic inflammatory disorder, appears to affect adults as well as children[11-13]. Some studies associate eczema with CVD risk, probably through inflammation[14, 15]. However, several studies have reported null findings about eczema and CVD[16, 17], so the association is still controversial. In addition, existing reports using population-based cohort studies are mainly from Western countries; no Japanese cohort study has investigated the association between eczema and risk of CVD.

Therefore, we aimed to prospectively examine the association of eczema with mortality from several major CVDs, including CHD, heart failure, stroke and aortic aneurysm, using a Japanese population-based cohort study. Furthermore, we examined whether the effect is modified by age or sex.

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Methods

Study Population

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks, sponsored by the Ministry of Education, Sport, and Science, conducted a baseline survey from 1988 to 1990 in 45 areas throughout Japan. Details of this survey have been described elsewhere[18]. Briefly, participants completed self-administered questionnaires about their lifestyles and medical histories, including previous CVD, cancer, and other diseases at baseline. The ethics committees of the Nagoya University School of Medicine and the Osaka University Graduate School of Medicine approved the study.

Of a total of 110,585 individuals, aged 40 to 79 years, 90,035 participants answered the question about their skin status. We further excluded participants who had any previous history of CHD, stroke or cancer at baseline. Consequently, 85,099 participants (35,489 men and 49,610 women) were included in this study.

Main Exposure: Self-Reported Frequency of Eczema

We asked participants about the frequency eczema appearance. Participants were requested to choose their answer to this question from the following three categories: "Often," "Sometimes," or "Seldom."

Other Cardiovascular Risk Factors

We selected a number of CVD risk factors, including age, sex, body mass index (sex-specific quintiles), history of hypertension, history of diabetes, smoking status (never, ex-smoker, or current smokers of 1 to 19 or ≥ 20 cigarettes per day), alcohol intake categories (never, ex-drinker, or current drinkers of ethanol at 1 to 22, 23 to 45, 46 to 68, or ≥ 69g per day), hours of walking (never, 1 to 2, 3 to 4, or ≥ 5 hours per week), sport participation (never, 1 to 2, 3 to 4, or ≥ 5 hours per week), perceived mental stress (low, medium, or high), hours of sleep (≤ 5, 6, 7, 8 or ≥ 9 hours per day), and educational attainment (attended school up to 12 years old, 15 years old, 18 years old, or older than 18 years old).

Outcomes: Mortality from Major Cardiovascular Diseases

Mortality surveillance was conducted systematically by checking death certificates, all of which were forwarded to their respective public health centers. Mortality data were then centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics according to the International Classification of Diseases. Death registration is required by the Family Registration Law in Japan. Deaths from major CVD were defined by the International Classification of Diseases (ICD)-10 codes as follows: total CVD as I00 to I99; CHD as I20 to I25.9; heart failure as I50 to I50.9; cardiac arrhythmia as I40 to I40.9; total stroke as I60 to I60.9; ischemic stroke as I63 to I63.9 or I69.3; hemorrhagic stroke as I60 to I62.9 or I69 to I69.2; and aortic aneurysm or dissection as I71 to I71.9.

Statistical Analysis

The person-years of follow-up for each participant were calculated from the baseline in 1988 to 1990 to the first endpoint: death, moving from the community, or the end of follow-up of 2009, except for four areas in 1999, four areas in 2003 and two areas in 2008 where follow-up had been terminated. Participants were divided into three categories ("Seldom," "Sometimes," or "Often") or two categories ("Seldom or sometimes" or "Often") according to their answers about eczema frequency, because it appears to be difficult for participants to distinguish "Seldom" and "Sometimes." Age, sex-adjusted mean values and prevalence of selected CVD risk factors were calculated according to eczema frequency. We tested the proportional hazards assumption in Cox regression using risk factors by time interactions and found it was not violated. Using Cox proportional hazard models, we calculated the hazard ratios (HRs) and their 95% confidence intervals (CIs) for mortality outcomes after adjustment for age, sex, and other CVD risk factors.

We also performed sex or age (40 to 59 vs. 60 to 79 years old)-specific analysis and tested multiplicative interactions between the eczema frequency and sex or age in relation to CVD mortality risk for sensitivity analyses. We tested interactions between sex or age and eczema frequency in relation to CVD mortality risk by adding multiplicative interaction terms in a multivariable for sensitivity analyses.

SAS Version 9.3 software (SAS Institute Inc., Cary, NC) was used for statistical analysis. All statistical tests were two-tailed and P values of <0.05 were considered significant.

Results

Baseline Characteristics According to Self-Reported Frequency of Eczema

As shown in **Table 1**, compared to individuals who "seldom" or "sometimes" had eczema, those who "often" had it tended to have higher level of body mass

Table 1. Age-, Sex-Adjusted Baseline Characteristics According to the Frequency of Eczema

	Frequency of Eczema				
	Three categories			Two categories	
	Seldom	Sometimes	Often	Seldom or Sometimes	Often
No. at risk	64 490	15 240	5 369	79 730	5 369
Age, years	57.0	56.5	57.1	56.9	57.0
Men, %	41.9	41.0	41.4	41.7	41.4
Body mass index, kg/m^2	22.8	22.8	23.0	22.8	23.0
History of hypertension, %	21.4	21.3	23.6	21.4	23.6
History of diabetes, %	4.7	5.8	7.3	4.9	7.3
Current drinker, %	40.2	41.3	41.4	40.4	41.4
Current smoker, %	26.6	26.2	26.9	26.5	26.9
High perceived mental stress, %	19.6	25.3	31.4	20.7	31.4
Walking ≥ 5 hour/week, %	51.5	48.6	47.9	50.9	47.9
Sport participation ≥ 5 hour/week, %	5.6	6.0	5.2	5.7	5.2
Educated over 18 years old, %	12.9	15.6	15.3	13.5	15.3
Sleep duration, hours/day	7.3	7.2	7.2	7.3	7.2

index, histories of hypertension and diabetes, and high perceived mental stress, to be current drinkers, and to walk for more than five hours per week.

Association of Self-Reported Frequency of Eczema with Mortality from Several Major Cardiovascular Diseases

There were 5,628 CVD deaths during the 6,389,818 person-years of follow-up. As shown in **Table 2**, 1,174 deaths resulted from CHD, 979 from heart failure, 366 from cardiac arrhythmia, 2,454 from total stroke, 1,357 from ischemic stroke, 1,013 from hemorrhagic stroke, and 201 from aortic aneurysm or dissection (**Table 2**). The age-, sex-adjusted model showed that, compared to individuals "seldom" having eczema, those "sometimes" or "often" having it had decreased or increased risk of mortality from CHD, respectively. Those "often" having eczema had an increased risk of mortality from CHD, than individuals who "seldom or sometimes" had it. Further adjustment for other CVD risk factors did not substantially change those associations; individuals who "sometimes" or "often" had eczema had 0.82 (95%CI: 0.69–0.97) or 1.26 (95%CI: 1.01–1.56) times the risk of mortality from CHD, compared to those who "seldom" did, respectively. Individuals who "often" had 1.30 (95%CI: 1.05–1.61) times the risk of mortality from CHD, compared with those who "seldom or sometimes" did it. There was no association of eczema with mortality from other CVD.

Sensitivity Analysis

We reran models for CHD after stratifying participants by sex or age (40 to 59 vs. 60 to 79 years old), and obtained similar results to main results (p values for interactions by sex or age were 0.99 in three categories and 0.97 in two categories, or 0.34 in three categories and 0.24 in two categories, respectively) (**Table 3**).

Discussion

In this prospective cohort study of Japanese men and women, we investigated the associations of eczema frequency with mortality from several major CVDs, and found that individuals who often had eczema had an increased risk of mortality from CHD, but not from stroke, heart failure, cardiac arrhythmia, stroke, either aortic aneurysm or dissection, compared to those who seldom or sometimes did. The association did not differ between men and women or younger and older people. To the best of our knowledge, this is the first study to find an association between eczema and mortality from CHD in a Japanese general population.

Previous reports about the association of eczema-related diseases with CVD are mainly from Western countries. A previous meta-analysis by Miller et al. reported that psoriasis was associated with increased risk of CHD (odds ratio [OR] 1.5; 95% CI 1.2–1.9), but not stroke (OR 1.1; 95% CI 0.9–1.3), and in a subgroup analysis, such a significant association was seen only in hospital-based studies (OR 1.7; 95% CI

Table 2. Hazard Ratios and 95% Confidence Intervals of Cardiovascular Mortality According to the Frequency of Eczema

	Frequency of Eczema				
	Three categories			Two categories	
	Seldom	Sometimes	Often	Seldom or sometimes	Often
No. at risk	64 490	15 240	5 369	79 730	5 369
Person-years	1 064 049	242 291	83 478	1 306 340	83 478
Total cardiovascular disease, cases.	4431	845	352	5276	352
Age-, sex-adjusted HR (95% CI)	1	0.94 (0.87-1.01)	1.10 (0.99-1.23)	1	1.11 (1.00-1.24)
Multivariable* HR (95% CI)	1	0.95 (0.88-1.02)	1.05 (0.95-1.18)	1	1.06 (0.95-1.19)
Coronary heart disease, cases	925	158	91	1083	91
Age-, sex-adjusted HR (95% CI)	1	0.84 (0.71-0.99)	1.35 (1.09-1.68)	1	1.39 (1.12-1.72)
Multivariable* HR (95% CI)	1	0.82 (0.69-0.97)	1.26 (1.01-1.56)	1	1.30 (1.05-1.61)
Heart failure, cases	758	159	62	917	62
Age-, sex-adjusted HR (95% CI)	1	1.05 (0.89-1.25)	1.15 (0.89-1.49)	1	1.14 (0.88-1.48)
Multivariable* HR (95% CI)	1	1.07 (0.90-1.27)	1.12 (0.86-1.45)	1	1.11 (0.85-1.43)
Cardiac arrhythmia, cases	285	58	23	343	23
Age-, sex-adjusted HR (95% CI)	1	1.02 (0.77-1.35)	1.16 (0.76-1.77)	1	1.15 (0.76-1.76)
Multivariable* HR (95% CI)	1	1.01 (0.76-1.34)	1.13 (0.73-1.72)	1	1.12 (0.74-1.72)
Total stroke, cases	1937	374	143	2311	143
Age-, sex-adjusted HR (95% CI)	1	0.95 (0.85-1.06)	1.02 (0.86-1.21)	1	1.03 (0.87-1.22)
Multivariable* HR (95% CI)	1	0.97 (0.87-1.08)	0.98 (0.83-1.16)	1	0.98 (0.83-1.17)
Ischemic stroke, cases	1081	199	77	1280	77
Age-, sex-adjusted HR (95% CI)	1	0.93 (0.80-1.08)	1.00 (0.79-1.26)	1	1.01 (0.80-1.27)
Multivariable* HR (95% CI)	1	0.97 (0.84-1.13)	0.95 (0.76-1.20)	1	0.96 (0.76-1.21)
Hemorrhagic stroke, cases	792	159	62	951	62
Age-, sex-adjusted HR (95% CI)	1	0.95 (0.80-1.13)	1.06 (0.82-1.37)	1	1.07 (0.82-1.38)
Multivariable* HR (95% CI)	1	0.95 (0.80-1.13)	1.03 (0.80-1.34)	1	1.04 (0.81-1.35)
Aortic aneurysm or dissection, cases	164	25	12	189	12
Age-, sex-adjusted HR (95% CI)	1	0.74 (0.48-1.12)	1.01 (0.56-1.81)	1	1.06 (0.59-1.89)
Multivariable* HR (95% CI)	1	0.76 (0.50-1.17)	0.97 (0.54-1.75)	1	1.01 (0.56-1.82)

HR, hazard ratio; CI, confidence interval.
*Adjusted for age, sex, body mass index, history of hypertension, history of diabetes, alcohol intake, smoking status, perceived mental stress, daily walking time, participation in sports, sleep duration, and educational attainment.

1.2–2.5) but not in population-based studies (OR 1.3 95% CI 1.0–1.8)[16]. Standl *et al.* reported that in AOK (Allgemaine Ortskrankenkasse) PLUS cohort from a statutory German health insurer data, atopic dermatitis was marginally associated with an increased risk of angina pectoris (risk ratio [RR] 1.17; 95%CI 1.12–1.23) and peripheral arterial disease (RR 1.15; 95%CI 1.11–1.19), but not myocardial infarction (RR 1.05; 95%CI 0.99–1.12) or stroke (RR 1.02; 95%CI 0.98–1.19). They concluded that relevant associations of atopic dermatitis with CVD could not be confirmed[17]. There are also some reports from Asian countries. Psoriasis Vulgaris was associated with CHD in a Japanese retrospective hospital-based study (OR: 1.27; 95%CI 1.01–1.58)[19]. A Chinese case-control study showed that the prevalence of myocardial infarction was 1.72 (95%CI 1.29–2.30) and 2.01 (95%CI 1.45–2.79) times higher in patients with mild and severe psoriasis, respectively, than those in controls[20]. In a Taiwanese longitudinal study, patients with mild, moderate and severe atopic dermatitis had 1.20 (95%CI 0.99–1.45), 1.64 (95%CI 1.23–2.19), 1.71 (95%CI 1.15–2.56) times higher risk of ischemic stroke, respectively, than those without atopic dermatitis in a dose-response manner[21].

In our study, frequent eczema was associated with increased risk of mortality from CHD but not from the other CVD. Inflammation may be associated with increased risk of stroke, another major atherosclerotic disease, as well as CHD, but its contribution to stroke risk was smaller than CHD risk[22-24]. In addition, the number of deaths from heart failure, cardiac arrhythmia and aortic aneurysm or dissection were fewer than those from CHD. Thus, we might have

Table 3. Multivariable Hazard Ratios and 95% Confidence Intervals of Mortality from Coronary Heart Disease According to the Frequency of Eczema

	Frequency of Eczema				
	Three categories			Two categories	
	Seldom	Sometimes	Often	Seldom or sometimes	Often
Coronary heart disease					
Men					
Person-years/cases.	435 433/523	97 741/92	33 909/56	533 173/615	33 909/56
Multivariable* HR (95% CI)	1	0.81 (0.64-1.01)	1.28 (0.97-1.68)	1	1.32 (1.00-1.74)
Women					
Person-years/cases	628 617/402	144 550/66	49 569/35	773 167/468	49 569/35
Multivariable* HR (95% CI)	1	0.85 (0.65-1.11)	1.28 (0.90-1.81)	1	1.31 (0.93-1.85)
40-59 years old					
Person-years/cases	660 907/205	157 620/33	54 278/27	818 527/238	54 278/27
Multivariable* HR (95% CI)	1	0.68 (0.47-0.99)	1.58 (1.06-2.38)	1	1.69 (1.13-2.52)
60-79 years old					
Person-years/cases	403 142/720	84 671/125	29 199/64	487 813/845	29 199/64
Multivariable* HR (95% CI)	1	0.84 (0.69-1.02)	1.20 (0.93-1.56)	1	1.24 (0.96-1.60)

HR, hazard ratio; CI, confidence interval.
*Adjusted for age, sex, body mass index, history of hypertension, history of diabetes, alcohol intake, smoking status, perceived mental stress, daily walking time, participation in sport, sleep duration, and educational attainment.

been able to identify only the association with risk of mortality from CHD.

Some skin diseases causing eczema may be associated with systemic inflammation. For example, in psoriasis, Th-1, Th-17 and Th-22 induce inflammation through deregulating interferon production and tumor necrosis factor[25]. In atopic dermatitis, there is a perivascular infiltration of immune factors or cells such as immunoglobulin E, T lymphocytes, and mast cells. C-reactant protein, thymus and activation-regulated chemokine, and immunoglobulin E, known as inflammatory markers, are elevated in patients with atopic eczema[13, 26]. Those inflammatory processes might have accelerated atherosclerosis[27-33], leading to increased risk of mortality from CHD.

In the present study, individuals who reported having eczema "sometimes" had a decreased risk of mortality from CHD, compared to those "seldom" having eczema. One reason for this finding may be chance, but another may be a misclassification between those two groups. Considering that possibility, we also compared participants who reported having eczema "seldom or sometimes" to those having eczema "often," and found that individuals who "often" had eczema had an increased risk of mortality from CHD compared to those who "seldom or sometimes" had it.

This study's strengths include its prospective design and a long follow-up duration. In addition, we used several major CVDs as outcomes, and found that the high frequency of eczema was associated with risk of CHD, but not other CVD outcomes.

We should acknowledge several limitations. Firstly, eczema was self-reported and was defined without any precise medical examination by dermatologists. In addition, our questionnaire about eczema frequency has not been validated. Thus, we cannot rule out the possibility of misclassification for exposure. Secondly, we did not include information on using the adrenal cortex hormone as a potential confounding factor. The adrenal cortex hormone is often used as an eczema treatment, and the adrenal cortex hormone is also known as a risk factor for cardiovascular disease[34]. Thirdly, we used mortality data, but not incident data, for endpoints. Although the death certificates diagnoses' validity was confirmed[35, 36], outcome misclassification is still possible. Fourthly, we assessed the association between eczema and CVD risk without considering blood lipids because data on blood concentrations of lipids was available for the subsample, but not for all participants. However, a previous study of US adults reported weak associations of eczema with history of high total cholesterol, told by a doctor or other health professionals[37]. When we analyzed the subsample of the participants who had serum total cholesterol level data (n=26,222), we found no HR alterations. The HRs (95%CIs) were 1.52 (1.01–2.28) in age- and sex-adjusted model and

1.51 (1.01–2.26) in age-, sex- and total cholesterol-adjusted model. The corresponding multivariable HRs (CIs) were 1.38 (0.92–2.08) and 1.38 (0.91–2.08). Thus, total cholesterol was unlikely to confound the association in the present study.

In conclusion, self-reported eczema was associated with increased risk of mortality from CHD, but not other major CVD such as stroke in a Japanese general population.

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Conflict of Interest

The authors declare no conflict of interest.

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