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Atopic dermatitis is not independently associated with non-fatal myocardial infarction or stroke among US women:

Eczema and cardiovascular disease in women

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Abstract

We aimed to determine the association between atopic dermatitis (AD) and cardiovascular events in the Nurses' Health Study 2, a cohort of US women. We used logistic regression models to calculate age- and multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the associations between history of AD and non-fatal MI and non-fatal stroke. Of the 78,702 participants in our analysis, 7,916 (10%) had a history of AD. There were 392 and 391 cases of

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non-fatal MI and stroke, respectively. AD was not associated with MI in age- or multivariate-adjusted analyses. AD was significantly associated with stroke in the age-adjusted analysis (OR 1.38, 95% CI 1.03-1.85). This was no longer significant in multivariate models that adjusted for hypertension, hypercholesterolemia and diabetes (OR 1.31, 95% CI 0.98-1.76) and atopic comorbidities (OR 1.17, 95% CI 0.86-1.58). AD was not independently associated with non-fatal MI or stroke in this study.

Keywords

Atopic dermatitis; cardiovascular disease; comorbidity; myocardial infarction; stroke

Introduction

Atopic dermatitis (AD) is associated with cardiovascular risk factors in adults.(1-3) However, there are few, inconsistent epidemiologic studies on AD and cardiovascular events. (4-6) We aimed to determine the association of AD with myocardial infarction (MI) and stroke in a large cohort of US women.

Methods

The Nurses' Health Study 2 (NHS2) is a prospective cohort study of female registered nurses. It began in 1989 with 116,686 US participants. Detailed data about participants' lifestyle and medical histories are collected by questionnaires biennially.

In 2009, participants were asked whether they "ever had clinician-diagnosed..." "Eczema (atopic dermatitis)", "Hayfever (allergic rhinitis)" and "Food allergies," with affirmative answers defining cases of ever having each condition. Participants who answered yes to having a history of food allergy were also asked about allergy to specific foods. Biennially since 1989, participants have been asked about clinician-diagnosed asthma. Those who reported a diagnosis of asthma at or before the 2009 questionnaire were defined as cases of ever having asthma.

New diagnoses of MI and stroke are self-reported biennially and confirmed by medical record review according to established criteria.(7-9) MI and stroke (ischemic, hemorrhagic or undetermined subtype) that occurred up to and including completion of the 2009 questionnaire were included. As completion and return of the questionnaire is an inclusion criterion for our analysis, all cases of MI and stroke were non-fatal. Cerebrovascular events caused by infection, trauma, or malignancy or silent strokes were excluded. MI and stroke events that could not be confirmed by medical records but for which confirmatory information was obtained by interview or letter were designated "probable" and were also included in the analysis.

Race/ethnicity and height were reported at cohort baseline. Body weight, physical activity, alcohol intake, smoking status, family history (parents or siblings) of MI, menopausal status, hormone replacement use and history of physician-diagnosed hypertension, hypercholesterolemia and diabetes have been collected and updated during cohort follow-up.

In 2009, 90,488 participants returned the questionnaire. We excluded participants missing data on atopic disease (n=10,392) or MI or stroke or who reported MI or stroke that could not be confirmed (n=1,394), leaving 78,702 participants in the analysis.

We used logistic regression to calculate age- and multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between AD and MI, and AD and stroke. The primary multivariate model adjusted for age, race/ethnicity, BMI, physical activity, alcohol intake, cigarette smoking, family history of MI and history of postmenopausal hormone use. In a second multivariate model, we additionally adjusted for history of hypertension, hypercholesterolemia and diabetes. A third multivariate model adjusted for history of other atopic conditions (food allergy, hayfever or asthma) in addition to the covariates in the primary model. An indicator variable was created for the missing data of each covariate. Although time-varying characteristics were updated during cohort follow-up, we used information from 2009 for BMI, smoking, alcohol intake, physical activity, family history of MI and postmenopausal hormone use.

All statistical analysis was performed with SAS, version 9.2 (SAS Institute, Inc., Cary, NC). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Of the 78,702 participants, 7,916 (10%) had a history of AD. Characteristics of the population by history of AD are presented in Supplementary table 1. In total there were 392 cases of non-fatal MI and 391 cases of non-fatal stroke.

AD was not associated with MI in the age- or multivariate-adjusted models (Table 1). We observed a positive association between AD and stroke prevalence in the age-adjusted model and in the multivariate model that included demographic and lifestyle risk factors as well as family history of MI and postmenopausal hormone replacement use (OR 1.35, 95% CI 1.00-1.80) (Table 2). In the model that adjusted for history of hypertension, hypercholesterolemia and diabetes, the OR did not change substantially but the association between AD and stroke was no longer statistically significant. In the third model that adjusted for other atopic comorbidities, the association between AD and stroke was further attenuated.

Discussion

In this study, AD was not associated with non-fatal MI. In contrast, we observed suggestive evidence that AD may be associated with an increased risk of non-fatal stroke. When controlling for major potential mediators of cardiovascular disease, though, the association between AD and stroke was not statistically significant.

Authors have speculated that chronic inflammation associated with AD may increase the risk for cardiovascular disease.(4, 5) This hypothesis is analogous to the increased risk of MI and stroke in psoriasis, which has been firmly established as an independent cardiovascular risk factor.(9) Cardiac computed tomography has been used to compare coronary artery disease in patients with severe AD and psoriasis as well as controls without skin disease.(10)

While AD patients did not have as severe coronary artery disease as psoriasis patients, 48% of subjects with AD had coronary artery plaques compared with 21% of controls. Furthermore, AD has been associated with increased platelet activation.(11)

Rather than the inflammation associated with AD leading directly to increased cardiovascular risk, it is possible that AD is associated with cardiovascular risk factors, which in turn increase the risk of cardiovascular events. AD has been variably associated with a number of cardiovascular risk factors, including higher BMI, lower physical activity, increased alcohol consumption, cigarette smoking, hypertension, hypercholesterolemia and adult-onset diabetes.(2, 3, 5, 12)

Atopic comorbidities, particularly asthma, may mediate potential associations of AD with cardiovascular disease. AD is the first step in the “atopic march,” leading to subsequent food allergy, hayfever and asthma.(13) Asthma was associated with MI and stroke in our analysis, which is consistent with previous reports.(14) When we added atopic comorbidities to our multivariate model for the association of AD with stroke, the OR was attenuated (1.35 to 1.17) and was no longer statistically significant.

The few prior studies of the association of AD with MI or stroke have variably attempted to control for traditional risk factors and atopic conditions. Silverberg constructed multivariate models to control for potential confounders in three separate population-based surveys.(5) In the National Health and Nutrition Examination Survey 2005-06, AD was not significantly associated with MI or stroke independent of lifestyle factors; AD was associated with MI (but not stroke) independent of hayfever and asthma (OR 2.58, 95% CI 1.31-5.06). In the National Health Interview Survey (NHIS) 2010, AD was associated with MI and stroke independent of lifestyle factors, hayfever and asthma. These results provided suggestive evidence that AD may be associated with MI and stroke. However, none of these models adjusted for hypercholesterolemia and hypertension.

A retrospective cohort study from an administrative database in Taiwan found AD was associated with increased risk of stroke, but not MI, controlling for several cardiovascular risk factors (including hypertension and hypercholesterolemia) and asthma.(4) A matched cohort study from the Danish general population examined the risk of MI, ischemic stroke and cardiovascular death associated with AD.(6) They stratified AD according to treatments used. Those with topically treated AD had no statistically significant increased risk for cardiovascular events. Participants with AD treated with systemic agents had increased risks of stroke and cardiovascular death, but in a multivariate model, none of the associations were significant. Moreover, their multivariate models did not include atopic comorbidities.

The major strength of our study is the large well-established cohort, with high-quality data on participant characteristics and cardiovascular outcomes. Nonetheless, our study has several limitations. All cases of MI and stroke were by necessity non-fatal. Our reliance on self-report of AD is another limitation. However, our population of registered nurses are likely to be more health-literate than the general population and can provide more reliable medical histories. Additionally, a recent validation study found that asking adults, “Have you ever been told by a doctor or other health professional that you had eczema or any kind of

skin allergy?" (a question similar to the one used in NHS2), had low sensitivity (0.43) but very high specificity (0.97) for AD.(15) As such, we may have underestimated the true lifetime prevalence of AD. In previous studies, factors associated with adult recall of childhood AD include having eczema after age 15, taking sick leave of more than 1 week due to eczema, long duration of AD in childhood, hand dermatitis as an adult and comorbid atopic disease.(16, 17) It is reassuring that the proportion of participants with AD (10%) in this study is similar to recent US population estimates, (18, 19) but our cases may be skewed toward a more persistent and severe AD phenotype.

While NHS2 is a longitudinal cohort study, ours is a cross-sectional analysis. At the moment, NHS2 does not have data on age of AD diagnosis, so we are not able to conduct a longitudinal analysis. Finally, NHS2 collects data on female nurses only, and our study population is predominantly of white race, limiting the generalizability of our results.

In summary, AD was not associated with non-fatal MI in a large cohort of US women. AD may be associated with increased risk of non-fatal stroke, which may be partly mediated by comorbid hypertension, hypercholesterolemia, diabetes and asthma and other atopic comorbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age- and multivariate-adjusted models of the association between atopic conditions and non-fatal myocardial infarction

	MI cases	Non-cases	Age-adjusted OR (95% CI)	MV-adjusted OR (95% CI) 1 ^a	MV-adjusted OR (95% CI) 2 ^b	MV-adjusted OR (95% CI) 3
No atopic dermatitis	354	70,432	1.00	1.00	1.00	1.00
Atopic dermatitis	38	7,878	0.97 (0.69-1.36)	0.94 (0.67-1.32)	0.91 (0.65-1.28)	0.91 (0.65-1.29) ^c
No food allergy	351	71,803	1.00	--	--	1.00
Food allergy	41	6,507	1.24 (0.90-1.72)	--	--	1.13 (0.80-1.59) ^c
No peanut allergy	386	77,724	1.00	--	--	1.00
Peanut allergy	6	586	2.08 (0.92-4.68)	--	--	1.99 (0.79-4.99) ^d
No tree nut allergy	386	77,527	1.00	--	--	1.00
Tree nut allergy	6	783	1.60 (0.71-3.60)	--	--	1.03 (0.38-2.79) ^d
No shellfish allergy	380	76,758	1.00	--	--	1.00
Shellfish allergy	12	1552	1.48 (0.83-2.63)	--	--	1.29 (0.71-2.36) ^d
No milk allergy	383	76,991	1.00	--	--	1.00
Milk allergy	9	1,319	1.33 (0.69-2.59)	--	--	1.35 (0.65-2.81) ^d
No egg allergy	389	77,455	1.00	--	--	1.00
Egg allergy	3	855	0.68 (0.22-2.13)	--	--	0.46 (0.14-1.57) ^d
No other food allergy	366	74,034	1.00	--	--	1.00
Other food allergy	26	4,276	1.18 (0.79-1.76)	--	--	0.96 (0.61-1.51) ^d
No hayfever	289	57,735	1.00	--	--	1.00
Hayfever	103	20,575	1.00 (0.80-1.26)	--	--	0.87 (0.68-1.11) ^c
No asthma	290	64,049	1.00	--	--	1.00
Asthma	102	14,261	1.55 (1.24-1.95)	--	--	1.37 (1.07-1.75)^c

MI: myocardial infarction; MV: Multivariate

^aAdjusted for age (per 5 years), race/ethnicity (White, Hispanic, Asian, or Black), BMI (<25, 25-29.9, 30-34.9, or ≥35 kg/m²), physical activity (by quintile in metabolic equivalent hours [MET]/week), alcohol intake (0, 1-4, 5-9, 10-14, 15-29, 30+ g/day), smoking status (never, past or current in cigarettes/day [15, 15-24, 25+]), family history of MI, hormone replacement use

^bAdjusted for the same factors as in (a) in addition to history of hypertension, hypercholesterolemia and diabetes.

^cAdjusted for the same factors as in (a), and for each atopic condition (atopic dermatitis, food allergy, hayfever and asthma), the other 3 atopic conditions were adjusted for.

^dAdjusted for the same factors as in (c) with the exception of overall food allergy. Each type of food allergy was adjusted for separately.

Table 2

Age- and multivariate-adjusted models of the association between atopic conditions and non-fatal stroke

	Stroke Cases	Non-cases	Age-adjusted OR (95% CI)	MV-adjusted OR (95% CI) 1 ^a	MV-adjusted OR (95% CI) 2 ^b	MV-adjusted OR (95% CI) 3
No atopic dermatitis	339	70,447	1.00	1.00	1.00	1.00
Atopic dermatitis	52	7,864	1.38 (1.03-1.85)	1.35 (1.00-1.80)	1.31 (0.98-1.76)	1.17 (0.86-1.58) ^c
No food allergy	337	71,817	1.00	--	--	1.00
Food allergy	54	6,494	1.74 (1.30-2.32)	--	--	1.39 (1.02-1.89) ^c
No peanut allergy	387	77,723	1.00	--	--	1.00
Peanut allergy	4	588	1.37 (0.51-3.68)	--	--	0.79 (0.27-2.31) ^d
No tree nut allergy	385	77,528	1.00	--	--	1.00
Tree nut allergy	6	783	1.58 (0.70-3.54)	--	--	0.98 (0.40-2.39) ^d
No shellfish allergy	372	76,766	1.00	--	--	1.00
Shellfish allergy	19	1545	2.46 (1.55-3.91)	--	--	1.88 (1.15-3.07) ^d
No milk allergy	379	76,995	1.00	--	--	1.00
Milk allergy	12	1,316	1.83 (1.02-3.25)	--	--	1.39 (0.73-2.65) ^d
No egg allergy	386	77,458	1.00	--	--	1.00
Egg allergy	5	853	1.16 (0.48-2.81)	--	--	0.61 (0.23-1.59) ^d
No other food allergy	355	74,045	1.00	--	--	1.00
Other food allergy	36	4,266	1.72 (1.22-2.43)	--	--	1.26 (0.85-1.85) ^d
No hayfever	289	57,752	1.00	--	--	1.00
Hayfever	124	20,554	1.31 (1.06-1.62)	--	--	0.99 (0.78-1.25) ^c
No asthma	268	64,071	1.00	--	--	1.00
Asthma	123	14,240	2.05 (1.65-2.53)	--	--	1.79 (1.41-2.26) ^c

MV: Multivariate

^a Adjusted for age (per 5 years), race/ethnicity (White, Hispanic, Asian, or Black), BMI (<25, 25-29.9, 30-34.9, or ≥ 35 kg/m²), physical activity (by quintile in metabolic equivalent hours [MET]/week), alcohol intake (0, 1-4, 5-9, 10-14, 15-29, 30+ g/day), smoking status (never, past or current in cigarettes/day [15, 15-24, 25+]), family history of MI, hormone replacement use

^b Adjusted for the same factors as in (a) in addition to history of hypertension, hypercholesterolemia and diabetes.

^c Adjusted for the same factors as in (a), and for each atopic condition (atopic dermatitis, food allergy, hayfever and asthma), the other 3 atopic conditions were adjusted for.

^d Adjusted for the same factors as in (c) with the exception of overall food allergy. Each type of food allergy was adjusted for separately.