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Title: Association between adult atopic dermatitis, cardiovascular disease and increased heart attacks in 3 population-based studies.

Running Title: Atopic dermatitis and cardiovascular disease.

Jonathan I. Silverberg, MD, PhD, MPH^{1,2}

1. Departments of Dermatology, Preventive Medicine and Medical Social Sciences,
Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

2. Northwestern Medicine Multidisciplinary Eczema Center, Chicago, IL 60611, USA

Abbreviations used: CI = confidence interval, OR = odds ratio, aOR = adjusted odds ratio, AD = atopic dermatitis

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Corresponding author:

Jonathan I. Silverberg, MD, PhD, MPH
Northwestern University
Department of Dermatology
Suite 1600
676 N. St. Clair St.
Chicago, IL 60611
JonathanISilverberg@Gmail.com
Tel: 312-503-4985

JI Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: JI Silverberg

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Analysis and interpretation of data: JI Silverberg

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Abstract

Background: Adults with eczema are more likely to smoke cigarettes, consume alcohol and have sedentary lifestyle. We sought to determine whether adult eczema is associated with increased cardiovascular and cerebrovascular disease.

Methods: Data from the 2005-2006 National Health and Nutrition Examination Survey (NHANES) (n=4,970) and 2010 (n=27,157) and 2012 (n=34,525) National Health Interview Survey (NHIS). History of coronary artery disease (CAD), angina, heart attack, stroke and peripheral vascular disease (PVD) were determined.

Results: In NHANES, flexural eczema in the past year was associated with significantly higher odds of CAD ($P \leq 0.04$), heart attack ($P \leq 0.01$) and congestive heart failure ($P \leq 0.02$), but not stroke ($P \geq 0.37$), in survey weighted multivariate logistic regression models that controlled for socio-demographics, comorbid asthma and hay fever. Similarly, in NHIS 2010 and 2012, 1-year history of eczema was associated with significantly higher odds of CAD ($P \leq 0.02$), angina ($P \leq 0.02$), heart attack ($P \leq 0.047$), other heart disease ($P < 0.0001$), stroke ($P \leq 0.02$) and PVD (< 0.0001) in multivariate models.

Conclusions: Adults with AD may have increased cardiovascular disease, heart attack and stroke.

Introduction

Atopic dermatitis (AD) is a chronic pruritic disorder of skin, affecting 7-10% of US adults (1Silverberg, 2014 #308, 2). AD is associated with intense itch that can interfere with all aspects of patients' quality of life (3, 4). In particular, patients with AD very commonly report worsening of their itch or disease flares from heat and sweating (5, 6). This might cause AD

patients to limit their physical activity in order to avoid worsening their disease. A recent study found that adult eczema was associated with lower frequency of vigorous physical activity (7). In general, a lower level of physical activity is a risk factor for the development of cardiovascular disease (8).

Aside from sedentary lifestyle, patients with eczema have other cardiovascular risk factors, including obesity (7, 9-13), cigarette smoking (7) and increased alcohol consumption (7). Moreover, patients with AD have a multitude of comorbid health disorders, including asthma (12), sleep disturbances (1, 14), depression and other mental health problems (15, 16) and high blood pressure (7, 9). All of these may increase cardiovascular risk in patients with eczema. However, few studies have examined the rates of cardiovascular or cerebrovascular disease in adult eczema. I hypothesized that adults with eczema have higher rates of heart attack and stroke. The present study sought to determine whether adult eczema is associated with cardiovascular disease and the clinical and/or behavioral factors that may underlie such an association.

Methods

National Health and Nutrition Examination Survey (NHANES)

This study was approved by the institutional review board at Northwestern University and the protocol is consistent with the principles of the Declaration of Helsinki. We studied participants from the 2005-2006 NHANES that was designed to assess the health and nutrition of persons in the US. NHANES was sponsored and conducted by National Center for Health

Statistics (NCHS) of Centers for Disease Control and Prevention. Households were selected through a stratified, randomized, multi-stage, probability-cluster design; introductory letters were sent and interviewers visited a few weeks later. Written informed consent was obtained from all participants. Health interviews were conducted in the home in either English or Spanish. The survey results were weighted to represent the population of non-institutionalized adults nationally and in each state using data from the U.S. Bureau of the Census, and to account for the complex survey design, survey non-response and post-stratification. The survey protocol was approved by the Research Ethics Review Board of NCHS.

National Health Interview Survey (NHIS)

We also used the 2010 and 2012 NHIS, which are collected by the NSCH and are the principal source of information on the health of the civilian non-institutionalized population of the United States. The survey was administered in-person to selected households by approximately 400 trained interviewers of the Bureau of the Census using computer-assisted personal interviewing in English and Spanish. Subsequently, one adult per household was randomly selected for the sample adult questionnaire. Using data from the US Bureau of the Census, weights were adjusted for age, sex, race, ethnicity, household size, and educational attainment of the most educated household member to provide a data set that was more representative of each state's population of non-institutionalized adults. The questions used to assess for history of eczema and cardiovascular risk factors are shown in Supplemental Table 1.

Data processing and statistical methods

All data processing and statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). Analyses of survey responses were performed using SURVEY procedures. Bivariate and multivariate associations were tested by logistic regression models. The dependent variables were history of coronary artery disease (CAD), angina, heart attack, congestive heart failure, other heart disease, stroke, peripheral vascular disease and the number of these outcomes. The independent variable was history of eczema. Multivariate regression models included age, sex, race/ethnicity, level of education and household income (model-1), 1-year history of asthma and hay fever (model-2), body mass index (BMI), ever history of smoking, history of alcohol consumption in the past year and frequency of vigorous physical activity (model-3).

Complete data analysis was performed for all variables included in the models, i.e. subjects with missing data were excluded. A 2-sided P value of less than 0.05 was taken to indicate statistical significance for all estimates. However, the multiple dependent tests performed in this study increase the risk of falsely rejecting the null hypothesis. Therefore, P-values near 0.05 should be interpreted with caution.

Results

Population characteristics

Data was collected on a total of 4,970 adults (≥ 20 years) in NHANES 2005-2006, 27,157 adults (≥ 18 years) in NHIS 2010 and 34,525 in NHIS 2012. The 1-year prevalence of flexural

eczema was 3.1% (2.5 – 3.6%) in NHANES 2005-2006. The 1-year prevalence of eczema was 10.2% (9.7 – 10.6%) in NHIS 2010. The 1-year prevalence of healthcare diagnosed eczema was 7.2% (6.9 – 7.6%) in NHIS 2012. The associations of adult eczema with socio-demographics and allergic disease in these cohorts has previously been described (Silverberg, 2014 #308, 2, 17).

Association between eczema and cardiovascular disease

In NHANES 2005-2006, flexural eczema in the past year was associated with significantly higher odds of CAD in bivariate models (survey weighted logistic regression; OR [95% CI]: 2.57 [1.45 – 4.53]), heart attack (2.59 [1.35 – 4.96]) and congestive heart failure (2.37 [1.27 – 4.41]), but only a marginal association with angina (1.87 [0.98 – 3.57]) (Table 1). These associations remained significant in multivariate models that controlled for socio-demographics (model-1), comorbid asthma and hay fever (model-2). In models that controlled for cardiovascular risk factors, only the association between eczema and CAD remained significant (model-3).

Similarly, in NHIS 2010 and 2012, eczema was associated with significantly higher odds of CAD ($P \leq 0.006$), angina ($P \leq 0.006$), heart attack ($P \leq 0.03$) and other heart disease ($P < 0.0001$) in bivariate models (Tables 2 and 3). The associations remained significant in multivariate models controlling for socio-demographics (model-1) and comorbid asthma and hay fever (model-2). The associations also remained significant in all models controlling for cardiovascular risk factors (model-3), except for heart attacks in NHIS 2012 ($P = 0.10$).

To identify the specific confounding variable(s), history of smoking, alcohol consumption, level of physical activity and BMI were all tested individually together with history of eczema. The association with heart attacks remained significant in models that included each variable individually (data not shown).

Associations between eczema and stroke

In NHANES 2005-2006, eczema was not associated with stroke in bivariate models or either multivariate models (Table 1). In contrast, eczema was associated with higher odds of stroke in NHIS 2010 (1.61 [1.27 – 2.05], $P=0.0001$) and 2012 (1.63 [1.27 – 2.09], $P=0.0001$) in bivariate models. These associations remained significant in multivariate models for NHIS 2010 ($P\leq 0.02$) and NHIS 2012 ($P\leq 0.004$).

Associations between eczema and PVD

History of PVD was only assessed in NHIS 2012. Eczema was associated with higher odds of PVD in bivariate (1.92 [1.67 – 2.21], $P<0.0001$) and in multivariate models 1, 2 and 3 ($P<0.0001$) (Table 3).

Association between eczema and multiple vascular outcomes

Eczema was associated with having multiple cardiovascular (CAD, angina and/or MI), cerebrovascular (stroke), peripheral vascular comorbidities and/or other heart conditions. In NHANES 2005-2006, eczema was associated with having 2-3 such comorbidities in bivariate models (2.03 [1.10 – 3.75], $P=0.02$) and in multivariate models controlling for asthma and hay fever ($P\leq 0.02$) but not in models controlling for cardiovascular risk factors ($P=0.44$). To identify the specific confounding variable(s), individual cardiovascular factors were all tested individually together with history of eczema. The association with heart attacks remained significant in models that included history of smoking and physical activity, but not alcohol consumption or BMI.

In NHIS 2010, eczema was associated with having 1, 2 or 3 such comorbidities in bivariate and most multivariate models. In NHIS 2012, eczema was associated with having 1, 2, 3 or 4 such comorbidities in bivariate (2.44 [1.79 – 3.33]) and all 3 multivariate models ($P<0.0001$).

Discussion

In the present study, eczema was found to be associated with increased odds of CAD, angina, heart attack, congestive heart failure and other heart disease in one or more studies. In addition, eczema was associated with increased odds of stroke in 2 of 3 studies and PVD in 1 study. The associations remained significant in multivariate models that controlled for socio-demographics, comorbid asthma and hay fever and cardiovascular risk factors, except for CHF in NHANES. The results suggest that adults with eczema are at increased risk of cardiovascular and

cerebrovascular disease, even after controlling for cardiovascular risk factors, suggesting that there are additional factors at play.

Previous studies demonstrated associations of eczema with obesity (7, 9-12). The association between eczema and obesity was recently confirmed in a meta-analysis (13). We recently analyzed data from NHIS 2010 and 2012 and found higher rates of cigarette smoking and alcohol consumption and decreased vigorous physical activity (7). In turn, adults with eczema had higher rates of hypertension, prediabetes, adult onset diabetes and hyperlipidemia (7). The present study builds upon those findings by demonstrating that the increased cardiovascular risk factors actually translate into increased cardio-/cerebrovascular disease in NHIS 2010 and 2012. Moreover, they demonstrate increased cardio-/cerebrovascular disease in NHANES using a more specific definition of AD analogous to the Hanifin and Rajka major criteria (18). A pediatric dermatology practice-based case-control study of 132 children ages 4-17 years with moderate-severe AD and 143 healthy controls found that AD was associated with increased central obesity and elevated systolic blood pressure (9). Finally, a study of 20,323 Taiwanese AD patients and 20,323 matched controls found that AD was associated with an increased incidence of ischemic stroke, with even higher risk in severe vs. mild AD (19). The present study builds upon those studies, demonstrating increased cardiovascular disease, heart attack and stroke across multiple studies, as well as PVD. Previous studies also showed increased risk of cardiovascular disease in adults with asthma (20), possibly related to decreased physical activity (21) and asthma medications (22). To address potential confounding from asthma, we included history of asthma and hay fever in multivariate models. All the significant associations

from bivariate models remained significant in these multivariate models, suggesting that there is increased cardiovascular risk secondary to eczema *per se*.

The effect sizes for some of the outcomes were not very large, suggesting that the increased risk occurs in a subset of eczema patients. Thus, increased screening for cardiovascular disease across-the-board does not appear to be warranted in adults with eczema. However, it seems prudent that physicians inquire about history of smoking, alcohol and level of physical in all adults with eczema.

The mechanism(s) of association between eczema and cardiovascular disease are not entirely clear. Lifestyle and behavioral factors, such as increased smoking and alcohol and decreased physical activity, are likely to play a major role. On the other hand, associations of eczema with CAD, stroke and PVD remained significant in most models that controlled for these factors. This raises an intriguing possibility that chronic inflammation in eczema may contribute to cardiovascular disease, similar to what has been demonstrated for psoriasis (23, 24). Future studies are warranted to determine the mechanism(s) of increased cardiovascular disease in adults with eczema.

The prevalence of eczema varied considerably across the three studies (3.x for active flexural eczema in NHANES, 7.2% for 1-year history of healthcare diagnosed eczema and 10.2% for 1-year history of eczema). There are a number of differences between the questions used to measure eczema prevalence in these studies. The question used in NHIS 2012 assessed for healthcare diagnosis of eczema. Whereas, the question used in NHIS 2010 did not specify

healthcare diagnosis of eczema and assessed for “eczema, dermatitis or red inflamed rash”. This question may be less specific but more sensitive than the one used in NHIS 2010. However, 24.9% of adults with eczema from NHIS 2010 reported not seeing a doctor for their eczema. Thus, the US prevalence of adults with eczema who were seen by a physician for their eczema is similarly ~7% in both studies. In contrast, the composite definition of AD used for NHANES was analogous to having 3 of the Hanifin and Rajka major criteria, i.e. pruritus, flexural involvement and chronic dermatitis (18). While this definition is likely more specific for classic flexural eczema, it likely underestimates the prevalence of AD by excluding many AD patients that have non-flexural distributions (25, 26). Regardless, the reproducibility of associations across the 3 different studies suggests that the association of eczema and cardio-/cerebrovascular disease is not merely related to the particular wording of a question.

This study has several strengths, including the use of 3 separate studies, each being US population-based, with complex survey weighting and a very large diverse sample. The associations between AD and cardiovascular outcomes were significant across multiple studies suggesting that the findings are reproducible. However, this study has potential limitations. History of eczema was self-reported and not assessed clinically or verified with any diagnostic testing. To address this, we used a composite definition in NHANES that combined self-report of flexural dermatitis that was active in the past year to minimize recall bias. In addition, NHIS 2012 assessed for self-report of a healthcare diagnosis of eczema in the past year. We previously performed a multicenter validation study that demonstrated good sensitivity, specificity and positive predictive value for AD (27). Thus, we believe that the case definitions of AD used in these studies are valid. In the present cross-sectional studies, no conclusions can be made

regarding the temporality of association. Future longitudinal studies are needed to determine the temporality of these associations.

In conclusion, adults with eczema have significantly higher odds of coronary artery disease, angina, heart attack, other heart disease, stroke and/or PVD. Lifestyle factors appear to play a role in this association. Future studies are needed to confirm the direction of the associations and determine the best interventions to prevent cardiovascular disease in adult AD.

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Table 1. Association between atopic dermatitis, cardiovascular and cerebrovascular disease in NHANES 2005-2006.												
Variable	No AD		AD									
	Freq	Percent (95% CI)	Freq	Percent (95% CI)	Crude OR (95% CI)	P	Model-1		Model-2		Model-3	
							Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Coronary artery disease												
No	4607	96.8 (96.2 – 97.3)	146	92.1 (88.2 – 96.1)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	182	3.2 (2.7 – 3.8)	18	7.9 (3.9 – 11.8)	2.57 (1.45 – 4.53)	0.001	2.11 (1.14 – 3.91)	0.02	2.46 (1.37 – 4.43)	0.003	1.96 (1.02 – 3.77)	0.04
Angina												
No	4629	97.5 (97.0 – 97.9)	153	95.4 (92.7 – 98.1)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	167	2.5 (2.1 – 3.0)	13	4.6 (1.9 – 7.3)	1.87 (0.98 – 3.57)	0.06	1.63 (0.84 – 3.15)	0.15	1.91 (0.98 – 3.69)	0.06	1.35 (0.55 – 3.28)	0.51
Heart attack												
No	4655	97.6 (97.1 – 98.1)	152	94.0 (90.5 – 97.5)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	142	2.4 (1.9 – 2.9)	13	6.0 (2.5 – 9.5)	2.59 (1.35 – 4.96)	0.004	2.33 (1.22 – 4.46)	0.01	2.58 (1.31 – 5.06)	0.006	1.98 (0.96 – 4.12)	0.07
Congestive heart failure												
No	4605	96.6 (96.0 – 97.2)	151	92.3 (88.1 – 96.6)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	199	3.4 (2.8 – 4.0)	16	7.7 (3.4 – 11.9)	2.37 (1.27 – 4.41)	0.007	2.01 (1.03 – 3.94)	0.04	2.25 (1.17 – 4.32)	0.02	1.01 (0.40 – 2.57)	0.99
Stroke												
No	4615	97.1 (96.6 – 97.6)	162	97.8 (95.9 – 99.7)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	187	2.9 (2.4 – 3.4)	6	2.2 (0.3 – 4.1)	0.76 (0.31 – 1.86)	0.54	0.71 (0.29 – 1.74)	0.46	0.74 (0.30 – 1.82)	0.51	0.61 (0.21 – 1.80)	0.37

Survey weighted logistic regression models were constructed with self-reported coronary artery disease, angina, heart attack, congestive heart failure and stroke as the dependent variables. The independent variable was 1-year history of eczema. Adjusted OR and 95% CI were estimated for eczema in two different multivariate models, including: 1. age, highest level of education in the household, race/ethnicity, sex and 2. 1-year history of asthma and hay fever and 3. body mass index, history of ever smoking cigarettes, consumption of alcohol in the past year and vigorous activity in the past 30 days as covariates.

Refusal to answer a particular question or response of “don’t know” occurred for the questions pertaining to eczema in 5 (0.05%), coronary artery disease in 26 (0.5%), angina in 17 (0.4%), heart attack in 8 (0.2%), congestive heart failure in 17 (0.4%), stroke in 9 (0.2%), age in 0 (0.0%), sex in 0 (0.0%), race/ethnicity in 0 (0.0%), asthma in 13 (0.1%), hay fever in 22 (0.2%), body mass index in 299 (6.4%), history of ever smoking cigarettes in 6 (0.1%), consumption of alcohol in the past year in 5 (0.1%), and vigorous physical activity in the past 30 days in 2 (0.03%), respectively.

Table 2. Association between atopic dermatitis, cardiovascular and cerebrovascular disease in NHIS 2010.												
Variable	No AD		AD									
	Freq	Percent (95% CI)	Freq	Percent (95% CI)	Crude OR (95% CI)	P	Model-1		Model-2		Model-3	
							Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Coronary artery disease												
No	21167	95.3 (95.0 – 95.7)	2219	93.2 (92.1 – 94.4)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	1067	4.7 (4.3 – 5.0)	181	93.4 (92.1 – 94.4)	1.48 (1.22 – 1.80)	<0.0001	1.38 (1.13 – 1.69)	0.002	1.41 (1.16 – 1.71)	0.0007	1.38 (1.12 – 1.70)	0.003
Angina												
No	21766	97.9 (97.7 – 98.1)	2297	96.1 (95.3 – 97.0)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	475	2.1 (1.9 – 2.3)	107	3.9 (3.0 – 4.7)	1.87 (1.44 – 2.42)	<0.0001	1.79 (1.37 – 2.35)	<0.0001	1.58 (1.21 – 2.05)	0.0008	1.73 (1.30 – 2.31)	0.0002
Heart attack												
No	21534	96.9 (96.6 – 97.1)	2267	94.7 (93.7 – 95.7)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	728	3.1 (2.9 – 3.4)	139	5.3 (4.3 – 6.3)	1.73 (1.39 – 2.16)	<0.0001	1.72 (1.36 – 2.17)	<0.0001	1.65 (1.32 – 2.06)	<0.0001	1.48 (1.15 – 1.90)	0.002
Other heart disease												
No	20661	92.9 (92.5 – 93.3)	2062	86.5 (84.9 – 88.1)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	1591	7.1 (6.7 – 7.5)	343	13.5 (11.9 – 15.1)	2.04 (1.76 – 2.37)	<0.0001	1.92 (1.64 – 2.25)	<0.0001	1.92 (1.65 – 2.23)	<0.0001	1.87 (1.59 – 2.20)	<0.0001
Stroke												
No	21584	97.3 (97.1 – 97.5)	2291	95.7 (94.8 – 96.6)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	678	2.7 (2.5 – 2.9)	112	4.3 (3.4 – 5.2)	1.61 (1.27 – 2.05)	0.0001	1.61 (1.25 – 2.07)	0.0002	1.53 (1.19 – 1.96)	0.001	1.39 (1.05 – 1.83)	0.02

Survey weighted logistic regression models were constructed with self-reported coronary artery disease, angina, heart attack, other heart disease and stroke as the dependent variables. The independent variable was 1-year history of eczema. Adjusted OR and 95% CI were estimated for eczema in two different multivariate models, including: 1. age, highest level of education in the household, race/ethnicity, sex and 2. 1-year history of asthma and hay fever and 3. body mass index, history of ever smoking cigarettes, consumption of alcohol in the past year and frequency of vigorous activity in the past week as covariates.

Refusal to answer a particular question or response of “don’t know” occurred for the questions pertaining to eczema in 16 (0.06%), coronary artery disease in 53 (0.2%), angina in 43 (0.2%), heart attack in 20 (0.08%), other heart disease in 31 (0.1%), stroke in 24 (0.1%), age in 0 (0.0%), sex in 0 (0.0%), race/ethnicity in 0 (0.0%), asthma in 17 (0.06%), hay fever in 20 (0.08%), body mass index in 837 (3.4%), history of ever smoking cigarettes in 145 (0.6%), consumption of alcohol in the past year in 229 (0.9%), and vigorous physical activity in the past week in 308 (1.1%), respectively.

Table 3. Association between atopic dermatitis, cardiovascular and cerebrovascular disease in NHIS 2012.												
Variable	No AD		AD									
	Freq	Percent (95% CI)	Freq	Percent (95% CI)	Crude OR (95% CI)	P	Model-1		Model-2		Model-3	
							Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Coronary artery disease												
No	30400	95.4 (95.2 – 95.7)	2319	93.9 (92.7 – 95.1)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	1660	4.6 (4.3 – 4.8)	161	6.1 (4.9 – 7.3)	1.36 (1.09 – 1.69)	0.006	1.50 (1.18 – 1.90)	0.007	1.31 (1.06 – 1.64)	0.01	1.32 (1.04 – 1.66)	0.02
Angina												
No	31388	98.1 (98.0 – 98.3)	2398	96.8 (95.7 – 98.0)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	671	1.9 (1.7 – 2.0)	86	3.2 (2.0 – 4.3)	1.73 (1.18 – 2.54)	0.006	1.81 (1.21 – 2.70)	0.004	1.58 (1.09 – 2.30)	0.02	1.77 (1.20 – 2.61)	0.004
Heart attack												
No	30907	96.8 (96.6 – 97.0)	2362	95.8 (94.8 – 96.7)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	1180	3.2 (3.0 – 3.4)	123	4.2 (3.3 – 5.2)	1.33 (1.03 – 1.70)	0.03	1.44 (1.11 – 1.87)	0.007	1.29 (1.01 – 1.66)	0.047	1.26 (0.96 – 1.64)	0.10
Other heart disease												
No	32083	93.4 (93.1 – 93.7)	2173	88.2 (86.7 – 89.8)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	2296	6.6 (6.3 – 6.9)	311	11.8 (10.2 – 13.3)	1.89 (1.61 – 2.21)	<0.0001	1.92 (1.62 – 2.27)	<0.0001	1.74 (1.48 – 2.05)	<0.0001	1.85 (1.56 – 2.19)	<0.0001
Stroke												
No	31081	97.4 (97.2 – 97.6)	2368	95.8 (94.9 – 96.8)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	1003	2.6 (2.4 – 2.8)	118	4.2 (3.2 – 5.1)	1.63 (1.27 – 2.09)	0.0001	1.75 (1.35 – 2.28)	<0.0001	1.52 (1.19 – 1.95)	0.0009	1.73 (1.33 – 2.25)	<0.0001
Poor circulation in legs												
No	28688	90.9 (90.6 – 91.3)	2033	84.0 (82.2 – 85.8)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
Yes	3379	9.1 (8.7 – 9.4)	452	16.0 (14.2 – 17.8)	1.92 (1.67 – 2.21)	<0.0001	2.07 (1.79 – 2.40)	<0.0001	1.74 (1.50 – 2.01)	<0.0001	1.90 (1.62 – 2.22)	<0.0001

Survey weighted logistic regression models were constructed with self-reported coronary artery disease, angina, heart attack, other heart disease and stroke as the dependent variables. The independent variable was 1-year history of eczema. Adjusted OR and 95% CI were estimated for eczema in two different multivariate models, including: 1. age, highest level of education in the household, race/ethnicity, sex and 2. 1-year history of asthma and hay fever and 3. body mass index, history of ever smoking cigarettes, consumption of alcohol in the past year and frequency of vigorous activity in the past week as covariates.

Refusal to answer a particular question or response of “don’t know” occurred for the questions pertaining to eczema in 39 (0.08%), coronary artery disease in 52 (0.1%), angina in 50 (0.1%), heart attack in 21 (0.06%), other heart disease in 26 (0.08%), stroke in 24 (0.07%), peripheral vascular disease in 43 (0.1%), age in 0 (0.0%), sex in 0 (0.0%), race/ethnicity in 0 (0.0%), asthma in 20 (0.05%), hay fever in 51 (0.1%), body mass index in 1699 (4.2%), history of ever smoking cigarettes in 262 (0.8%), consumption of alcohol in the past year in 345 (1.0%), and vigorous physical activity in the past 30 days in 496 (1.4%), respectively.

Variable	No AD		AD									
	Freq	Percent (95% CI)	Freq	Percent (95% CI)	Crude OR (95% CI)	P	Model-1		Model-2		Model-3	
							Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
NHANES 2005-2006												
0	9440	93.8 (93.2 – 94.4)	347	90.5 (87.0 – 94.0)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
1	376	4.5 (4.0 – 5.1)	19	6.2 (3.1 – 9.3)	1.42 (0.83 – 2.44)	0.21	1.53 (0.85 – 2.75)	0.16	1.42 (0.77 – 2.61)	0.26	1.22 (0.62 – 2.38)	0.57
2-3	152	1.7 (1.4 – 2.0)	14	3.3 (1.4 – 5.1)	2.03 (1.10 – 3.75)	0.02	2.19 (1.14 – 4.23)	0.02	2.08 (1.07 – 4.05)	0.03	1.39 (0.62 – 3.18)	0.44
NHIS 2010												
0	19319	87.2 (86.7 – 87.7)	1873	79.3 (77.5 – 81.2)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
1	2225	9.6 (9.1 – 10.0)	364	14.3 (12.6 – 15.9)	1.64 (1.42 – 1.89)	<0.0001	1.60 (1.37 – 1.87)	<0.0001	1.56 (1.35 – 1.80)	<0.0001	1.81 (1.37 – 2.38)	<0.0001
2	629	2.8 (2.6 – 3.1)	149	5.7 (4.6 – 6.7)	2.20 (1.77 – 2.74)	<0.0001	2.20 (1.74 – 2.77)	<0.0001	2.06 (1.65 – 2.57)	<0.0001	1.92 (1.15 – 3.21)	0.01
3	100	0.4 (0.3 – 0.5)	22	0.7 (0.4 – 1.1)	2.14 (1.25 – 3.68)	0.006	2.25 (1.29 – 3.91)	0.004	1.83 (1.03 – 3.26)	0.04	1.35 (0.30 – 6.14)	0.70
NHIS 2012												
0	25730	82.3 (81.8 – 82.8)	1722	71.4 (69.1 – 73.7)	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–	1.00 [ref]	–
1	4380	12.4 (11.9 – 12.8)	516	20.1 (18.0 – 22.2)	1.88 (1.63 – 2.16)	<0.0001	2.02 (1.74 – 2.34)	<0.0001	1.74 (1.51 – 2.00)	<0.0001	1.91 (1.52 – 2.42)	<0.0001
2	1440	3.9 (3.6 – 4.2)	168	5.5 (4.5 – 6.5)	1.62 (1.31 – 2.00)	<0.0001	1.90 (1.52 – 2.38)	<0.0001	1.48 (1.19 – 1.83)	0.0003	2.01 (1.32 – 3.06)	0.001
3-4	550	1.42 (1.27 – 1.57)	82	3.0 (2.2 – 3.8)	2.44 (1.79 – 3.33)	<0.0001	2.94 (2.11 – 4.09)	<0.0001	2.22 (1.61 – 3.06)	<0.0001	2.45 (1.11 – 5.37)	0.01

Survey weighted logistic regression models were constructed with number of self-reported cardiovascular and/or cerebrovascular outcomes (coronary artery disease / angina / heart attack, other heart disease / congestive heart failure, stroke or peripheral vascular disease) as the dependent variables. The independent variable was 1-year history of eczema. Adjusted OR and 95% CI were estimated for eczema in two different multivariate models, including: 1. age, highest level of education in the household, race/ethnicity, sex and 2. 1-year history of asthma and hay fever and 3. body mass index, history of ever smoking cigarettes, consumption of alcohol in the past year and frequency of vigorous activity in the past week as covariates.

Supplemental Table 1. Questions used in the studies.

Variable	Question	Study
Eczema	1. Have you ever had an itchy rash which was coming and going for at least 6 months? 2. Have you had this itchy rash at any time in the last 12 months? 3. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the	NHANES 2005-2006
Eczema	During the past 12 months, have you had dermatitis, eczema, or any other red, inflamed skin rash?	NHIS 2010
Eczema	During the past 12 months, have you been told by a doctor or other health professional that you had eczema or any kind of skin allergy?	NHIS 2012
Asthma	1. Has a doctor or other health professional ever told you that you have asthma? ~~2. During the past 12 months, have you had an episode of asthma or~~	NHANES 2005-2006
Asthma	During the past 12 months, have you been told by a doctor or other health professional that you had asthma?	NHIS 2010, 2012
Hay fever	1. Has a doctor or other health professional ever told you that you have hay fever?	NHANES 2005-2006
Hay fever	During the past 12 months, have you been told by a doctor or other health professional that you had hay fever?	NHIS 2010, 2012
Coronary artery disease	Has a doctor or other health professional ever told you that you had coronary artery disease?	NHANES 2005-2006
Coronary artery disease	Have you ever been told by a doctor or other health professional that you had coronary heart disease?	NHIS 2010, 2012
Angina	Has a doctor or other health professional ever told you that you had angina, also called angina pectoris?	NHANES 2005-2006
Angina	Have you ever been told by a doctor or other health professional that you had angina, also called angina pectoris?	NHIS 2010, 2012
Heart attack	Has a doctor or other health professional ever told you that you had a heart attack (also called myocardial infarction)?	NHANES 2005-2006
Heart attack	Have you ever been told by a doctor or other health professional that you had a heart attack (also called myocardial infarction)?	NHIS 2010, 2012
Congestive heart failure	Has a doctor or other health professional ever told you that you had congestive heart failure?	NHANES 2005-2006
Other heart disease	Have you ever been told by a doctor or other health professional that you had any kind of heart condition or heart disease (other than the	NHIS 2010, 2012
Stroke	Have you ever been told by a doctor or other health professional that you had a stroke?	NHIS 2010, 2012
Peripheral vascular disease	Have you ever been told by a doctor or other health professional that you had poor circulation in your legs?	NHIS 2012
Ever smoking	Have you smoked at least 100 cigarettes in your entire life?	NHIS 2010, 2012
History of alcohol	In any one year, have you had at least 12 drinks of any type of alcoholic beverage?	NHIS 2010, 2012
Vigorous activity	How often do you do vigorous leisure-time physical activities for at least 10 minutes that cause heavy sweating or large increases in	NHIS 2010, 2012