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The association between cardiovascular disease and type 2 diabetes in adults with atopic dermatitis: a systematic review and meta-analysis

Running head: Atopic dermatitis and cardiovascular disease

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Author Contributions

Drs. Egeberg and Jacob Thyssen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Thyssen and Egeberg. Acquisition, analysis, and interpretation of data: All authors. Drafting of the manuscript: Thyssen, Andersen, and Egeberg. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Egeberg. Obtained funding: None. Administrative, technical, or material support: All authors. Study supervision: All authors.

Declaration of interests

Dr. Thyssen has attended an advisory board for Roche and Sanofi-Genzyme, and been a speaker on atopic dermatitis for LEO Pharma and Sanofi-Genzyme. Dr. Skov has received consultancy and/or speaker honoraria from Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme, and Leo Pharma and is a member of the advisory boards of Abbvie, Pfizer, Janssen-Cilag, Merck Sharp & Dohme, Eli Lilly, Celgene and Novartis. Dr. Egeberg has received research funding from Pfizer and Eli Lilly, and honoraria as consultant and/or speaker from Leo Pharma, Samsung Bioepis Co., Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals. Dr. Gislason is supported by an unrestricted research scholarship from the Novo Nordisk Foundation. Anne-Sofie Halling-Overgaard and Yuki Andersen have not conflict of interest.
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Key words: Atopic dermatitis, cardiovascular disease, diabetes, meta-analysis, risk

What’s known/what’s new statements

What’s known:

- Atopic dermatitis has been associated with atopic, psychiatric, and autoimmune comorbidities. Recent studies investigating a possible association with cardiovascular comorbidities and type 2 diabetes have been conflicting.

What’s new:

- Based on a systematic review and meta-analysis, atopic dermatitis is unlikely to represent an independent risk factor for cardiometabolic disease.
- Observed differences in risk estimates between North American and European studies may be explained by variations in cardiovascular risk factors such as body weight.

Abstract

Recent studies examining the association between atopic dermatitis (AD) and cardiovascular disease (CVD) and type 2 diabetes have shown inconsistent results. We compared the risk of CVD and diabetes between adult patients with and without AD by searching the Pubmed, Embase, and Web of Science databases. Data extraction was done by two independent reviewers. We found a total of 2,855 citations, of which 53 were considered relevant based on title and abstract. Sixteen publications were
included in the qualitative analysis, of which 13 were also included in a quantitative meta-analysis of crude data. No association was observed between AD and unspecified, but suspected type 2, diabetes (pooled odds ratio [OR] 1.11; 95% confidence interval [CI] 0.87-1.42), hypertension (pooled OR 1.16; 95% CI 0.98-1.37), stroke (pooled OR 1.15; 95% CI 0.95-1.39) or myocardial infarction (pooled OR 1.14; 95% CI 0.83-1.56), but a positive association was observed with angina pectoris (OR 1.73; 95% CI 1.27-2.37). Meta-analysis on adjusted data gave similar results. While adults with AD in some populations have increased prevalence of cardiovascular risk factors, such as obesity and smoking, it is unlikely that AD represents an independent and clinically relevant risk factor for cardiometabolic disease.

Introduction

Atopic dermatitis (AD) is a chronic and relapsing pediatric inflammatory skin disease, which may persist into adulthood.\textsuperscript{1} Established adult AD comorbidities include atopic, psychiatric, and autoimmune diseases.\textsuperscript{2} Presence of systemic low-grade inflammation has been put forward as a potential explanation for the observed increased cardiovascular disease (CVD) risk in patients with psoriasis.\textsuperscript{3} Along similar lines, recent studies have examined the AD-associated risk of CVD and diabetes,\textsuperscript{4-10} but results have been conflicting. We performed a systematic review and meta-analysis, to examine the possible association of AD with diabetes and CVD.

Materials and methods

Inclusion and exclusion criteria

No protocol was registered prior to study start, but was developed in Danish. A priori, all studies investigating the association between AD and, respectively, type 2 diabetes, stroke, hypertension, myocardial infarction, angina, coronary artery disease, heart failure, and cardiovascular death were included in the systemic review. Studies on the association between AD and bacterial endocarditis
were excluded. Studies were also excluded if there was no reference group comprising patients or individuals without AD, as were studies that specifically stated that they examined type 1 diabetes. Since the vast majority of diabetes cases in adults are type 2, studies that examined diabetes as outcome were considered to be mostly type 2 diabetes cases. The search process is presented in Figure 1.

**Literature search**

We searched the medical databases Pubmed, Embase, and Web of Science using the following search term: “(atopic dermatitis or atopic eczema) AND (cardiovascular or heart or myocardial or stroke or hypertension or ischemia or angina or diabetes or mortality or death)”. We chose not to use the broader terms ‘eczema’ or ‘dermatitis’ as these are non-specific for AD. The search included articles in any language, between inception and August 2017, and only studies in adults (age ≥18 years) were included. Reference lists of key-articles and reviews were also screened.

**Data extraction**

Two of the authors (JPT and AE) independently screened all titles and/or abstracts prior to retrieving full-text articles. If data were duplicated in more than one study, the study with most comprehensive data was included. Study quality in the quantitative analysis was assessed using the Newcastle-Ottawa scale (NOS). Each study was appointed up to 10 points according to the adapted NOS.

**Statistical Analysis**

We chose to meta-analyze crude as well as adjusted data from included articles. For the meta-analysis on crude data, we only included studies that listed the number of total patients with AD, patients with AD with the examined outcome, total reference individuals, and reference individuals with the examined outcome, respectively. For the meta-analysis on adjusted data, we took the fully adjusted estimates from the relevant articles. In case multiple adjusted models were presented in an article, we chose the one that included smoking.

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Statistical analyses were performed using StatsDirect version 3.0.192 (StatsDirect Ltd., Cheshire, UK). Odds ratios (OR) with 95% confidence intervals (CI) of cardiometabolic endpoints in individuals with AD compared to reference individuals were estimated. Specifically, these included myocardial infarction, diabetes, hypertension, angina pectoris, and stroke. For each endpoint category the heterogeneity of included studies was assessed using Cochran Q and $I^2$ statistics, and forest plots were constructed. The Cochran’s Q is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, whereas the $I^2$ statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance. Random effects models with DerSimonian-Laird methods were utilized for all analyses, and between-studies heterogeneity was found in all studied endpoint categories. Consequently, for all analyses all Cochrane Q statistics p-values were <0.05 and all $I^2$ values were > 75%. Funnel plot progression of logarithmic OR and standard errors was used to assess for publication bias. All statistical tests were 2-sided, with a significance level of <0.05.

**Results**

A total of 2,855 citations were identified in the screening process, of which 53 were considered relevant based on title and abstract review. The remaining 2,802 articles did not include information on any of the study endpoints. Thirty-seven manuscripts were excluded due to reasons listed in the PRISMA flow-chart (Figure 1). A total of 16 publications were included in the qualitative analysis and further details about the publications are presented online and below (see Table E1-E6 in the Online Repository).
Meta-analysis based on crude data

Thirteen studies were included in the quantitative meta-analysis on crude data. Studies originated from Taiwan (2),\textsuperscript{15,18} Germany (1),\textsuperscript{6} Denmark (5),\textsuperscript{4,9,10,12,14} Canada (1),\textsuperscript{20} and the US (4).\textsuperscript{5,7,8,13} Two of the publications contained data from multiple cohorts (total n=3),\textsuperscript{5,8} which were treated separately in the analyses, i.e. all cohorts were included. All studies included in the quantitative analysis had a NOS score of 7 or higher, which indicates good study quality. The studies were grouped according to the endpoints; myocardial infarction, presumed type 2 diabetes, hypertension, angina pectoris, and stroke.

Each endpoint in the meta-analysis comprised studies from at least two continents. A test for publication bias yielded asymmetrical funnel plots except for the category ‘diabetes’, however the number of studies in each category was low, thereby limiting the interpretation. In particular, the funnel plot for hypertension was skewed to the far right indicating considerable publication bias.

A total of seven studies including 100,382 patients with AD and 1,657,116 reference individuals were analyzed in the category ‘myocardial infarction’ (Figure 2),\textsuperscript{6-9,20} of which five originated from North America and two from Europe. Overall there was no significant association between AD and myocardial infarction (pooled OR 1.14; 95% CI 0.83-1.56; $I^2$ 95.5%). Most of the nine studies included in the diabetes category did not specify the type of diabetes (type 1 vs. 2). The meta-analysis based on these nine studies\textsuperscript{4,5,7,10,12,13,18,20} and a total of 80,357 patients with AD and 579,036 reference individuals showed no association between AD and presumed type 2 diabetes (pooled OR 1.11; 95% CI 0.87-1.42; $I^2$ 97.1%) (Figure 3A). For stroke, a total of eight studies\textsuperscript{6-9,15,20} including 120,706 patients with AD and 1,677,441 reference individuals were included in the meta-analysis, but again showed no association with AD (pooled OR 1.15; 95% CI 0.95-1.39; $I^2$ 89.8%) (Figure 3B). Similar no association between AD and hypertension was observed in a meta-analysis based on seven studies\textsuperscript{5,7,14,18,20} including 93,837 patients with AD and 1,626,771 reference individuals (pooled OR 1.16; 95% CI 0.98-1.37; $I^2$ 98.9%) (Figure 3C). Pooled analysis for angina pectoris showed a significant association based on 41,660 patients with AD and 1,203,168 reference individuals from four cohorts (pooled OR 1.73; 95% CI 1.27-2.37; $I^2$ 89.3%) (Figure 3D).\textsuperscript{6,8} No quantitative analyses

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were performed for the endpoints coronary artery disease/ischemic heart disease’, ‘cardiovascular death’, and ‘heart failure’ due to the low number of published studies.

**Meta-analysis based on adjusted data**

Twelve studies were included in the quantitative meta-analysis on adjusted data and these originated from Taiwan (1), South Korea (1), Germany (2), Denmark (4), Canada (1), and the US (3). A total of nine studies including 121,077 patients with AD and 1,686,548 reference individuals were analyzed in the category ‘myocardial infarction’ (see Figure E1 in the Online Repository), of which five originated from North America, three from Europe and one from Asia. Overall there was no significant association between AD and myocardial infarction (pooled OR 1.03; 95% CI 0.88-1.21; I² 74.1%).

A meta-analysis of five studies including 56,688 patients with AD and 443,542 reference individuals showed no association between AD and presumed type 2 diabetes (pooled OR 0.97; 95% CI 0.80-1.18; I² 81.6%) (see Figure E2A in the Online Repository). For stroke, a total of nine studies including 121,078 patients with AD and 1,686,550 reference individuals were included in the meta-analysis. No association was found between AD and stroke (pooled OR 1.12; 95% CI 0.95-1.32; I² 81.3%) (see Figure E2B in the Online Repository). No association was observed between AD and hypertension in a meta-analysis based on six studies including 71,040 patients with AD and 1,520,340 reference individuals (pooled OR 1.10; 95% CI 0.97-1.24; I² 94.5%) (see Figure E2C in the Online Repository). A total of four studies including 41,660 patients with AD and 1,203,168 reference individuals were included in the meta-analysis on angina pectoris which showed a positive association (pooled OR 1.48; 95% CI 1.23-1.79; I² 44.3%). Three of the studies originated from North America and one study originated from Germany (see Figure E2D in the Online Repository).
**Qualitative analysis**

In addition to results from the quantitative analysis, a general population study from Germany found no association between AD and coronary artery disease.\(^{19}\) In an experimental study, 17 of 31 adult Danish patients with AD had a coronary artery calcium score > 0 as well as presence of atherosclerotic plaques, when assessed with cardiac computed tomography angiography. In data analysis, AD was significantly associated with mild single-vessel disease.\(^{10}\) A Danish cohort study analyzing data from the same national register as the study by Andersen et al.,\(^9\) showed that the risk of myocardial infarction was increased among patients with at least two hospital diagnosis of AD (in- or outpatient) (adjusted HR 1.74; 95% CI 1.21–2.49). However, this study lacked adjustment for important risk factors such as smoking as opposed to the study by Andersen.\(^9,21\) In addition to the studies in the meta-analysis, no association between elevated blood pressure and AD was found in a German cohort (n=2,990; high systolic blood pressure; p=0.6513, high diastolic blood pressure; p=0.7972 in linear regression models).\(^6\) Notably, another German study found a decreased prevalence ratio of hypertension in patients with AD when compared to non-AD reference individuals (n=1,312,215; prevalence ratio=0.83; 95% CI 0.81-0.85).\(^{17}\)

AD was associated with coronary artery disease in three US cohorts (ORs [95% CI] 1.96 [1.02–3.77], 1.38 [1.12–1.70], and 1.32 [1.04–1.66]),\(^8\) and in one Taiwanese cohort (p<0.0001).\(^{18}\) However, a Germany study found a decreased prevalence of coronary artery disease in patients with AD when compared to reference individuals (n=1,312,215; prevalence ratio=0.83; 95% CI 0.80-0.86).\(^{17}\) Thus far, peripheral artery disease has been associated with AD in one German study (n=1,180,678; OR 1.32; 95% CI 1.04–1.66)\(^6\) and one US study (n=34,552; OR 1.90; 95% CI 1.62–2.22).\(^8\) An increased risk of heart failure in patients with AD was reported from a Taiwanese cohort study (n=40,646; HR 1.46; 95% CI 1.10-1.93),\(^{15}\) while a US cross-sectional study reported no association between AD and congestive heart failure (n=4,971; OR 1.01; 95% CI 0.40-2.57).\(^8\)

**Discussion**

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Main findings

In this systematic review and meta-analysis, we found no association between AD and hypertension, presumed type 2 diabetes, myocardial infarction, and stroke, in the quantitative crude data analyses. Similar analyses using fully adjusted data from the articles gave essentially identical results. Overall, quantitative analysis indicated that AD was associated with angina pectoris based on only two publications and four cohorts.

Interpretation

Most studies included in the quantitative meta-analyses used questionnaire data to define AD. These studies are particularly vulnerable to misclassification as AD may be confused by responders with other skin conditions such as psoriasis, lupus, and non-atopic eczema, e.g. allergic and irritant contact dermatitis. Moreover, these studies used questions that were rather non-specific for AD (e.g. ‘has a doctor ever told you that you had eczema?’ and ‘during the past 12 months, have you had dermatitis, eczema, or any other red, inflamed skin rash?’).\(^{20}\) Importantly, the UK Working Party Criteria for AD may not reliably identify individuals with a history of AD when used in adults.\(^{22}\) Since AD often resolve in adolescence most adults classified as having AD, no longer have active disease. Therefore, systemic inflammation can no longer be present. Based on these observations, future studies examining the association with CVD should be conducted in patient populations with active AD, as seen when using registry data of current AD diagnoses.\(^{4,9}\)

Systemic low-grade inflammation in AD has been put forward as an explanation for the increased risk of CVD in some studies\(^ {23}\), albeit we could not confirm an association in this systematic review and meta-analysis. Indeed, increased serum levels of cytokines have been measured in patients with AD,\(^ {24}\) and elevated serum total IgE levels, that are observed in many patients with AD, have been linked CVD.\(^ {25}\) Yet, the levels of specific IgE, in particular to house dust mites, were inversely associated with CVD in an American study,\(^ {26}\) whereas a recent Danish general population based study refuted these observations.\(^ {27}\) Moreover, the T helper (Th) cell 2 bias in AD and other atopic disorders, which is mutually suppressive to the Th1 bias observed in arteriosclerotic CVD, would further argue against

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a higher risk of CVD in adults with AD. There appears to be increased blood platelet activation in patients with AD compared to reference individuals, and especially in patients with concomitant allergic rhinitis.\textsuperscript{28} A very recent study showed increased occurrence of cardiovascular risk proteins in serum.\textsuperscript{29} Finally, one mouse study showed that persistent interleukin (IL)-1 secretion from the skin was associated with CVD,\textsuperscript{30} and in line with this observation, an ‘epidermal IL-1 march’ was recently described as a potential link between the skin and vascular disease in AD.\textsuperscript{31}

The higher risk estimates of CVD observed in selected North American and Asian populations could be related to obesity\textsuperscript{32} and AD misclassification as described above. However, in Denmark where a recent register based study showed decreased risk of CVD in AD patients,\textsuperscript{9} an inverse association with occurrence of gallstones and erectile dysfunction, i.e. conditions traditionally associated with obesity and CVD, has also been observed in the same registers.\textsuperscript{33,34} Few data on physical activity are available, but one study showed that American patients with AD had decreased levels of physical activity, whereas no difference in physical activity was found between Swedish adults with and without AD.\textsuperscript{35,36} The higher risk estimates of in particular myocardial infarction observed in selected North American populations could therefore at least in part be due to differences in environmental, behavioral, and cardiovascular risk factors. However, it should also be emphasized that the definition of myocardial infarction was based on relatively unspecific questionnaire data in the studies by Silverberg, but ICD-10 codes in the studies by Standl\textsuperscript{6} and Andersen\textsuperscript{9} (see Table E1 in the Online Repository). In a recent meta-analysis, AD was significantly associated with smoking, hereby suggesting yet another causative factor for CVD.\textsuperscript{37} Patients with AD often suffer from poor and interrupted sleep, mostly due to itch, but psychiatric disorders such as attention deficit hyperactivity disorder, anxiety and depression may also play a role. A cross-sectional questionnaire-based survey from the US showed that adult patients with AD had higher odds of sleep disturbances including shorter sleep duration, trouble falling asleep, and early morning awakenings.\textsuperscript{38} Importantly, there is a positive relationship between sleep deprivation and, respectively, hypertension, CVD, and diabetes in adults possibly due to increased activity of the sympathetic nervous system.\textsuperscript{39} Topical and systemic medication may also affect the risk of CVD and type 2 diabetes. For example, topical corticosteroid
use was associated with type 2 diabetes in a large Dutch register based study, and a recent Danish study showed that use of topical corticosteroids was a strong predictor of the occurrence of type 2 diabetes among patients with AD. Moreover, systemic corticosteroids are often used to treat AD flares, and well-established long-term effects include hypertension and type 2 diabetes.

A few remaining causative factors for CVD in AD warrant mentioning. Autoimmune comorbidities co-occurring in patients with AD, e.g. rheumatoid arthritis and inflammatory bowel disease, have been associated with CVD and could add to the overall burden although the prevalence of these conditions in patients with AD remains low. Furthermore, vitamin D insufficiency in AD could affect the risk of e.g. hypertension, myocardial infarction, and diabetes. A large Germany study showed no evidence for shared genetic risk variants of AD and CVD. Increased expression of IL-17 has been shown in predominately Asian subtypes of AD as well as in ichthyoses, which at least in theory could increase the risk of CVD in Asians who might suffer from more psoriatic AD.

Certain limitations apply to the interpretation of the present results. A limited number of studies were available for meta-analysis and none were from outside Germany/Denmark/United States/Canada/Taiwan. Information about AD severity and smoking were often lacking. Importantly, a causal link cannot be determined based on observational data, and furthermore, most studies were cross-sectional. Misclassification possibly affected the association estimates between AD and presumed type 2 diabetes, since not all studies provided sufficient information about the type of diabetes. While most cases of diabetes are expected to be type 2 diabetes, we cannot exclude that type 1 diabetes cases affected the estimates. However, the number of type 1 cases is assumed to be low and would therefore not affect the estimates to a large extent. Since AD is an umbrella term that covers different endophenotypes, stratification by specific IgE levels or filaggrin gene mutations might have detected specific risk groups, however, this was not possible. We only searched for articles using the term atopic to increase specificity. However, studies using other common terms such as children or flexural eczema to study AD were potentially missed which obviously could have biased the outcome. Publication bias may have occurred since the initial studies found more positive associations than more recent studies. We emphasize that meta-analyses such as the present one are not designed to
assess whether an association is independent of traditional risk factors. Lastly, although we presented estimates based on both crude and adjusted data, we emphasize that data based on adjusted estimates should be interpreted with caution since studies may differ considerably with regards to included covariates in the adjusted models. Nonetheless, no significant difference was observed between analyses using crude and adjusted data in any of the analyses.

Conclusion

AD was not associated with myocardial infarction, hypertension, diabetes, or stroke. There was a modest association with angina pectoris based on four studies. The current sum of evidence renders it unlikely that AD itself is an independent risk factor for cardiometabolic disease. Differences in estimates are likely explained by study design differences and AD misclassification, variations in body-weight, physical activity, use of corticosteroids, and other lifestyle features although their relative contributions remain unknown. Importantly, as demonstrated in multiple cohorts,\textsuperscript{14,17} the magnitude of CVD and associated risk factors is markedly lower in AD compared with psoriasis populations. Future well-designed prospective clinical studies may help elucidate the relationship between life-style and environmental factors, AD disease severity, and associated comorbidities.
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Figures

Figure 1. Flow Diagram
Figure 2. Odds ratio meta-analysis of association between atopic dermatitis and myocardial infarction based on crude data.

Odds ratio meta-analysis plot [random effects]

- Silverberg (2015a): 2.80 (1.42, 5.09)
- Silverberg (2015b): 1.81 (1.49, 2.19)
- Silverberg (2015c): 1.36 (1.12, 1.65)
- Andersen (2016): 1.01 (0.83, 1.23)
- Drucker (2016): 0.96 (0.67, 1.34)
- Standl (2016a): 0.90 (0.83, 0.98)
- Drucker (2017): 0.55 (0.48, 0.64)
- Combined [random]: 1.14 (0.83, 1.56)
Figure 3. Odds ratio meta-analysis of association between atopic dermatitis and, respectively, type 2 diabetes (A), stroke (B), hypertension (C), and angina pectoris (D) based on crude data.