

Atopic dermatitis and cardiovascular disease: What are the clinical implications?



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A 48-year-old woman presents to your ambulatory clinic for treatment of atopic dermatitis. She has had atopic dermatitis since early childhood, and although it was not always severe, it has been so for the last 9 years. She is very itchy and wakes at night scratching, and her mood is affected. She no longer exercises because sweating makes her symptoms worse. She has tried emollients, topical steroids, and calcineurin inhibitors and has been given a few short courses of prednisone, all of which provide temporary but inadequate relief.

She is in your office today to discuss potential systemic therapy and has brought up another topic for discussion. She read in the news that eczema is associated with an increased risk for heart attacks and strokes and wonders whether this is something she should worry about and whether there are any specific tests or treatments she should have to decrease that risk.

In this issue of the *Journal*, a systematic review and meta-analysis by Ascott et al¹ tries to get at the heart of that clinical scenario. The research question is whether atopic dermatitis is associated with an increased risk for cardiovascular disease. Furthermore, it seeks to determine whether more severe skin disease is associated with an increased risk greater than that seen in patients with milder disease; this feature is novel and was not investigated in a previous systematic review on the topic.² The systematic review is well done, including adherence to a published protocol and a broad search strategy. Another excellent feature of the analysis is use of prediction intervals in addition to CIs around the effect estimates; these provide a better sense of the uncertainty in effect estimates.

The meta-analyses for each outcome were done separately for cross-sectional and cohort studies. This is important for a number of reasons. In addition to an inability to determine temporal relationships, cross-sectional surveys are particularly problematic for cardiovascular disease: only patients with less disabling and nonfatal cases of heart attack and stroke will be alive and functional enough to participate. Additionally, cross-sectional

studies on this topic have yielded heterogeneous results, with some studies showing positive associations, others showing negative associations, and still others showing null associations. This is reflected in the I^2 statistics for the meta-analyses of cross-sectional studies: 97% for myocardial infarction and 96% for stroke. Put plainly, cross-sectional studies of the association of atopic dermatitis with cardiovascular disease were a good place to start and were hypothesis generating but at this point should not be given much weight as we try to sort out a true causal relationship.

It is in the meta-analyses of cohort studies for outcomes in which more than 2 studies are pooled that we see some consistency. The CIs and prediction intervals are tightest around the relative risk for ischemic stroke (17% increased risk). Although CIs are fairly precise around relative risks for myocardial infarction (12% increased risk) and overall “stroke” (10% increased risk), the prediction intervals widen. Analyses comparing the risk of cardiovascular outcomes between atopic dermatitis severity strata (mild, moderate, and severe) are also fairly consistent, with positive associations found for each of the outcomes under study. Although it was only examined in 2 studies, the results for cardiovascular death are striking: with an increase in the severity of atopic dermatitis, the risk of cardiovascular death increases by 25%.

When considering the potential clinical implications of those results, we must understand why a relationship might exist between atopic dermatitis and cardiovascular disease. There are a number of potential explanations for the epidemiologic association (Fig 1). First, one of the best documented associations with atopic dermatitis is sleep disruption,³ and insomnia and poor sleep have been associated with cardiovascular events.⁴ Therefore any relationship between atopic dermatitis and cardiovascular disease could be mediated through the effect of skin disease on sleep. Atopic dermatitis has also been associated with traditional cardiovascular risk factors, such as obesity.⁵ The direction of this association is less clear (eg, atopic dermatitis can lead to an increased risk for obesity or *vice versa*), and therefore it is possible they are mediators or confounders in the relationship. Patients with asthma are also at increased risk for cardiovascular disease, and therefore the atopic link between asthma and atopic dermatitis could explain the association.⁶ Although many of the included studies in the systematic review accounted for those and other factors through adjustment and mediation analyses, these are likely imperfect, and residual confounding is likely.

It is possible that the inflammatory nature of atopic dermatitis itself is responsible for the association, as is hypothesized to be the case for other inflammatory conditions, such as psoriasis and rheumatoid arthritis. The dose-response relationship found by Ascott et al¹ between atopic dermatitis severity and cardiovascular disease is suggestive of an inflammatory connection, although the gradient seen with severity could also be mediated or confounded by the same factors mentioned above for the overall relationship between atopic dermatitis and cardiovascular disease. Additionally, the inflammation present in patients with

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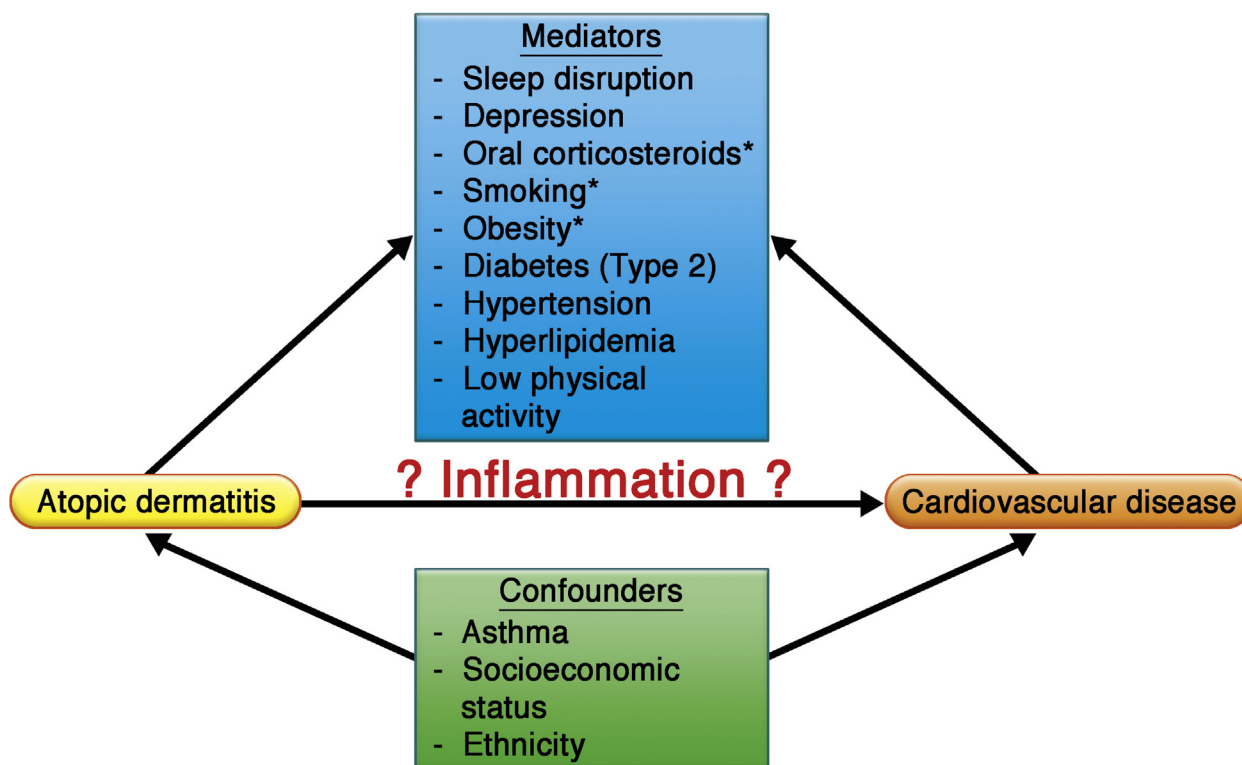
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Items marked * represent factors that could be both mediators or confounders

FIG 1. Schematic of the potential causal relationship between atopic dermatitis and cardiovascular disease. It is unclear whether there is a direct causal relationship between the inflammation of atopic dermatitis and cardiovascular disease. This relationship could be mediated through the effect of atopic dermatitis on sleep, depression, systemic corticosteroids used for atopic dermatitis, or major cardiovascular risk factors, which have previously been associated with atopic dermatitis. The relationship could also be confounded by the association between asthma and atopic dermatitis and previously described relationships between socioeconomic status and ethnicity with atopic dermatitis. In addition to being potential mediators, smoking and obesity are potential confounders because the direction of their relationship with atopic dermatitis is unclear and possibly bidirectional. Because oral corticosteroids are also used to treat asthma, their use for respiratory symptoms could be a confounder.

atopic dermatitis, with a skew toward T_H2 cytokines, is very different than the inflammatory milieu underlying psoriasis and rheumatoid arthritis. Unlike T_H1 cytokines, which are clearly implicated in the pathogenesis, acceleration, and thrombotic complications of atherosclerosis, the pathogenic role of T_H2 cytokines remains less certain and contradictory. For example, the T_H2 cytokine IL-5 might in fact suppress inflammation and protect against the development of atherosclerosis. In contrast, the T_H2 cytokine IL-4 has been implicated in the promotion of vascular inflammation and consequent potential proatherogenic effects.⁷ Thus further research is needed to better elucidate the role of the T_H2 cytokines in promotion of and/or protection against the development of vascular inflammation, atherosclerosis, and related complications.

An additional mediating factor in the relationship is that systemic corticosteroids, which are often used to treat severe atopic dermatitis, can lead to adverse cardiovascular consequences.⁸ Ascott et al¹ point out that 6 of 7 studies examining atopic dermatitis severity in their review rely on the use of systemic medications to define severity. Although some observational studies have tried to account for this by stratifying

analyses based on use of these specific medications,⁹ their role in the relationship cannot be ruled out. If future research is to be done on atopic dermatitis and cardiovascular risk, it should focus on patients at higher risk, on those with high or current exposure to risky medications, and on potential underlying mechanisms.

What is the bottom line for the patient described at the beginning of this editorial? Based on the results of the systematic review and meta-analysis by Ascott et al,¹ you might tell the patient that patients with atopic dermatitis appear to have a somewhat higher risk of a heart attack or stroke compared with the general population, but it is unclear why. You could also explain to her that the absolute risk is very low. For example, in one study in which an increased risk was seen, there were only 12 more heart attacks per 100,000 person-years in those with atopic dermatitis compared with the general population.⁹ Therefore she should have age-appropriate cardiometabolic screening and counseling with her family physician, with no additional specific testing or treatment necessary related to her skin disease. There are no data to suggest that treating the systemic inflammation of her atopic dermatitis with immunomodulating therapy will have

any effect on her cardiometabolic profile; such an approach has been disappointing thus far in patients with psoriasis.¹⁰ Her atopic dermatitis should be treated with the aim of improving her symptoms. Although not the primary aim, this might in turn improve her sleep, mood, and ability to tolerate exercise, thereby decreasing her overall cardiovascular risk.

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