

Atopic dermatitis and cardiovascular disease: have we seen enough to refute a causal link?

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Linked Article: Thyssen *et al.* *Br J Dermatol* 2018; **178**:1272–1279.

The observation that psoriasis is associated with cardiovascular risk factors and disease^{1,2} has spurred dermatologists and investigators to look for similar associations with other skin diseases such as atopic dermatitis (AD). Could AD, another chronic inflammatory skin disease, also confer an increased cardiovascular risk? This question has been addressed in a systematic review by Thyssen *et al.* in this issue of the *BJD*.³

A matched cohort study from Taiwan found no association with myocardial infarction but a 33% increased risk of ischaemic stroke.⁴ Subsequently, an analysis of three U.S. population-based cross-sectional surveys found numerous positive associations with AD, including a 2.5-fold increased prevalence of myocardial infarction and a 1.5-fold increased prevalence of stroke.⁵ However, since then, multiple cohort and cross-sectional studies from the U.S.A., Canada, Germany and Denmark have found either no associations or negative associations between AD and cardiovascular comorbidities.^{6–9} In addition, the meta-analyses for the association of AD with myocardial infarction, stroke, hypertension and type-2 diabetes using adjusted-effect estimates found no significant associations. So what should we make of the more recent findings, which conflict with earlier reports?

When attempting to establish a causal link, well-designed and adequately controlled cohort studies are superior to cross-sectional ones, as they are able to look at the temporal sequence of events and whether an exposure preceded disease onset. The majority of studies examined by Thyssen *et al.* are cross-sectional, and the only longitudinal cohort study to demonstrate a positive association between AD and cardiovascular disease (specifically stroke) was the study from Taiwan.⁴ In a subsequent analysis in the same database, a similar association with stroke was found with contact dermatitis, making residual confounding a likely explanation for the positive association with AD.¹⁰

A major concern in most of the included studies is the way AD cases were identified. For instance, the large U.S. cross-sectional studies with positive associations relied on questionnaire-based diagnoses, none of which are specific to AD, potentially leading to misclassification of psoriasis and other pruritic skin conditions as AD.⁵ Reliance on International Classification of Disease codes, as in Su *et al.*,⁴ can lead to similar issues, but such misclassification is likely to weaken risk estimates.¹¹

It must be acknowledged that the null studies, including two by the first author of this commentary, are also not without problems related to study design, confounding and

misclassification. However, most importantly, when the entire body of evidence is examined in aggregate, there is no convincing evidence for an increased risk of cardiovascular disease with AD. Further, as Thyssen *et al.* point out, there is little biological plausibility for an association.³

If future studies are to change this assessment, they should use validated AD case definitions, ideally based on physician diagnosis. Comprehensive control for confounding factors is essential, including adjustment for known cardiovascular risk factors. Stratification by AD severity would be interesting, as patients with more severe and recalcitrant disease might have a different risk profile than patients with milder and more transient disease. In the meantime, the current evidence suggests that patients with AD are not at increased risk of developing cardiovascular disease.

Conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Audio S1. Author audio.

Building the evidence base for current systemic treatments for severe, chronic atopic dermatitis: methotrexate vs. azathioprine

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This issue of the BJD includes the important paper by Gerbens et al., 'Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial', providing first answers on the efficacy and safety of these commonly used drugs for long-term treatment of severe atopic dermatitis (AD).¹

As many as 5–10% of adults suffer from AD, which implies the largest global burden of disability due to skin disease.² Systemic treatments are frequently needed for individuals with severe AD; until recently, only one oral drug was approved for AD although several oral treatments are used off label.³ New treatments are eagerly anticipated and it is therefore essential to gain evidence on all currently used systemic treatments for AD.^{4,5} It is astonishing that no long-term study of oral AD treatment has been performed until now.

The Dutch study was an open-label follow-up of a clinical trial on the treatment of AD with methotrexate (MTX) vs. azathioprine (AZA). In total, the study covers a period of 5 years in adult patients with moderate-to-severe AD; 43 patients were included in the study. The dosing of the study drug, either AZA or MTX, could be adjusted, therapy could be switched and additional treatments could be added. Follow-up was every 3 months; clinical signs, symptoms, quality of life, long-term control and adverse events were assessed.

Gerbens et al.¹ showed that both MTX and AZA seemed to be effective; the mean absolute reduction in total SCORAD (SCORing of Atopic Dermatitis) was 32.1 in both groups. Both MTX and AZA seemed to be safe for the long-term treatment of AD. The most common adverse events were mild-to-moderate infections. Other mild-to-moderate adverse events probably related to the study medication were 'hepatobiliary' and 'gastrointestinal disorders' for MTX, and 'blood and lymphatic system disorders' for AZA. Three serious adverse events possibly related to the study medications were registered.

This study has the strength of being a well-performed longitudinal study: efficacy, safety and tolerability were all assessed using relevant outcome measures regularly.⁶ Choosing a head-to-head design was beneficial for comparing the effect of the two drugs. However, the interpretation of the effectiveness requires caution, as participants were able to change medication, which might have confounded the results. Furthermore, unknown adverse events cannot be excluded as the study involved relatively small numbers.^{7,8} Indeed, only 35 of 43 originally included patients participated, of whom 27 completed follow-up. Survival in both groups was low after 5 years (MTX $n = 5$, AZA $n = 1$), and some patients discontinued due to controlled AD. Thus, it is essential that the results of this study are confirmed in larger future trials.

The findings of this study are of high importance for both clinical management and decision-makers. Until now there was a knowledge gap regarding the effect of treatment with MTX and AZA for a period of several years on the clinical course of severe AD and potential adverse events. As the study provides data for up to 5 years, the effect of long-term treatment could be explored in detail for the first time in an adult population. Furthermore, this study is the longest pragmatic study ever performed on this topic, and investigated two important drugs that are frequently prescribed for this indication. Based on this study, both MTX and AZA seem to be treatment options for patients with moderate-to-severe AD for up to 5 years. However, few patients in both groups remained on their originally allocated drug at the study end. This highlights the urgent need for effective long-term regimens of currently used drugs as well as new drugs. Informed decisions for individualized treatment need evidence on the long-term effect and safety profile of drugs.

The results of the current study stress the importance of more well-designed studies with long-term follow-up to adequately address public health problems. However, these studies are difficult to carry out and expensive, and may be hard to fund. Therefore, the Dutch study, which overcame these