

What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008. Part 1. Definitions, causes and consequences of eczema

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Summary

This review summarizes clinically important findings from nine systematic reviews indexed in bibliographical databases between August 2007 and August 2008, dealing with the definitions, causes and consequences of atopic eczema (AE). One review of diagnostic criteria found that out of 10 sets of criteria, only the UK refinement of the Hanifin and Rajka criteria have been adequately tested (in 19 studies). Another review of 20 named outcome measures found that only three [SCORing Atopic Dermatitis (SCORAD), the Eczema Area and Severity Index (EASI) and the Patient Oriented Eczema Measure (POEM)] had been tested and found to perform adequately. In terms of risk factors for developing disease, a review found that birth by caesarean section increased the risk of asthma and hay fever but not eczema in offspring. A review of cohort studies also found evidence that adverse psychological factors in early life predispose to more atopic disease and a worse prognosis. Another review found that filaggrin gene mutations were a consistently strong risk factor for AE, with a person carrying one of these mutations being over three times more likely to exhibit eczema. It has been suggested that eczema might protect against some forms of cancer, and a detailed systematic review of brain cancers that included 53 233 participants from eight case-control and cohort studies found that having atopic disease was associated with a 39% reduction in glioma risk, a finding that was also present for just those with AE (odds ratio 0.69, 95% CI 0.58–0.82). A further review of case-control and cohort studies failed to find any association between keeping furry pets at birth and subsequent risk of eczema, although pet fur might still exacerbate established disease. In terms of disease consequences, a review found that eczema was the commonest cause of chronic sleep loss in young people, affected the whole family. A review of four economic studies from the US found that the annual cost of AE in the States was as high as \$3.8 billion when indirect costs are included.

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A similar and more detailed review to the material published in this review appeared in the National Library for Health Skin Disorders Specialist Library's Annual Evidence Update in September 2008 (<http://www.library.nhs.uk/skin/Page.aspx?pagename=ECZEMANEW>) and explicit reference is given to that fuller version throughout. There are no copyright issues with using material from that source.

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Background

This review summarizes nine systematic reviews dealing with definitions, causes and consequences of atopic eczema (AE) that were indexed in bibliographical databases between August 2007 and August 2008 and were included in the 2008 Annual Evidence Update on Atopic Eczema from the National Library for Health Skin Disorders Specialist Library (now NHS Evidence – skin disorders). A second review summarizes the clinical implications of systematic reviews on the prevention and treatment of AE that were indexed in the same period.¹

The aim of this review is to keep the busy clinician up to date with recent high-quality evidence in the field of AE. This review is not an in-depth quality analysis of all the included systematic reviews, but a guide to clinically relevant points with the busy clinician in mind. Readers are encouraged to read the full report and original papers cited in the 2008 Annual Evidence Update (<http://www.library.nhs.uk/skin/ViewResource.aspx?resID=292501&tabID=289&catID=8310>), where omitted citations and reasons for omission are given. The full methods for the search can be found elsewhere in the methods (<http://www.library.nhs.uk/skin/Page.aspx?pagename=ECZEMAMETH>). This review comments on systematic reviews only because they are generally considered to be the most reliable evidence source, whereas the results of single randomized controlled trials (RCTs) are often contradicted by subsequent trials.² A review of the 19 systematic reviews included in the 2007 Annual Evidence Update has been published previously in this journal.³

Eczema definition and outcome measures

Diagnostic criteria are essential when describing groups of people who participate in clinical studies if sensible comparisons are to be made between studies conducted in different countries and settings. At least 10 sets of

diagnostic criteria for AE have been used in research studies, which is not helpful for promoting comparisons. The key issue is: which is best? To answer this question, Brenninkmeijer *et al.*⁴ undertook a methodologically rigorous systematic review of 27 published validation studies of various diagnostic criteria for AE. They concluded that the UK Working Party's refinement of the Hanifin and Rajka criteria⁵ had been the most extensively validated (19 studies), with a sensitivity ranging from 10% to 100% and a specificity from 89% to 99%. Despite the criteria being quoted in hundreds of scientific studies, only two validation studies of the full Hanifin and Rajka criteria had been published, and these found low specificity (ability to exclude cases that were not AE), in the range 78–94%. Most healthcare professionals will not need diagnostic criteria for AE in routine clinical practice, but they may find the simplified UK Working Party criteria (Table 1) useful for diagnosing borderline cases or when conducting clinical studies.

In addition to a good definition of study participants, it is equally important that outcome measures used in treatment studies are both valid and reliable. Schmitt *et al.*⁶ undertook a systematic review of eczema outcome measures and identified 20 named scales. They found that only three of the scales [SCORing Atopic Dermatitis (SCORAD), the Eczema Area and Severity Index (EASI) and the Patient Oriented Eczema Measure (POEM)] had been tested sufficiently and performed adequately. Just noting whether a scale has been tested does not mean that it has passed that test, and this review was unique in the way that it pre-specified what constituted 'adequate' performance. The profusion of poorly tested outcome measures for AE is a bad reflection on our scientific community. In addition to research studies, validated outcome measures can also be used in clinical practice for documenting progress of patients. At a practical level, POEM may be especially useful for measuring patient outcomes in the clinic and is available free in the public domain (<http://www.nottingham.ac.uk/dermatology/3resourcesoutcome.htm>). POEM was

Must have:

An itchy skin condition (or parental report of scratching or rubbing) in the past 12 months

Plus three or more of the following:

History of involvement of the skin creases (fronts of elbows, behind knees, fronts of ankles, around neck or around eyes)

Personal history of asthma or hay fever (or history of atopic disease in first-degree relative if child aged > 4 years)

History of generally dry skin in the past year

Onset before the age of 2 years (not used if child aged < 4 years)

Visible flexural dermatitis (including dermatitis affecting cheeks or forehead and outer areas of limbs in children aged < 4 years)

Table 1 The UK refinement of the Hanifin and Rajka diagnostic criteria for atopic dermatitis.⁴

derived from interviews with patients, and was composed of seven questions that parents could answer before they present at the clinic.

Causes of atopic eczema

As the incidence of AE⁷ and caesarean section (C-section) is increasing, Bager *et al.*⁸ performed a systematic review of 26 observational studies that evaluated the possible association between birth by C-section and subsequent risk of an allergic disease in the child. They found that C-section was associated with a 32% increased risk of food allergy, a 23% increased risk of hay fever and an 18% increased risk of asthma in the child, but not with a subsequent increased risk of AE (OR = 1.03, 95% CI 0.98–1.09).

Although there is already much evidence to suggest that people with existing atopic disease experience poorer mental health than those without, an interesting systematic review of 43 cohort studies by Chida *et al.*⁸ found robust evidence to suggest that adverse psychosocial factors in early life lead to more atopic diseases, and to more severe and persistent disease if it develops, although most of the included studies refer to asthma.

Not a month goes by nowadays without a new study on the role of filaggrin gene mutations being associated with a defective skin barrier and increased risk of AE, so it was nice to see all them all summarized together in a systematic review by Baurecht *et al.*⁹ Their meta-analysis of nine case-control and family studies found a strong and consistent association between the combined filaggrin mutations and subsequent eczema (OR = 3.58, 95% CI 2.43–5.26). Based on a pooled allele frequency for the combined genotype of around 4.1% in European populations from the case-control studies, around 10% of all eczema cases could be attributed to such mutations.

It is a popular pastime for the public and some doctors to blame a furry pet kept at home if a child develops AE, but the evidence for such an assertion is not convincing. A systematic review of cohort, case-control and cross-sectional studies by Langan *et al.*¹⁰ found no evidence to support such an increased risk. They even found some evidence to suggest a protective effect, although that protective effect was lost in the only cohort study that adjusted for avoidance behaviour (i.e., parents with atopic disease deliberately avoiding keeping a pet after the birth of a child). The authors could not find any good evidence on whether keeping a furry pet makes existing eczema worse – an important area for further research.

Consequences of atopic eczema

One possible reason why atopic disease is common is that it might confer some benefit. A previous review¹¹ indicated that AE may be associated with a decreased risk of pancreatic cancer, brain tumour and childhood leukaemia. Linos *et al.*¹² did a further, systematic review on this theme by looking at brain tumours. They reviewed eight case-control and cohort studies covering 53 223 participants and 3450 patients diagnosed with glioma, and found a strong protective effect of having an atopic condition for subsequent risk of glioma (odds ratio of 0.61 and 0.69 for AE alone), but no protective effect for developing meningioma. This high-quality systematic review provided additional evidence to suggest that publication bias was unlikely to explain the results.

Meltzer *et al.*¹³ undertook a systematic review of 19 studies that documented the prevalence, causes and consequence of sleep loss in young people with chronic illness. AE was top of the list, accounting for 15–86% of parental sleep disruption, associated with poor sleep quality, depression and anxiety.

Finally, the systematic review carried out by Mancini *et al.*¹⁴ of the socioeconomic effect of AE in the USA summarized four studies that contained good data on direct costs. They found a wide variation in estimated overall direct costs of AE in the USA, from \$364 million to \$3.8 billion per year. The large variation in estimates probably reflects the very different methods used in the various studies, and only one study measured indirect costs.

Clinical and research implications

A summary of the most important clinical 'take-home' messages from this review is given below. Collectively, this group of systematic reviews has provided evidence of the need for well-validated diagnostic criteria and outcome measures in clinical research studies, and given useful evidence on the consequences of atopic disease. The finding that eczema might be associated with a reduction in glioma is new and interesting. Filaggrin mutations and adverse psychological factors in early life increase the risk of disease, whereas being born by C-section or having furry pets around do not; information that is of great practical interest when discussing eczema in the clinic using the educational approach encouraged in the recent National Institute for Health and Clinical Excellence guidelines.¹⁵ Future research needs to explore risk factors for adult AE and factors that may be related to disease exacerbations.

Learning points

- The UK diagnostic criteria for AE (Table 1) are the most extensively validated criteria available for population studies. They may also be useful in primary care.
- Only three disease outcome measures (SCORAD, EASI and POEM) have been tested sufficiently and perform adequately. POEM may be useful for monitoring disease in routine clinical practice.
- Birth by C-section appears to be associated with an increase risk of food allergy, hay fever and asthma, but not AE.
- Adverse psychological factors early in life may increase the risk of allergic diseases. In addition, having an allergic disease in early life may lead to subsequent poorer mental health.
- Mutations in filaggrin genes are strongly associated with increased atopic eczema risk, and probably account for around 10% of cases in Europe.
- Keeping furry pets early in life does not seem to increase the risk of subsequent eczema.
- There is some evidence that atopic diseases decrease the risk of developing a glioma.
- Having a child with eczema leads to considerable family sleep loss, anxiety and depression. The direct costs associated with caring for someone with AE can be large.

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