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How should an incident case of atopic dermatitis be defined? A systematic review of primary prevention studies

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Abstract

Background—Eczema prevention is now an active area of dermatologic and allergic research. Defining an incident case is therefore a prerequisite for such as study.

Objective—We sought to examine how an incident case of atopic dermatitis was defined in previous atopic dermatitis prevention studies in order to make recommendations on a standard definition of new atopic dermatitis cases for use in future prevention trials.

Methods—We conducted a systematic review of controlled interventional atopic dermatitis prevention studies using searches of Medline and Cochrane databases from 1980 to the end of January 2011. Studies that included atopic dermatitis as a secondary outcome, such as asthma prevention trials, were included.

Results—One hundred and two (102) studies were included in the final analysis, of which 27 (26.5%) did not describe any criteria for defining an incident case of atopic dermatitis. Of the remaining 75 studies with reported disease criteria, the Hanifin-Rajka criteria were the most commonly used (28 studies). A disease definition unique to that particular study (21 studies) was the second most commonly used disease definition, although the sources for such novel definitions were not cited.

Conclusions—The results from this systematic review highlight the need for improved reporting and standardization of the definition used for an incident case in atopic dermatitis prevention studies. Most prevention studies have used disease definitions such as the Hanifin-Rajka criteria that include disease chronicity. While acceptable for cumulative incidence outcomes, inclusion of disease chronicity precludes the precise measurement of disease onset. We propose a definition based on existing scientific studies that could be used in future prospective studies.

Keywords

outcomes; atopic dermatitis; eczema; systematic review; definition; incident case; disease criteria

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INTRODUCTION

Atopic dermatitis (AD) has a world-wide distribution with a prevalence as high as 22% in developed countries.[1] In many areas of the developing world, eczema represents a growing public health problem, especially in younger populations. The development of AD increases one's risk for the development of food allergies, allergic rhinitis, and asthma as a child grows. Because of the high disease prevalence and the link with these other allergic diseases, AD prevention strategies could yield substantial public health benefits. Despite decades of research, primarily in allergen avoidance, no prevention strategy for AD has proven consistently effective.[2,3] New discoveries such as identifying genes, which predispose to the dry skin and impaired barrier associated with AD, opens up the possibility of new prevention strategies that need to be evaluated through rigorous randomized controlled prevention trials.

Research into the prevention of AD has been hampered by inconsistency in study methodology, especially with regards to methods for defining high-risk populations and disease outcomes.[4-6] Although there are well-established validated definitions for diagnosing *established* AD, there are no standardized definitions for defining an *incident case* as is needed for longitudinal birth cohort studies or interventional prevention studies.

The problem is not a straightforward one since many definitions of AD include chronicity as a diagnostic criterion – clearly unsuitable for defining an incident case. While many prevention studies measure cumulative incidence rates at one or two years, a more precise determination of the date of onset of AD is especially important when evaluating prevention strategies that may only delay the onset of disease. Identifying strategies that even delay the disease onset would still have a significant public health impact, given the high prevalence of AD and the finding that the earlier onset disease predicts a more severe disease course.[7] We sought to conduct a systematic review of how an incident case of AD has been defined in previous primary prevention studies of AD using systematic review methodology.

METHODS

Included studies

Prospective, interventional, prevention trials published after 1980, which specified AD as an outcome, were eligible. Studies whose primary outcome was not AD, such as asthma prevention trials, but included AD as a secondary outcome, were included. There were no age or language restrictions. Observational cohort studies were excluded as these studies most often use cumulative incidence as an outcome. Current validated definitions for the diagnosis of AD are suitable for the measurement of cumulative incidence with a maximum precision of one year. We aimed to investigate incident case definitions that would capture cases as they occur in a primary prevention trial enabling a time of disease onset to be determined.

Information sources

Studies were identified by searching electronic databases, scanning reference lists of articles and AD reviews, and consultation with experts in the field. The search was applied to Medline (1980-current), Cochrane (1980-current) and the last database search was run on January 5, 2011. Multiple articles were identified through hand searching, predominantly of reviews identified in search results, reviewing the literature, and from the NHS Evidence mapping exercise of systematic reviews for AD prevention.[8]

Search String

See Figure 1.

Study selection

All database search results were entered into RefWorks ("Refwork Co," U.S.), where duplicates were removed. Screening for eligibility was performed independently in a standardized manner by two reviewers (ELS and LEK) based upon titles and abstracts. Discrepancies between reviewers were resolved by consensus. Full-text articles for all studies past screening were obtained. Full-text copies of studies with seemingly eligible titles but without abstracts were automatically included and scrutinized further for eligibility. All full-text articles were assessed for eligibility by one reviewer prior to data collection. Of note, if multiple publications of a larger longitudinal trial were identified, they were counted as only one definition unless the definitions significantly differed between publications, in which case they were kept separate.

Data collection process / items

Data collection was performed by one reviewer using a data extraction database created for the study. Information extracted from each trial included the type of intervention and the AD definition used. One author (LEK) extracted the above data from the included studies and a second reviewer (ELS) double-checked all verbatim definitions that were considered to lack a true definition of AD. Disagreements were resolved by discussion between the two reviews and consultation with a third arbitrating author.

Summary measures

The primary outcome measured was the presence of any specified definition for AD.

RESULTS

Study selection

The study selection procedure is summarized in the flowchart (Figure 2). A total of 108 articles met the criteria for inclusion. Seven of these were multiple publications from the same longitudinal study, so this definition was only counted once, resulting in 102 distinct studies for inclusion in the analysis.

Greater than 80% of the included 102 studies evaluated a dietary intervention on either the mother or the infant, with infant formula as the most common AD prevention strategy used. The other interventions were non-dietary allergen avoidance, vaccination, and an emollient intervention (Figure 3).

Study result – definitions

Of those 102 studies selected for further analysis of AD definition, only 75 (73.5 %) included some form of a description of the criteria used to diagnose AD. The other 27 articles mentioned either a diagnosis made by a questionnaire that was unavailable for review (1 study), a general morphological description of eczema (4 studies), a physician or investigator diagnosis of "eczema" without further elaboration of specified criteria (20 studies), or no description at all (2 studies).

Of the 75 studies with reported disease criteria, the Hanifin-Rajka criteria were the most commonly used disease criteria in 28 studies (Table 1). Of those studies that used the Hanifin-Rajka criteria (which includes chronic or chronically relapsing dermatitis as one of its four major diagnostic criteria), only two studies specified how they dealt with the

anomaly of disease chronicity in relation to definition a new case.[9,10] The study by Laitinen and colleagues required visible eczema to be present for at least four weeks at the 6- and 12-month visits and for at least eight weeks at the 24- and 48-month visits. Arslanoglu and colleagues required "symptoms" to be present for at least four weeks to meet criteria for AD.[10]

A disease definition that was unique to that particular study (21 studies) was the second most commonly used disease definition. They did not cite a specific source and none described a scientific method or even more detailed empirical reasoning for justifying their choice of a novel definition of an incident case.

Closer examination of the 21 definitions that were unique to an individual study, most definitions included pruritus, the presence of visible eczema, and disease distribution requirements. Only 50% of these definitions had a time requirement, which ranged from requiring "chronic disease" to four weeks of eczema needing to be present (data not shown).

DISCUSSION

Main findings

This review found a large degree of variability in the methods used to define an incident case of AD in relevant prevention studies, with one quarter of studies failing to report *any* form of definition whatsoever. Of the studies reporting some form of definition of an incident case, many used a definition that was unique to that particular study, rendering comparisons between studies very difficult. Additionally, most studies used AD incident case definitions without strict time requirements. Combined, these data demonstrate an urgent need for a standardized, valid and repeatable definition of an incident case of AD in order to improve the ability to compare outcomes between studies and to allow more informative meta-analyses of prevention studies. While no previous studies have examined incident case definitions for AD, our results are consistent with the larger problem of the lack of standardized disease outcome measures in AD research. For example, Schmitt and colleagues found 20 different scoring systems for measuring the severity of AD.[11] Mancini and colleagues found 30 different definitions for defining an individual as high risk for developing AD.[4] Recently an international group called the Harmonizing Outcome Measures for Eczema (HOME) initiative began the process of creating an accepted core group of outcome measures for AD research.[12]

Problems with existing definitions

The two most commonly used validated criteria found in our review were the U.K. Working Party refinement of the Hanifin-Rajka criteria and the original Hanifin-Rajka criteria themselves. Despite the potential usefulness of these criteria in reliably identifying cases of established AD, as would be used for determining cumulative incidence over time in cohort studies,[13] they were not designed for defining an *incident case* in prospective prevention studies. By defining an incident case in prevention trials, as opposed to a cumulative incidence, incidence rates can be more accurately calculated and a more accurate date of disease onset can be established. In order to qualify as a case of AD using the Hanifin-Rajka criteria, at least three out of four of the following major criteria need to be fulfilled: 1) the presence of eczema, 2) typical distribution, 3) pruritus, and 4) a relapsing and remitting course. The definition of "relapsing and remitting" is not further defined and is left to the discretion of the investigator. The U.K. criteria state that a child must have an itchy skin condition in the past 12 months. These time requirements, while appropriate for diagnosing established cases of AD, become problematic when diagnosing new onset AD during the course of a prospective study.

Defining an incident case of AD is not simply a question of noting the first time an eczematous rash appears in an infant because previous studies have shown that many forms of transient eczematous rashes occur often in infants, even in those children who do not eventually develop true AD.[14] There is thus an urgent need for a standardized definition of an incident case of AD that offers a satisfactory trade-off between over-inclusion of transient eczematous eruptions of irritant and other etiologies and over-exclusion of genuine milder short-lived forms of AD that still represent a health care problem.

Proposed solution

Until more sophisticated validation studies can be performed, we suggest a modification of the U.K. Working Party criteria for AD, adapted for prospective observational or interventional studies. This modification specifies a time frame that the eczema must be present in order to be considered as a case of AD, and allows for a diagnosis to be made even if the rash is treated early in its course. We propose the following definition based on empirical reasoning considering the requirements of such a definition and informed by previous studies that signal the best markers of true AD.[14]

A history of an itchy skin condition which is either continuous or intermittent lasting at least four weeks plus three or more of the following:

1. A history of a rash in the skin creases (folds of elbows, behind the knees, fronts of ankles or around the neck), or on the extensor aspects of the forearms or lower legs
2. A personal history of asthma or hay fever or a history of atopic disease in a first-degree relative
3. A history of a generally dry skin since birth
4. Visible flexural dermatitis and/or visible dermatitis on the forearms or lower legs with absence of axillary involvement as defined by our online photographic protocol.[15,16]

Visual confirmation of eczema diagnosis by a clinician, dermatology nurse or a research nurse suitably trained in recognising the symptoms of eczema is recommended.

Clearly it is important to add the proviso that any infant fulfilling these criteria but who, on examination by a suitably trained health professional, are deemed to have a different skin disease, will be classified as not having eczema.

There are several benefits of our proposed definition, the strongest being that it is based on a current AD definition that has undergone extensive scientific development that has assessed validity and repeatability and applicability. The only change added to the U.K. Working Party definition is the addition of a specified time requirement of four weeks. This time requirement should exclude most transient eczematous rashes that are typically irritant in nature and usually of little medical consequence. The use of an established AD definition for incident AD which is derived from one used of prevalent AD allows for consistency in defining the public health burden of disease when assessed using different study designs. Another benefit of this proposed definition is that it does not allow a definition of AD to be made based on the presence of facial eczema alone. Halkjaer and colleagues found that 40% of children with facial eczema do not eventuate into chronic AD.[14] Finally, this definition allows for early treatment intervention during the course of a prospective study and does not require the disease to be untreated for a full four weeks if anti-inflammatory therapy is needed. Therefore, if a child develops significant eczema in the classic locations, it would be unethical to withhold treatment. Treatment can begin immediately if needed, and provided

some degree of symptoms last for a four-week period, a diagnosis of AD will still be captured using this definition.

Very mild cases of new eczema treated immediately resulting in complete clearance will not be captured by such an approach, although it is debatable how often such cases truly have AD and it is probably wiser to treat such new very mild cases with emollients alone until the disease declares itself – a situation somewhat analogous to the avoidance of labelling an infant who has one episode of wheezing as having asthma.

Other strengths of the current study include its systematic approach to the review of the literature and extensive searching of reference lists for prevention studies not found on the initial search. It is also a timely study in that there is a renewed interest in AD prevention research and prevention has become a focus for the National Eczema Association in the United States (http://www.nationaleczema.org/research/grants/, accessed 11/1/2011). It is possible that we could have missed some important studies in our searches, and we could have missed some unpublished well-developed definitions for incident cases if we had corresponded with all study authors. Our proposed AD definition is also a limitation at this stage, as it has not undergone extensive validity testing in prospective studies in the field. This limitation has to be tempered with the alternative practice to date, which has been to use unsuitable definitions or an array of poorly defined or completely undefined definitions. Our proposed definition is meant to be a starting point and we encourage those undertaking or designing new prospective studies of AD to include it along with their preferred definitions so that knowledge of its utility and validity can be built up.

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Abbreviations

AD atopic dermatitis

Clinical Implications

Our results show that atopic dermatitis is often poorly defined in primary prevention trials. A standardized incident case definition is needed that can accurately measure clinically relevant disease and establish a date of onset.

Medline

1. exp Dermatitis, Atopic/
2. exp Asthma/ep, et
3. (eczem$ or (atop$ adj3 dematit$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. 2 and 3
5. 1 or 4
6. exp Cohort Studies/
7. exp Incidence/
8. 6 and 5
9. 5 and 7
10. 8 or 9
11. exp Primary Prevention/
12. 5 and 11
13. 10 or 12
14. limit 13 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)")
15. limit 14 to yr="1980 – current "

Cochrane

1. (eczem$ or (atop$ adj3 dematit$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. (cohort$ or longitud$ or prospect$ or follow$ or incidence).mp.
3. 1 and 2
4. ((eczem$ or (atop$ adj3 dematit$)) adj7 prevent$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5. 4 or 3

Figure 1.
Search Strings for Medline and Cochrane databases

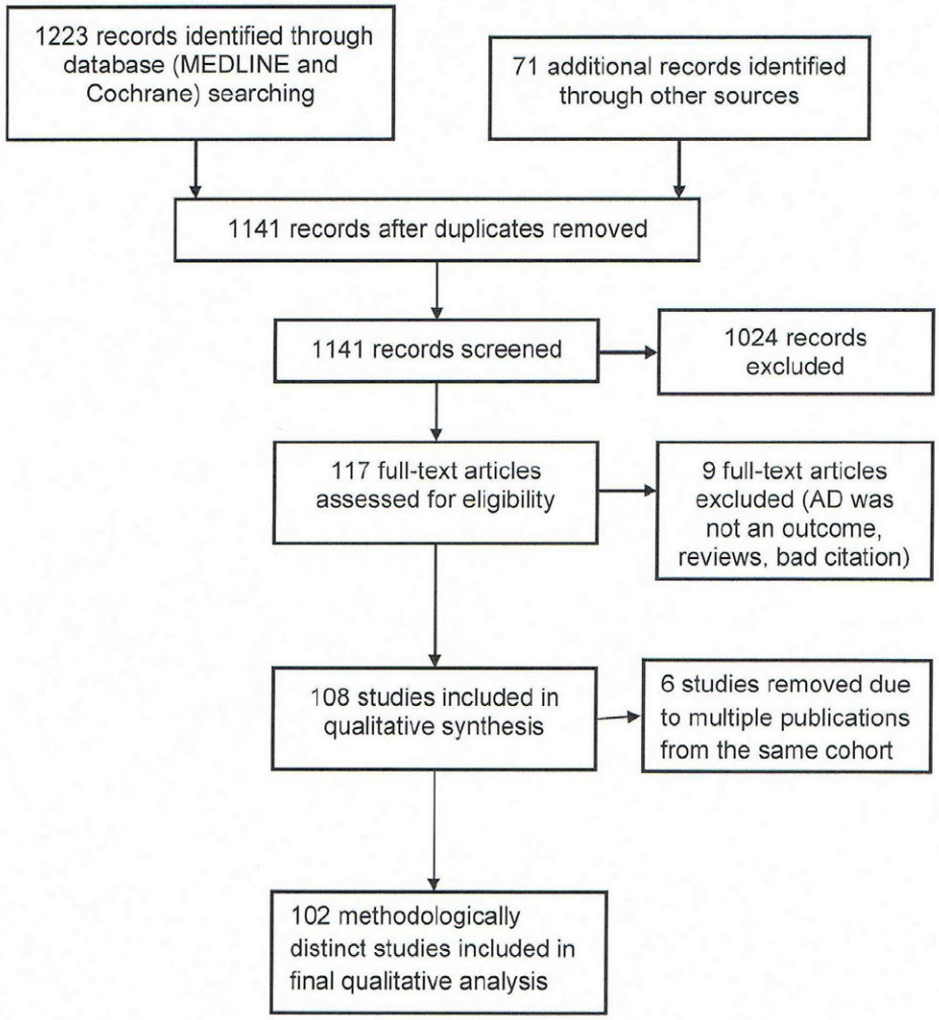

Figure 2.
Study flow chart

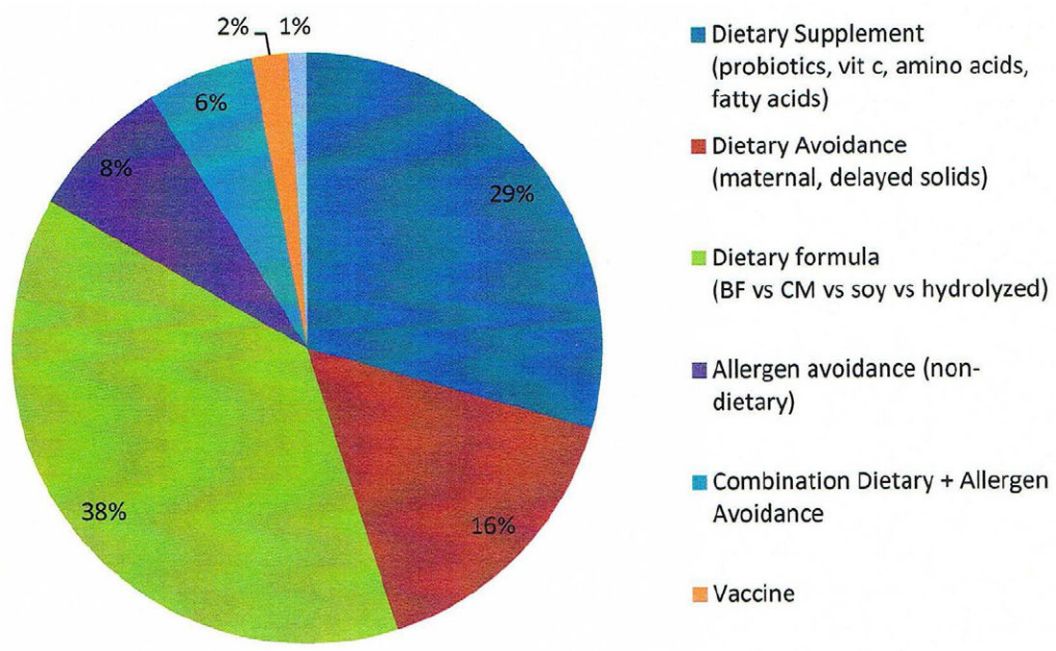

Figure 3.
Interventions

Table 1

Disease definitions cited in atopic dermatitis prevention studies

Definition	Number (n=102)	Percent of studies	Definition	Reference No.
Hanifin-Rajka	28	27%	Must have 3 or more basic features: Pruritus, Typical morphology and distribution, chronic or chronically-relapsing, personal or family history of atopy plus 3 minor criteria. See reference for full definition[17]	9,10,18-43
Unique Definition	21	21%	Variable	44-64
ISAAC	4	4%	Has your child had this itchy rash at any time in the last 12 months? 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 ankles, under the buttocks, or around the neck, ears or eyes?	65-68
U.K Working Party	7	7%	Must have: An itchy skin condition in the last 12 months Plus 3 or more of: Onset below age 2 History of flexural involvement History of generally dry skin Personal history of other atopic disease Visible flexural dermatitis as per photographic protocol *not used in children under 4 years ** in children aged under 4 years, history of atopic disease in a first degree relative may be included	69-74
Hanifin-Lobitz	5	5%	Must Have Each of the Following: **1** Pruritus **2** Typical morphology and distribution **3** Tendency toward chronic or chronically relapsing dermatitis Plus Two or More of the Following Features: **1** Personal or family history of atopic disease **2** Immediate skin test reactivity **3** White dermographism and /or delayed blanch to cholinergic agents **4** Anterior subcapsular cataracts Or Ffur or more of the following features[75]	76-80

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Definition	Number (n=102)	Percent of studies	Definition	Reference No.
Seymour	4	4%	The criteria used in selecting infants with atopic dermatitis were the presence of at least two major, or one major and one minor, feature from the following lists. **Major features.** Major features included: **1** Family history of atopic disease (asthma, seasonal rhinitis, or atopic dermatitis) **2** Evidence of pruritic dermatitis **3** Typical facial or extensor, eczematous, or lichenified dermatitis **Minor features.** Minor features included: **1** Xerosis/ichthyosis/hyperlinear palms **2** Perifollicular accentuation **3** Chronic scalp scaling **4** Periauricular fissures	81-84
Halken	4	4%	atopic eczema was diagnosed if physical examination revealed areas of scaly, erythematous, and itchy eczematous rash, primarily of the face, the scalp, and the flexural folds. Only eczema with at least two locations in typical areas relapsing with a duration of at least three months was recorded.	85-88
Moore	2	2%	Eczematous skin lesions were classified into one of four grades: 0=normal skin; 1=dry skin, cradle cap, and mild perioral erythema; 2=some or all of these features with, in addition, an area of skin, usually on the face or behind the ears, that was red, scaly, cracked, or weeping; and 3=as 2 but more extensive lesions, usually on the face, trunk, and limbs. Grades 2 and 3 were regarded as eczema, but grades 0 and 1 were not.	89,90
No Reported Definition	27	26%		91-117