A PROSPECTIVE STUDY OF THE EFFECTS OF ENVIRONMENTAL FACTORS ON ECZEMA IN CHILDREN

Sinéad Langan

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The role I have played in the research:

I had a central role at all of the stages of development of this project. First, I designed and carried out the pilot study under the guidance of my supervisors. Subsequently, I applied for a one year research fellow post in open national competition in order to allow me to move to Nottingham to apply for research funding and ethical approval for my study. Then, having successfully obtained funding, I developed and wrote the study protocol with my supervisors and collaborators. I have carried out four full systematic reviews to update knowledge relevant to this thesis and to highlight important research gaps and areas where greater clarification was required. These systematic reviews are included as part of this PhD submission, since each represents a significant research project in their own right, and are all essential building blocks for the main cohort study. I have recruited all patients (from hospital and community clinics) and carried out monthly follow up visits, including monthly downloading of data. I have visited the human genetics laboratory in Dundee to learn about analysis of saliva samples for filaggrin mutations. I have carried out all the data analysis myself, including the use of ARMA regression for correlated data and meta-analysis under the supervision of Dr Paul Silcocks with further advice from Professor Mike Campbell. My training also involved the completion of an MSc in Epidemiology by distance learning at the London School of Hygiene and Tropical Medicine between 2005 and 2007. The MSc thesis for these studies was on a separate topic and lead to a publication in the British Medical Journal (Langan BMJ 2008;337:a180).

Sinéad M Langan June 29th 2008

Supervisors:

- Professor Hywel C Williams, Professor of Dermato-epidemiology, Centre of Evidence-based dermatology, University of Nottingham
- Dr Paul Silcocks, Clinical Senior Lecturer, Trent Research and development support office, University of Nottingham

I am very grateful to both of my supervisors for their support and supervision during this study. I am particularly thankful to Professor Williams for his constant encouragement, guidance and clarity. His main role was a mentor and guide with extensive expertise in eczema research. He has taught me an enormous amount about writing papers and completing projects. Dr Silcocks main role involved close supervision and advice when I performed the statistical analyses.

Independent statistical advisor:

Professor Mike Campbell, Senior Statistician, Department of Health Services Research, ScHARR, University of Sheffield.

Collaborators:

- Professor Alan Irvine, Consultant Paediatric Dermatologist, Our Lady's Hospital for Sick children, Crumlin, Dublin 12 who involved us in a fruitful collaboration looking at gene-environment interactions relevant to the filaggrin mutations.
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Output from this work:

Published peer-review papers

- Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. Arch Dermatol 2007;143(12):1570-7.
- Schmitt J, Langan SM, Williams HC. What are the best outcome measures for atopic eczema? A systematic review. J Aller Clin Immunol 2007;120:1389-98
- What causes worsening of eczema? A systematic review. Langan SM, Williams HC. Br J Dermatol 2006 Sep;155(3):504-14
- What is meant by a "flare" in atopic dermatitis? Langan SM, Thomas K, Williams HC. Arch Dermatol 2006 Sep;142(9):1190-6
- An exploratory prospective observational study of environmental factors exacerbating atopic dermatitis in children. Langan SM, Silcocks P, Williams HC. Br J Dermatol 2006 154(5):979-980

Papers in preparation

- A prospective study of the effects of environmental factors on eczema in children. Langan SM, Silcocks P, Williams HC. In preparation for submission to the New England Journal of Medicine as an original research paper. Submitted as an abstract to the International Dermatoepidemiology Association meeting in Nottingham, September 2008.
- The performance of proposed definitions of flares, totally and well controlled weeks in an observational study of eczema in children. Langan SM, Thomas K, Williams HC. In preparation for submission as a letter to the Archives of Dermatology.

Presentations at meetings

- What constitutes a flare of atopic eczema? Langan SM, Thomas KS, Williams HC. J Invest Dermatol 2005;125(3 Suppl):A79. European Society for Dermatology Research, Tubingen, Germany.

- Should furry pets be banned for atopic eczema? Langan SM, Flohr C, Williams HC. J Invest Dermatol 2005;125(3 Suppl):A77. European Society for Dermatology Research, Tubingen, Germany.
- What causes flares of atopic eczema? Langan SM, Williams HC. J Invest Dermatol 2005;125:592. International Society for Atopic Dermatitis, Archachon, France. A longer version of this presentation was also given as an invited speaker at a Paediatric Allergy meeting, London 2007.

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List of abbreviations

FLG	Filaggrin
IGA	Investigator Global Assessment
SCORAD	SCORing Atopic Dermatitis
SASSAD	Six area, six sign atopic dermatitis (SASSAD) severity score
TIS	Three Item Severity score
GINA	Global Initiative for Asthma
PEFR	Peak Expiratory Flow Rates
TCAW	Totally Controlled Asthma Weeks
WCAW	Well Controlled Asthma Weeks
DBPCFC	Double Blind Placebo Controlled Food Challenge
IGADA	Investigators' Global Atopic Dermatitis Assessment
TCW	Totally controlled week
WCW	Well controlled week
HDM	House dust mite
SAFT	Skin application food test
RCT	Randomised controlled trial
APT	Atopy patch test
SA-EASI	Self-assessed eczema area and severity index
NESS	Nottingham eczema severity score
FSSS	Four step severity score

IGADA	Investigators' Global Atopic Dermatitis Assessment
OSAAD	Objective Severity Assessment of Atopic Dermatitis
POEM	Patient-oriented Eczema Measure
RL score	Rajka and Langeland score
SIS	Skin Intensity Score
SSS	Simple Scoring System
TBSA	Six-area Total Body Severity Assessment
WAZ-S	Atopic dermatitis severity score (in Polish)
CDLQI	Children's Dermatology Life Quality Index
Gllamm	Generalized linear latent and mixed models
ISAAC	International study of asthma and allergies in childhood
BAF	British aerobiology federation
PRO	Patient reported outcome
PDA	Personal digital assistant
SPDC	Smart patient diary card
ICE	Imputation by chained equations
ARMA	Autoregressive moving average
AIC	Akaike Information Criteria
OPT	Oral provocation test
Dp	Dermatophagoides pteronyssinus
FEV1	Forced expiratory volume in one minute

SPT	Skin prick tests

Appendices

Abstract

Background

Eczema is an important condition as it affects 20% of children in the UK and is associated with significant morbidity for children and their families. Although some progress in understanding factors associated with the occurrence of eczema has been made, very little is known about factors associated with disease worsening. Most textbooks and review articles quote long lists of exacerbating factors but with very little scientific data to support them. Before I could begin to study this topic, I first had to define a disease flare in eczema, systematically review the literature on flare factors in eczema and review available outcome measures for eczema.

Objectives

The objectives of the main study described in this thesis were to assess the role of various environmental factors on the severity of eczema in a cohort of children with eczema.

Hypotheses

1. In hot weather, the combination of heat, sweating and grass pollen precipitates increased severity in children with eczema in the UK.

2. In cold weather, the combination of cold weather, indoor aeroallergen exposure and reduced relative humidity from central heating lead to increased severity in children with eczema in the UK.

These first two hypotheses were informed by previous research which proposed "summer" and "winter" types of eczema.

3. Detergents (soap, shampoo) increase the propensity to disease flares triggered by other factors at all temperatures, but more in cold weather due to impaired skin barrier function.

4. UK children with filaggrin mutations are more prone to the effects of climatic factors such as cold and heat than individuals who are wild type for filaggrin.

5. Any combination of greater than or equal to three exposures at any time is associated with worsening of eczema. The exposures assessed included: dust, exposure to pets, shampoo, sweating, swimming, nylon clothing next to the skin and a change in mean temperature of more than 3°C from the previous weekly average.

Methods

Pilot study

30 children with moderate to severe eczema aged 0 to 15 years participated in a panel study over a one month period in June 2003 in Cork, Ireland. This study involved daily completion of a paper diary recording eczema severity and exposures. Feasibility of a panel study design was assessed and associations between exposures and disease severity were analysed.

Main study

A prospective cohort study (n=60) of children aged up to 15 years with moderate to severe eczema was studied for between six and nine months with overlapping start dates to allow study of seasonal factors. Exposures studied included: temperature, relative humidity, sun exposure, sweating, clothing, cleansing products/ washing, outdoor pollen level, extent and nature of exposure to household pets, dusty environments and swimming. Children or their parents completed daily novel electronic diaries recording eczema severity and exposures. Portable dataloggers were used to

record indoor temperature and relative humidity. External meteorological data was obtained from a local monitoring centre.

The primary outcome was a daily "bother" score and the secondary outcomes were daily "scratch" scores and flares of eczema. Autoregressive moving average models (ARMA) were used to model the impact of each exposure on eczema severity for each individual. Standard random effects meta-analysis techniques were used to pool estimated coefficients across participants. Heterogeneity of responses as detected using Chi-squared tests represented inter-individual variation. The body site-specificity of reactions was also examined as was the interaction between filaggrin mutations and disease worsening with exposures.

Findings

Pilot study

The pilot study highlighted the issue of drop outs and missing data during the study. 83% (n=25) returned the diaries at the end of the study period, and within these, recording of disease severity was good (97% complete). However, there was variability in recording of exposures (65% to 83% complete). Preliminary findings suggested a temporal association between eczema severity and heat (lag 0, i.e. the day of exposure, p=0.04), damp (lag day 2, p=0.03), sweating and stress (lag day 3, p=0.03 and p=0.02 respectively) and damp (lag day 4, p=0.001).

Main study

Primary outcome: "bother scores"

Increased disease severity was associated with direct contact with nylon clothing (pooled regression coefficient 0.23, 95% CI 0.03 to 0.43), increasing exposure to dust (pooled regression coefficient 0.53, 0.23 to 0.83), exposure to unfamiliar pets (pooled regression coefficient 0.22, 0.10 to 0.34), sweating (pooled regression coefficient 0.24, 0.09 to 0.39) and shampoo exposure (pooled regression coefficient 0.07, 0.01 to 0.13).

The association between shampoo use and worsening of eczema was enhanced in cold weather (pooled regression coefficient 0.30, 0.04 to 0.57). Body site specificity was observed for the reactions to nylon clothing, which was greater on covered sites (trunk p=0.02, limbs p=0.03), reactions to wool clothing on truncal covered sites (p=0.03) but not limbs (p=0.62), while worsening of hand eczema was associated with exposure to pets (p<0.001). The only interaction with filaggrin mutations was observed for the 2282del4 mutation and worsening of eczema in summer. Significant heterogeneity of responses between individuals was observed for exposure to grass pollen and outdoor temperature. In regard to the final hypothesis, a combination of any three of seven likely variables was associated with worsening of eczema (pooled regression coefficient 0.41, 0.20 to 0.63).

Secondary outcome: "scratch" scores

Increased disease severity was seen associated with swimming (pooled regression coefficient 0.14, 0.00 to 0.28), exposure to wool clothing (pooled regression coefficient 0.28, 0.11 to 0.45), sweating (pooled regression coefficient 0.15, 0.04 to 0.26), shampoo (pooled regression coefficient 0.07, 0.01 to 0.13), dust (pooled regression coefficient 0.36, 0.12 to 0.59) and high grass pollen levels (pooled regression coefficient 0.10, 0.01 to 0.73).

Secondary outcome: flares of eczema

Only swimming was clearly associated with worsening of eczema using this outcome measure (pooled regression coefficient 0.42, 0.05 to 0.80).

Conclusions

The following factors were shown to be associated with disease worsening in children with eczema in this UK study: clothing (wool and nylon), sweating, shampoo, swimming, dust, contact with unfamiliar pets and high grass pollen levels. Relative to the study hypotheses, the association between shampoo exposure and eczema worsening was

shown to be increased in cold weather. There was also evidence showing an association between various combinations of exposures and disease worsening. There was insufficient evidence to support the other hypotheses tested in this study but this may be explained by low prevalence of these exposures. The implications of the findings of this study for clinical practice are that for the first time, it has been shown that shampoo exposure may be associated with eczema worsening and that this is more pronounced in cold weather. This study also suggests that worsening of eczema may be more complicated in that multiple exposures acting in concert may be associated with worsening of disease. Future research with increased participant numbers is required to specifically study possible gene-environment interactions with filaggrin mutations and their relevance in relation to disease flares and to look at shampoo formulations in relation to worsening of eczema.

Introduction

Eczema affects around 20% of UK schoolchildren and can have a significant detrimental effect on the quality of life of children and their families.

The prevalence of the disease is increasing and at present it is the commonest reason for referral of a child to a dermatology clinic in the UK (Williams 1992; Williams, Stewart et al. 2008). Eczema causes significant morbidity including hospital admissions, social exclusion, missed school days, failure to thrive and sleep loss. It necessitates parental time and financial outlay for treatment. Investigators have shown costs per patient to vary between US$71 in the Netherlands and US$2,559 in Germany (Rathjen G 2000; Verboom, Hakkaart-Van et al. 2002). The constant itch of eczema results in bleeding and secondary skin infection, as well as sleepless nights for the sufferer and family members.

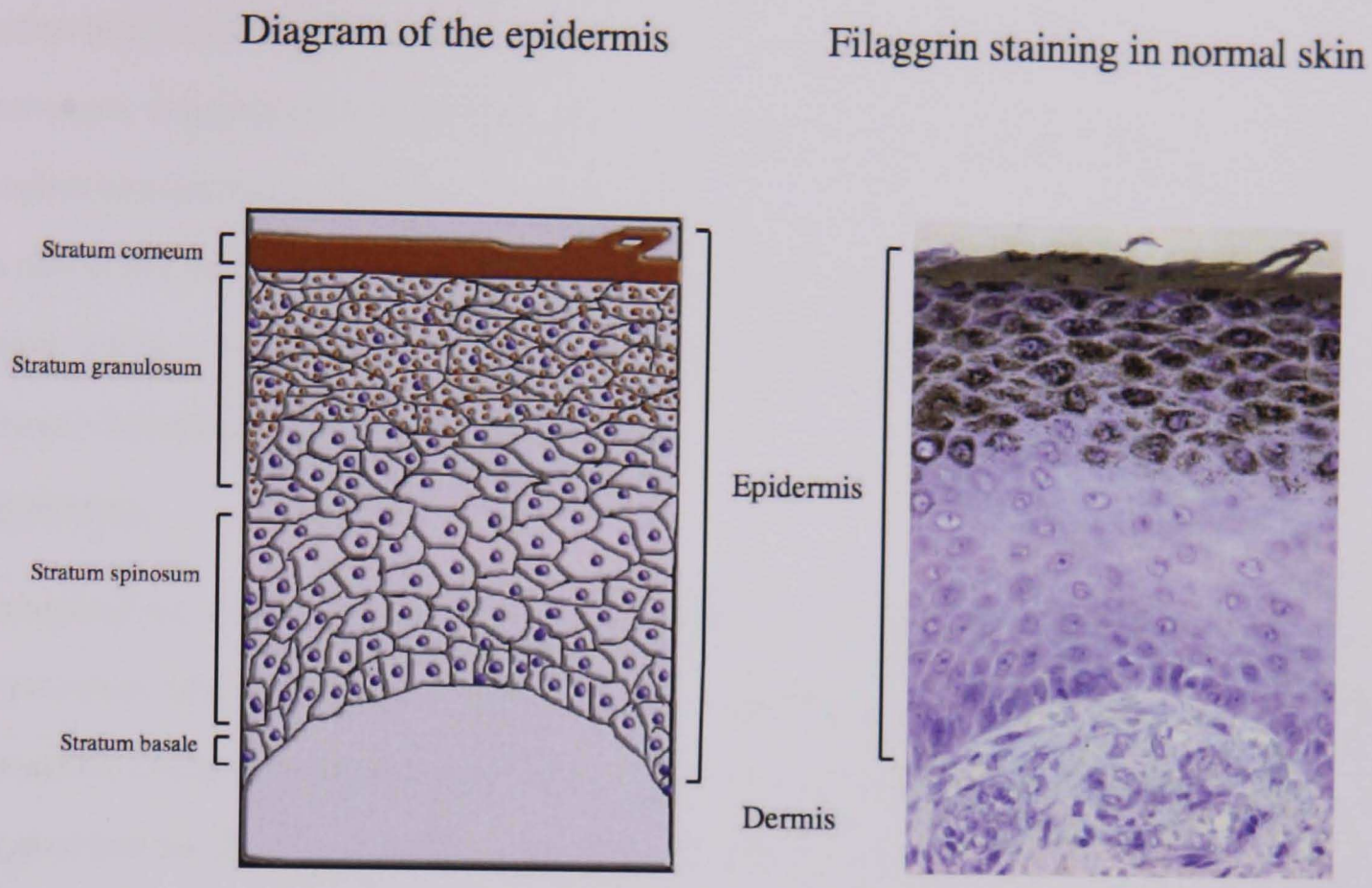
Possible exacerbating factors are one of the primary concerns of parents of children with eczema. In some cases, the cause of disease flares is obvious to parents, but most of the time it is not, leading to avoidance behavior such as restrictive diets and missed recreational activities. Yet, there is very little objective analytic scientific data to support the roles of these potential triggers in provoking flares of eczema. Analytical studies are now required to clarify the confusion and some of the myths about possible flare factors and to establish whether flare factors work in concert as in a complex disease model or independently.

Filaggrin

It is well established that eczema is a multifactorial disease with a clear genetic component. The focus of genetic research into eczema has been mainly on the immunological basis for disease. A key shift in the understanding of the genetics of eczema has been the discovery of mutations which affect skin barrier function.

Recently two null mutations in the gene (*FLG*) encoding the skin barrier protein filaggrin (filament-aggregating protein) have been shown to strongly predispose to eczema, acting in a semi-dominant genetic model (Palmer, Irvine et al. 2006; Smith, Irvine et al. 2006; Sandilands, Terron-Kwiatkowski et al. 2007). The two FLG null mutations, R501X and 2282del4 have been shown to be strongly associated with eczema, with odds ratios for risk of eczema between 3.7 and 7.1. These mutations are also highly prevalent, seen in approximately 10% of white European populations (Smith, Irvine et al. 2006). The association between filaggrin mutations and eczema have been repeatedly demonstrated in case-control and association studies (>20) from a variety of European populations and a number of other mutations have been identified, 5 of which are highly prevalent. *FLG* is located in the epidermal differentiation complex (EDC) on chromosome 1q21. Profilaggrin, a filaggrin precursor is found in the keratohyalin granules in the epidermal granular layer (Figure 0-1).

Figure 0-1 Filaggrin staining in normal human skin



Legend to figure 0-1

This figure shows intense filaggrin staining in the stratum granulosum of normal human epidermis.

Permission to use this image given by Dr Alan Irvine

Profilaggrin is cleaved producing filaggrin which allows keratinocytes to flatten by aggregating their keratin cytoskeleton and producing squames. When filaggrin is subsequently degraded, its degradation products are composed of hygroscopic amino acids. Thus filaggrin may be important in two ways: to maintain barrier function of the skin and to keep the skin moisturised. It is estimated that up to 50% of children with eczema may carry one or two mutations in the gene encoding filaggrin (Palmer, Irvine et al. 2006). Individuals carrying one null-allele for filaggrin make only 50% of the normal amount of filaggrin. Often these individuals have a mild form of ichthyosis vulgaris and are at risk for eczema. Individuals who have two null-alleles make no

filaggrin and have a more severe form of ichthyosis vulgaris and are at greater risk of eczema (Palmer, Irvine et al. 2006; Smith, Irvine et al. 2006). Recent case-control studies have also highlighted an association between *FLG* null mutations and eczema phenotype, suggesting probable associations with early onset persistent severe eczema and asthma in association with eczema.

As part of this study, the role of filaggrin mutations in the response to environmental factors will be assessed to determine if this is an important source of heterogeneity between individuals.

Terminology

Throughout this study, I will use the term, eczema (using the new World Allergy Organisation term to denote what was previously described as atopic eczema or dermatitis) (Johansson, Bieber et al. 2004). The reasons for this are that studies suggest that the majority of children with eczema, particularly in community settings, are not atopic, as defined by positive skin prick tests or serum IgE antibodies to common allergens (Flohr, Johansson et al. 2004).

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Background:

Chapter 1: What is meant by a "flare" in eczema?

1.1 Why is defining a flare an issue?

Defining a flare is clearly a key component of a thesis that seeks to establish the possible causes of flares of eczema. Eczema is a chronic relapsing and remitting disease characterised by flares or exacerbations over years. Despite this, most trials in eczema have been of short duration (4 to 6 weeks), thereby concentrating on short-term disease control (Hoare, Li Wan Po et al. 2000). More recent trials have begun to consider the issue of long-term control, with particular emphasis on the prevention of flares or relapses (Kapp, Papp et al. 2002; Wahn, Bos et al. 2002; Meurer, Fartasch et al. 2004; Papp, Staab et al. 2004; Gollnick, Kaufmann et al. 2008). This shift in focus has highlighted methodological issues regarding the definition of a flare, for which there is currently no clear guidance or agreement.

The aim of this Chapter is to systematically review the current literature relating to the definition of disease flares for eczema and other chronic intermittent diseases, and to make preliminary recommendations regarding the most appropriate definition of a flare for use in clinical research based on the literature review and experience of trying to define an eczema flare in cohort studies and clinical trials.

1.2 Materials and methods

A detailed electronic search of Medline biographic database was done in April 2005 and updated in May 2008 using the following possible search terms "flare$"; "exacerbation$"; "relaps$"; remission$; worse$ and *recurrence". The search was restricted to all prospective studies of eczema in humans; using the Cochrane search terms for eczema (Appendix 2, 1-9) and prospective studies (Hoare, Li Wan Po et al.

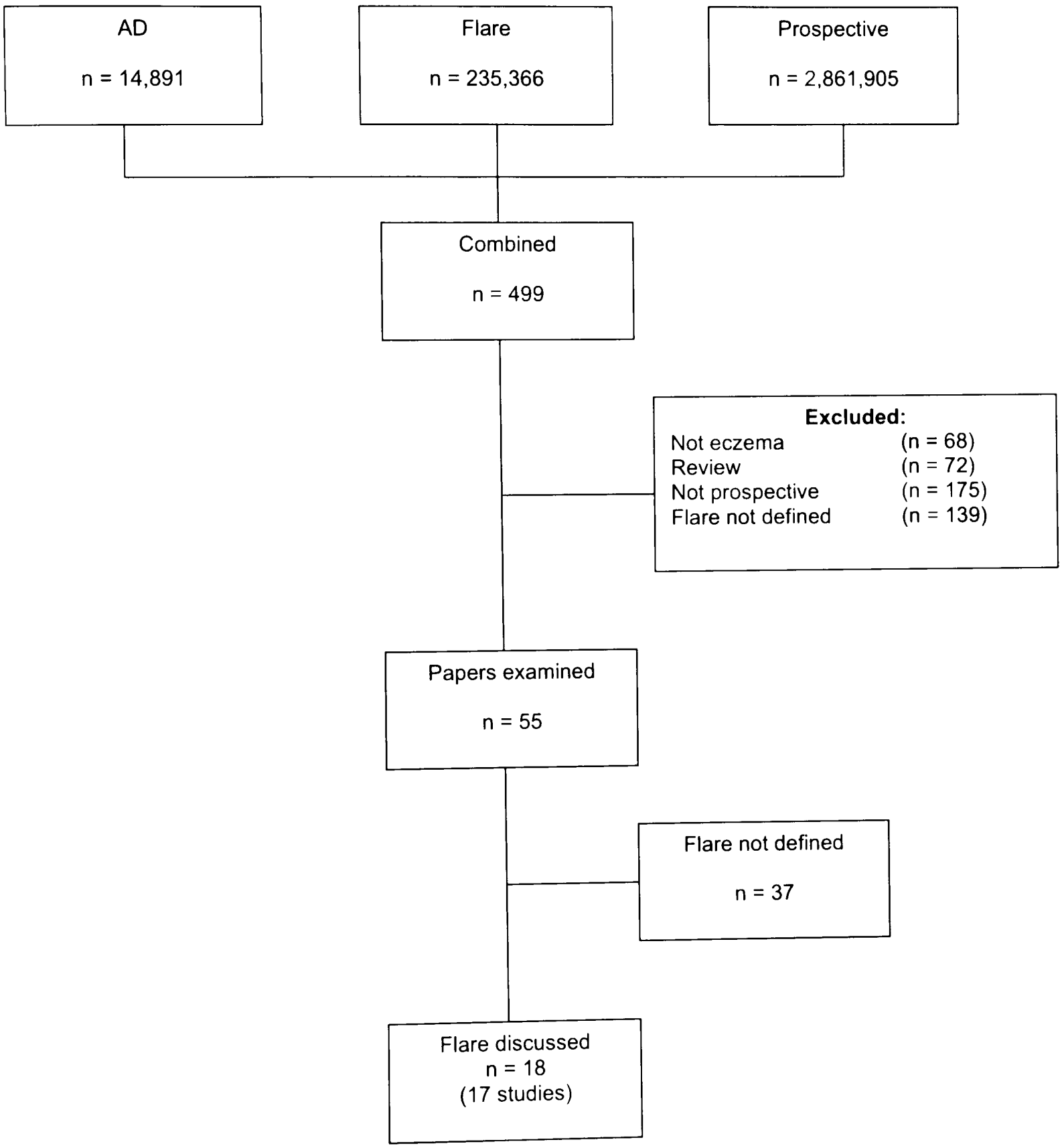
2000). This included case series, case controlled trials and randomised controlled trials. The search resulted in 499 articles and was supplemented by reference checking of articles found in the primary search. Articles not written in English were first translated. An additional search of flare definitions in other chronic relapsing diseases such as asthma and rheumatoid arthritis was conducted to explore how other specialists had tackled the problem of defining flares and relapses.

1.3 Results:

1.3.1 How other researchers have defined flares in prospective studies

The outcome of the search strategy is outlined below (Figure 1-1).

Figure 1-1 Outcome of search strategy for definitions of flares in eczema



Legend to figure 1-1

This figure shows that while 499 papers were identified by the search strategy, only 18 (17 studies) defined flares.

Most papers were either not relevant, or did not attempt to define disease flares. In total, 18 papers (17 studies) measured disease exacerbation or flare. The criteria used in defining a flare varied widely, but generally included some measure of worsening symptoms (8/17); the application of treatment (5/17); or duration of symptoms and / or treatment (7/17). All of the papers which provided a definition of disease flares were reports of clinical trials. No study was designed for the purposes of validating a definition of a disease flare in eczema. Definitions of disease flare or relapse in the 17 trials could be categorised into 3 broad themes: i) composite definitions – describing a definition which includes at least two different factors (e.g. symptoms, severity, duration or treatment) (4 trials); ii) score thresholds or changes in severity scores (9 trials) and iii) behavioural definitions, i.e. defining a flare based on an action such as recourse to additional therapy or medical consultation (4 trials). A detailed summary of the 17 studies which have defined a disease flare is given (Appendix 1) and discussed in more detail below according to the three broad categories.

Composite definition of flare:

Four articles used a composite definition of eczema flares; three of these articles derive from the same investigative group (the Multicentre Investigator Study Group) and the definitions are identical. Papp, Kapp and Wahn defined flares as an Investigator Global Assessment score (IGA) of ≥4 (range 0 to 5) requiring corticosteroid therapy to begin within 3 days of the visit (either scheduled or unscheduled and prompted by a flare) and preceded by seven days without corticosteroid use (Kapp, Papp et al. 2002; Wahn, Bos et al. 2002; Papp, Staab et al. 2004). Thomas *et al* defined relapse as a scratch score (range 1 to 5) of more than 2 for at least three consecutive days (Thomas, Armstrong et al. 2002).

Arbitrary score threshold or change in score:

Nine articles provided a definition of disease flare based on a change in disease severity. Four groups of investigators used varying levels of change in the SCORAD

score to define disease exacerbation (European Task Force 1993; Akatan N 1998; Bunikowski, Gerhold et al. 2001; Ehlers, Worm et al. 2001; Granlund, Erkko et al. 2001; Salo, Pekurinen et al. 2004). Other investigators have used the three item severity (TIS) score, the total body disease activity score, the investigator global assessment score (IGAS) and a modified Costa scoring system (Appendix 1) (Costa, Rilliet et al. 1989; Sowden, Berth-Jones et al. 1991; George, Bilsland et al. 1993; Granlund, Erkko et al. 1995; Wolkerstorfer, de Waard van der Spek et al. 1999; Hanifin, Gupta et al. 2002; Berth-Jones, Damstra et al. 2003; Siegfried, Korman et al. 2006).

Behavioural definition:

Three articles used operational definitions of relapse based solely on behavioural responses. The CASM-DE-01 study group defined relapse in their three papers as a period of at least three consecutive days during which moderately potent topical corticosteroid application was considered necessary (a named corticosteroid was selected for use in each participating country). In this group's second paper in 2004, they specified that the corticosteroids must be considered necessary by the investigator in their definition of flare, a point that was not clear in the 2002 paper (Meurer, Folster-Holst et al. 2002; Meurer, Fartasch et al. 2004; Gollnick, Kaufmann et al. 2008). Zaki *et al* stated that the need to use potent topical steroids, or further systemic treatment constituted a relapse (Zaki, Emerson et al. 1996).

1.3.2 Lessons from other chronic diseases

The need to define flares and what constitutes disease control within the context of clinical research has been faced by those researching other chronically relapsing diseases. In some cases, consensus agreement had been achieved. For example, the Global Initiative for Asthma / National Institutes of Health guidelines have been adopted as a suitable definition of disease control for use in clinical trials of asthma (1997; (GINA) 1998). Similarly, the American College of Rheumatology has issued guidelines

on the definition of disease improvement for use in trials of rheumatoid arthritis (Felson, Anderson et al. 1995).

In asthma, the definitions include totally and well controlled asthma weeks (TCAW and WCAW); based on symptoms, use of treatment and peak expiratory flow rate (PEFR), emergency room visits or medication related adverse events over a one week period (1997; (GINA) 1998; Bateman, Boushey et al. 2004) . Exacerbations are defined as deterioration in asthma requiring treatment with an oral corticosteroid, an emergency room visit, or hospitalisation. If the patient needs to use oral corticosteroid treatment for >10 consecutive days, the eleventh day is considered to be a second exacerbation (Aalbers, Backer et al. 2004). Thus, the definition of control incorporates duration, symptoms, medication use, peak expiratory flow rates (PEFR) and need for further treatment. For investigators the options include using single composite measures such as TCAW and WACW or multiple outcome measures, such as PEFR and medication use. Both options have advantages and disadvantages, the former being simpler to analyse but at the cost of possible loss of statistical power.

In rheumatoid arthritis, the American College of Rheumatology (ARC) and other groups have formulated well established definitions of remission (Pinals, Masi et al. 1981; Scott, Spector et al. 1989; Prevoo, van 't Hof et al. 1995; Eberhardt and Fex 1998; Makinen, Kautiainen et al. 2005). The concept of a "flare" of rheumatoid arthritis does not appear to have been agreed as a consensus; the focus in research being mainly on levels of disease activity. The definition of exacerbation or relapse in relation to rheumatoid arthritis as used in trials is usually based on a cut off on an arbitrary remission score, but in some studies descriptive terminology has been used (Yazici, Erkan et al. 2002; Verstappen, van Albada-Kuipers et al. 2005). In relation to multiple sclerosis, investigators have studied the concept of flares and a definition coined by Schumacher *et al* is widely used (Schumacher GA 1965; Panitch, Goodin et al. 2002; Schwid, Thorpe et al. 2005). This definition of relapse incorporates symptoms, signs

and duration. Some investigators have added arbitrary cut offs on disability scales to this definition in an effort to incorporate an objective scoring system and improve the clarity of the definition (Kurtzke 1983; 1998; Barbero, Verdun et al. 2004).

1.4 Discussion

1.4.1 Strengths and limitations of different approaches to defining flares

Composite definitions:

Composite scales have emerged in the literature recently. Their main advantage is the use of a multi-dimensional scale incorporating several factors, such as duration, symptoms, signs and/or treatment. However, their increased complexity can lead to difficulties in interpretation, classification and high proportions of missing data.

To illustrate some practical difficulties of using composite scales, data from previous research has been used (Thomas, Armstrong et al. 2002). An exacerbation of disease (relapse) was defined as a daily itch score of >2 for 3 consecutive days (Figure 1-2).

Figure 1-2a Schematic representation of typical pattern of eczema relapse and remission (relapse defined as 3 consecutive days with a scratch score of >2)

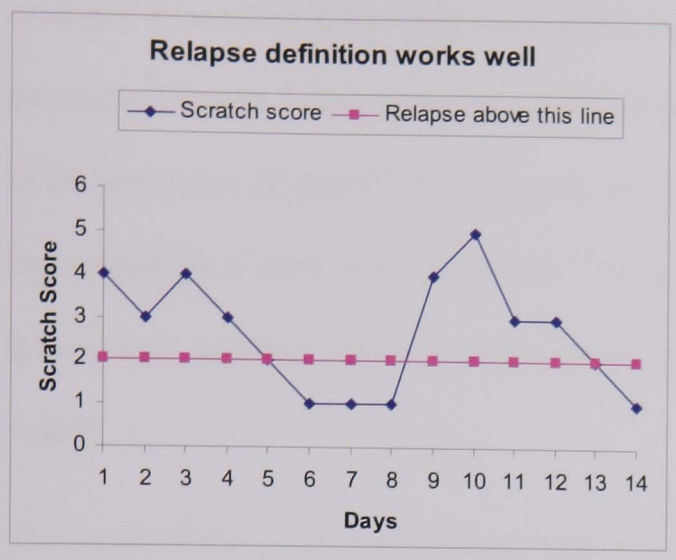


Figure 1-2b Typical problem of brief unsustained remissions- is this one or two relapses?

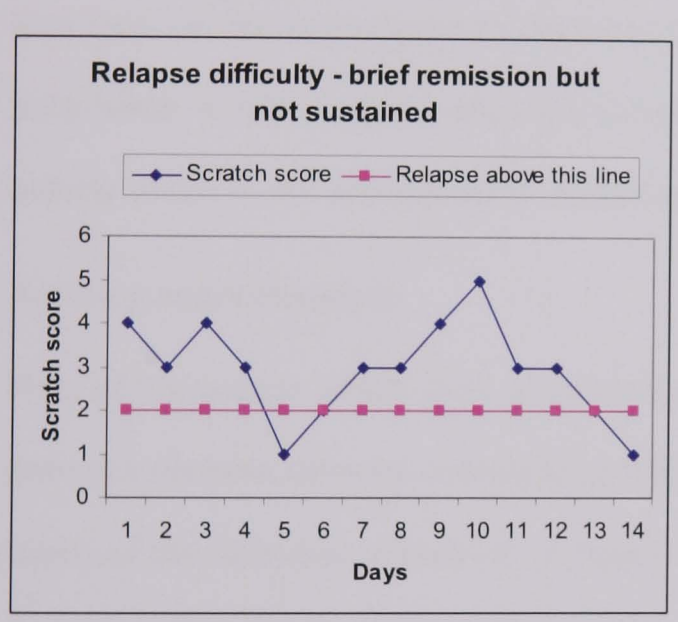
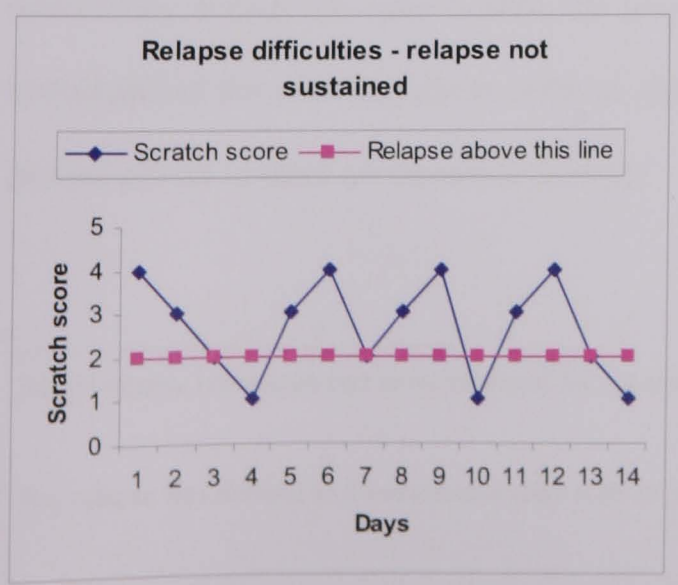


Figure 1-2c Typical problem of constant exacerbations but never for three consecutive days yet this would not fit the definition of relapse



This definition generally worked well as illustrated in Figure 1-2a. However, during data analysis it became clear that rules were required for occasional cases. A further example (Figure 1-2b) illustrates a situation where a lengthy relapse was broken by a brief remission (2 days)[1]. Should this be classed as a single relapse, or two relapses separated by a period of remission[1]? Similarly, if there is high disease activity throughout, but this never persists for three consecutive days, is this a relapse? (Figure 1-2c)[2].

The application of topical therapy was not required to define a flare in this study. Some participants recorded raised itch scores but did not use treatment. The opposite was also true, i.e. some participants documented low scores but used active treatment on a daily basis. In other words, does the behaviour represent habit or genuine disease activity which is not articulated in questionnaires or interview?

Arbitrary score threshold

Most of the papers which used an arbitrary threshold to define a relapse used the patient's disease severity compared to baseline. The advantage of this system is the clarity of the definition. However, in reality the baseline in a relapsing disease such as eczema will fluctuate. If the patient's disease is severe at baseline, they are unlikely to experience the percentage increase in score necessary for a relapse, due to a "ceiling effect". A further assumption is that baseline represents 'normal' or 'stable disease', which may not be the case unless the patient's disease is deliberately stabilised prior to enrolment in the trial. Inclusion criteria, study population and the use of a washout period will all impact on baseline scores.

---

[1] Single relapse (remission had to be sustained for at least 3 days for it to signify the end of a flare).

[2] No, relapse was defined as 3 consecutive days with an itch score >2 (1-5).

A further important issue with definitions of disease flare based on arbitrary score definitions is that it involves little or no input from the patient. Whilst SCORAD does incorporate patient symptoms (itch and sleep loss), some of the other scoring systems, such as TIS and SASSAD, rely entirely on signs (Berth-Jones 1996; Wolkerstorfer, de Waard van der Spek et al. 1999). For a concept such as disease flare, the patient may be best placed to judge whether or not his/her disease is well controlled.

Behavioural definition

A definition of disease flare based on a behavioural response to disease activity includes actions such as applying a potent topical corticosteroid or a visit to a health-care professional appears attractive. Such a definition incorporates the patient's reaction to the status of their skin and may be less subjective than concepts such as reporting itch in a questionnaire. However, the decision to treat is governed by many more factors than simple disease activity. Habit often plays a large part, as does anxiety, parental instructions, personality and treatment expectation. The side effects of topical corticosteroids are a particular concern for eczema patients, which means that those patients who are worried about using topical corticosteroids (or their carers in the case of children), may choose not to treat, despite increased disease activity (Charman and Williams 2003).

1.5 Recommendations

This review highlights the lack of consensus on how to definite flares and capture long-term control in eczema. In relation to this particular thesis, it has lead to the proposal of novel definitions of what constitutes a flare in eczema which can be used as an outcome measure for the formal cohort study. It has also lead to the proposal of definitions of totally and well controlled eczema weeks, the usefulness can be compared against other measures of disease control in the formal study.

Definition of flare

A "flare" of eczema is defined as an episode requiring escalation of treatment or additional medical advice. This should be pre-defined by investigators at the outset of a study. For instance, in a study of participants with mild eczema, escalation to the use of topical corticosteroids might constitute a "flare", in studies of moderate or severe eczema, the need to use potent or super-potent topical steroids or to attend a primary care physician or dermatologist for disease worsening might be more appropriate. It is not possible to develop an entirely standardised definition for "flare" as the true meaning is in relation to the individual patient and his/her perception of disease worsening above baseline. This definition will require validation in clinical trials.

Totally and well controlled weeks (TCW and WCW)

As a disease model, asthma has many similarities with eczema and the work of the Global Initiatives for Asthma / National Institutes of Health guidelines provides a useful model to follow. The concepts of totally controlled weeks (TCW) and well controlled weeks (WCW) should be considered for adoption in eczema research and some simple definitions have been outlined (Figure 1-3).

Figure 1-3 Summary of recommendations for totally controlled and well controlled weeks

Totally controlled week (TCW)

Rescue treatment not required *

Plus

Zero days with symptoms** above a pre-specified level ***

Well controlled week (WCW)

Rescue treatment used for ≤2 days *

Plus

≤2 days with symptoms** above a pre-specified level***

*Rescue treatment is defined as any additional treatment which has been specified in the study protocol to deal with disease deterioration. Standard co-treatment such as emollients can be allowed if specified in the treatment protocol. In some study designs, study treatment is used as an "as required" treatment in response to disease worsening and therefore study treatment could be considered as rescue treatment.

** Valid symptom assessment tools include either:

i) Patient global assessment, or ii) Self reported itch/scratch

***Pre-specified symptom level:

5-point Likert scale (0-4)	>1
VAS (0-10cm)	>4

These definitions provide an intuitive means of assessing long-term disease control and are appropriate for use in a variety of clinical trial settings, as well as for epidemiological research.

Using these definitions, a TCW is one in which no rescue treatment has been applied and in which symptoms are well controlled every day. Rescue treatment is defined as any treatment (other than emollient) which is applied in response to a worsening of the disease. Within the confines of a clinical trial, this would usually be "rescue treatment" as defined by the study protocol, but could also be the study treatment itself if it is applied in response to changes in disease activity.

A WCW is one in which treatment has been applied for a period of ≤2 days and symptoms are controlled most of the time. These definitions are based on assessments over consecutive seven day periods.

Choosing treatment, symptoms and duration as the components of these definitions, rather than signs, is pragmatically chosen to suit clinical research where daily or weekly patient review is often impractical.

Potential limitations

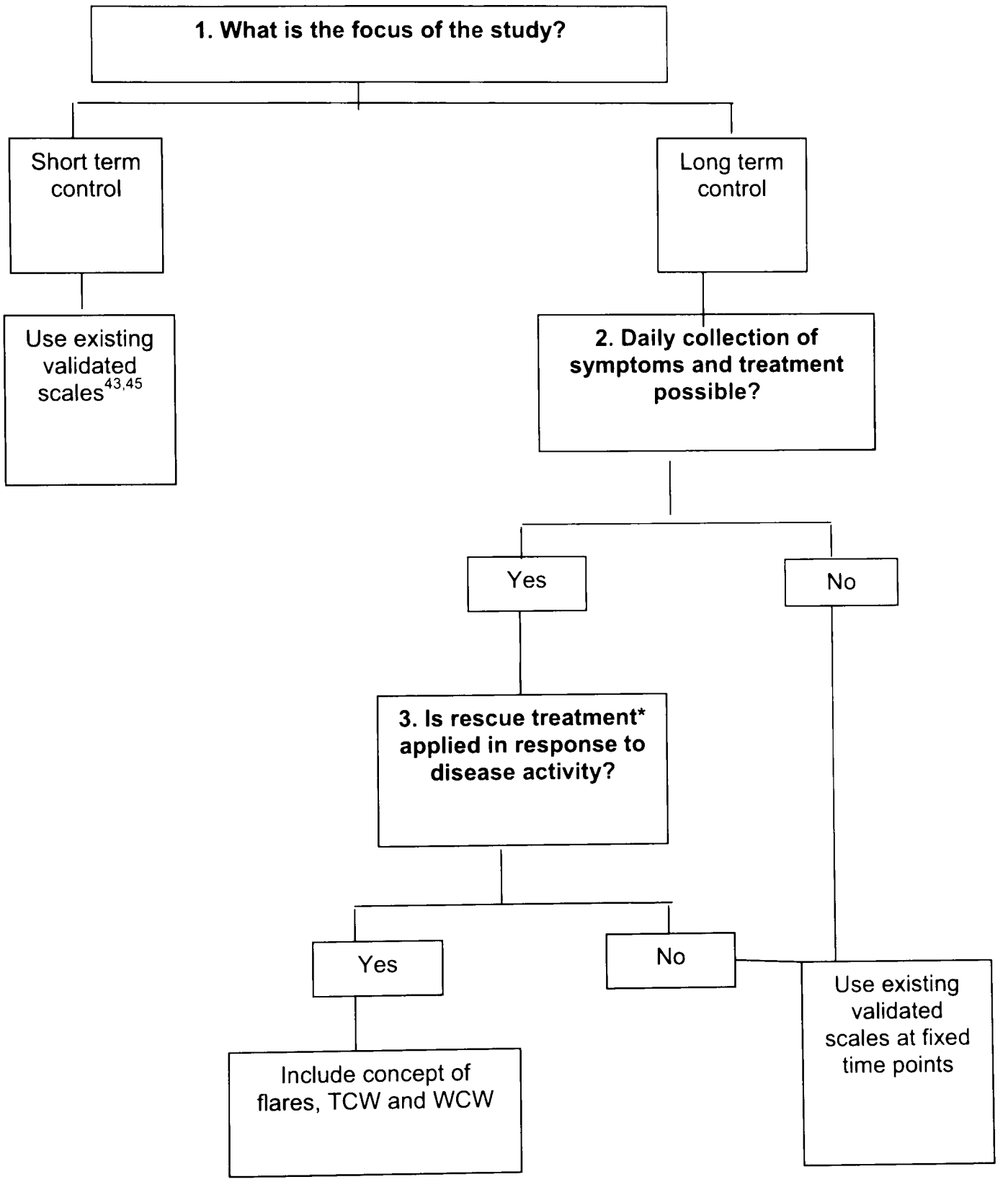
This is a retrospective review of studies which were not primarily devised to define flares of eczema. These recommendations will therefore require validation in clinical studies of eczema.

Factors to consider when choosing this outcome measure for use in a clinical trial

In relation to this study, it was decided to use flares as a secondary outcome measure as it captures meaningful outcomes that are understood by patients and clinicians. This measure was not used a primary outcome as it has not been validated and there were some concerns that it might not be sufficiently sensitive and might be associated with a loss of statistical power. It was also decided to assess the performance of totally and

well controlled weeks against monthly measures of severity. Using the latter measures as an outcome would have been inappropriate in this study where the focus is on short term disease flares. In order to inform this decision process, a possible decision pathway has been outlined. (**Figure 1-4**)

Figure 1-4 Decision process for choosing appropriate outcome measures in clinical trials



*Or study treatment if applied "as required" in response to disease activity. TCW= totally controlled week, WCW= well controlled week

Legend to figure 1-4

This figure provides guidelines for when it might be appropriate to incorporate definitions of flares, TCW and WCW in clinical research.

The use of a single categorical variable may lead to a loss of power; this needs to be weighed against the inherent simplicity of the measure. For the purposes of this thesis, this issue led to the use of this measure as a secondary, not a primary outcome.

Chapter 2: What causes flares in eczema?

2.1 Introduction

Having defined what is meant by a "flare" in eczema, I performed a systematic review of the literature to identify what evidence there is to support the roles of commonly blamed "flare factors" in eczema. This area needed more examination in order to inform the best exposure measures for use in this study and to confirm the suspected research gap this study was designed to counter.

2.2 What causes flares in eczema? A systematic review of the literature

2.2.1 Background

"Flare factors" for eczema are frequently quoted in anecdotal lists and accepted as "facts" (Dahl 1990). However little scientific evidence is available to support the role of many of these factors as causes of disease exacerbations. As discussed in *Chapter* 1, several definitions of what constitutes a flare in eczema exist, predominantly for use in clinical trials. Most incorporate a combination of an increase in the severity of symptoms and/ or signs over a period of time requiring medical intervention. The ideal means by which the role of a "flare factor" in causing a flare of disease is established is to demonstrate a temporal relationship between exposure and disease worsening, a dose-response effect and, ideally, remission of the flare following withdrawal of the relevant factor.

Cross-sectional studies and case series have assessed patients' beliefs regarding factors causing disease exacerbations. The list of beliefs is surprisingly uniform worldwide. Factors such as sweating, heat, sunlight, wool fabrics, grass intolerance, dust, stress, seasonality, holidays and hormonal influences are quoted as causing worsening in series from the UK, Germany, Finland, Japan and Nigeria, despite

cultural, climatic and racial variation (Schudel and Wuthrich 1985; Kemmett and Tidman 1991; Lammintausta, Kalimo et al. 1991; Turner, Devlin et al. 1991; Kissling and Wuthrich 1993; Katayama, Taniguchi et al. 1997; Tay, Khoo et al. 1999; Mattila, Kilpelainen et al. 2003; Nnoruka 2004; Williams, Burr et al. 2004). Such questionnaire studies suffer from the major potential for response bias. Cross-sectional studies are also unable to distinguish the temporal relationship between a factor and subsequent flare. Randomised controlled trials, e.g. of reduction of house dust mite (HDM) around the house, can imply that factors such as HDM may generally have something to do with overall eczema activity in groups of individuals, however, they rarely provide enough direct data to evaluate the relationship between specific factors and disease flares in individuals (Friedmann 1999). There is also an issue of whether studies of exposure reduction actually succeed in reducing exposure. I have therefore not included HDM reduction studies in this review as demonstrating improvement on HDM reduction does not confirm worsening on exposure. In relation to ultraviolet radiation, while this is proposed as a possible "flare factor", natural sunlight can improve eczema and ultraviolet radiation is also used in the treatment of severe eczema (Green, Diffey et al. 1992). The focus of this review is therefore not on therapeutic trials of withdrawal of exposures but on prospective observational and experimental studies such as double-blind provocation studies since these are best placed to answer questions about what contributes to flares in eczema.

2.2.2 Materials and methods

A systematic review of the literature was carried out using Medline between 1950 and May 25th 2008 to address the following question: What causes flares of eczema?

Criteria for study inclusion

Type of study

A range of study types was included and ranked according to potential to minimise bias. Included studies were restricted to provocation and observational studies that evaluated worsening of disease after exposure to a potential flare factor. As discussed, studies looking at the impact of removing a potential provocation factor such as HDM were not included in this review as disease improvement on withdrawal of an exposure does not confirm worsening on exposure. Experimental or provocation studies were restricted to those with a prospective double blind design due to the high degree of potential information bias associated with open studies. Randomised controlled trials were included if they involved a provocation. Open or unblinded studies were excluded.

Types of participants

Only studies involving participants with eczema as defined by a physician were included (Johansson, Bieber et al. 2004). Studies concerning all age groups were assessed.

Types of outcome measures

The main outcome measures were worsening of disease, if relevant using severity scoring systems, for instance the SCORAD (European Task Force 1993). Studies which did not assess the impact of a challenge or provocation on the severity of eczema were excluded.

Search terms

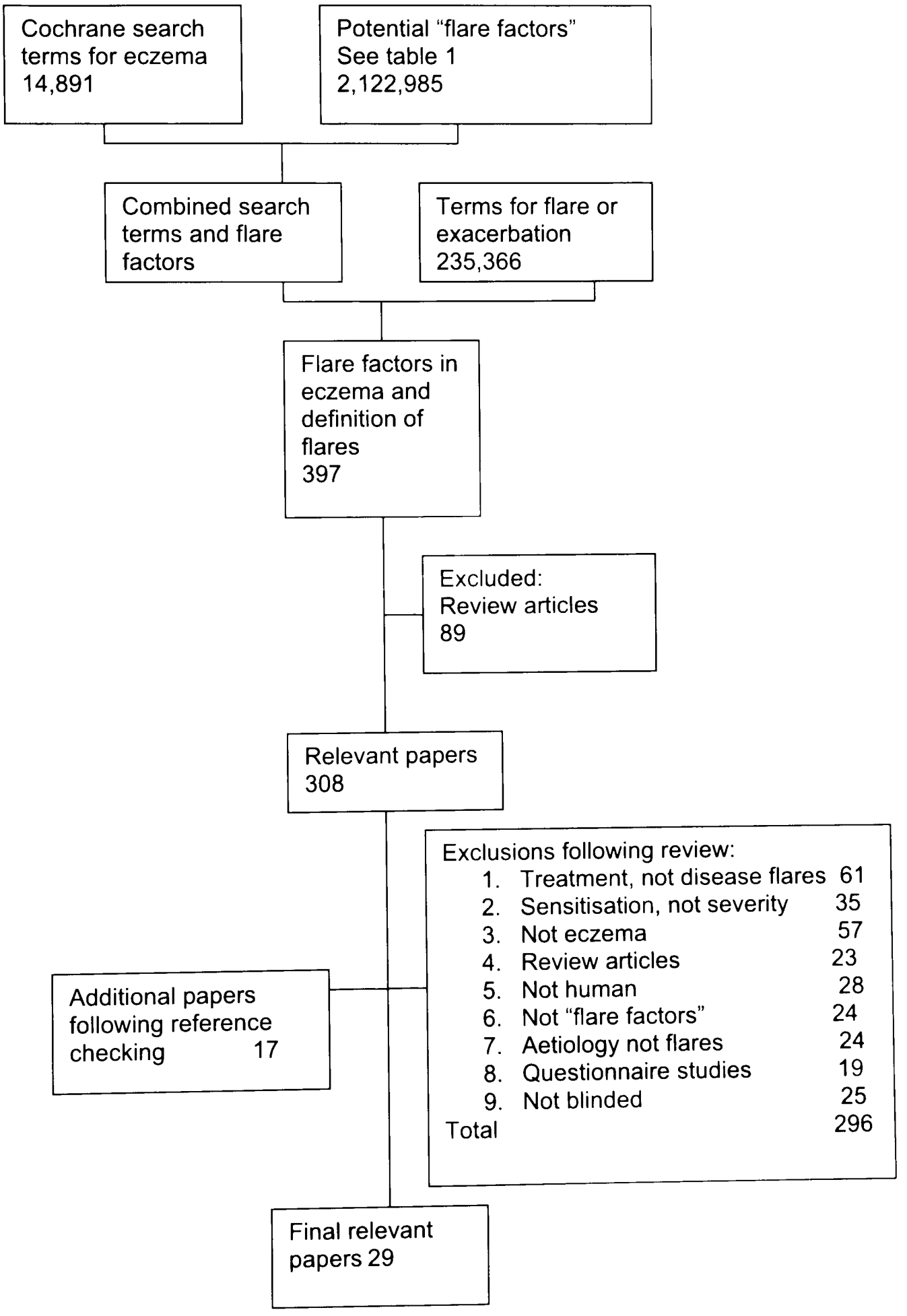
The Cochrane Skin Group search strategy for eczema was used and combined with search terms for potential flare factors and disease exacerbations (Appendix 2) (Hoare, Li Wan Po et al. 2000). The online search was supplemented by an extensive hand search of the literature identified from retrieved articles and by

contact with experts in the field. Searching was not restricted by language and where required, translation and/or interpretation services were used.

2.2.3 Results

The Medline search identified 29 relevant studies (Figure 2-1).

Figure 2-1 Outcome of search strategy for flare factors in eczema



Meta-analysis was not considered appropriate due to the heterogeneity between studies in terms of study population, design, duration and outcomes. The summary assessment was therefore qualitative and results are presented in tabular form by factor studied.

The results of studies of various "flare factors" are discussed in detail in Appendix 3. Briefly, thirteen studies assessed the role of foodstuffs in causing eczema flares. Of these, eleven studies were double blind placebo controlled food challenges performed after exclusion diets of possible foods associated with worsening of eczema. In these studies, skin status is assessed before, during and after exposure to either food or placebo given in a double blind placebo controlled fashion. In most of these studies, an elimination diet is given prior to the double blind placebo controlled food challenge (DBPCFC) and in some of the studies the double-blinded challenge is only given to those who improve following the elimination diet. Seven studies were carried out on participants with severe eczema and none incorporated a control group (Sampson and McCaskill 1985; Pike, Carter et al. 1989; Van Bever, Docx et al. 1989; Devlin and David 1992; Vieluf, Wieben et al. 1999; Worm, Ehlers et al. 2000; Breuer, Wulf et al. 2004). Nine studies included children only; the other studies involving either only adults or a mixture of age groups. Only three studies did not show a relationship between the exposure (sugar, tartrazine and various foodstuffs) and skin reactions although in most instances it was not clear if this was worsening of eczema (Pike, Carter et al. 1989; Devlin and David 1992; Ehlers, Worm et al. 2001). The two studies which were not DBPCFCs used a method called the skin application food test (SAFT) whereby the possible "flare foodstuff" was applied to the forearm under experimental conditions to determine if it was associated with the development of eczema at the site (Oranje, Aarsen et al. 1992; Oranje, van Toorenenbergen et al. 1992).

Three studies assessed the role of dust mite, two using topical and one an inhalant approach (Norris, Schofield et al. 1988; Tupker, De Monchy et al. 1996; Shah, Hales et al. 2002). Only one of these studies had a control group (Norris, Schofield et al. 1988). All three showed a worsening of eczema in at least 30% of participants. Two small studies looked at other aeroallergens using the atopy patch tests; the results of these studies are difficult to interpret (Wananukul, Huiprasert et al. 1993) (Bygum, Mortz et al. 2003). Briefly patch tests involve the application of potential allergens to the skin for a 48 hour period followed by examination of the skin at 96 hours to look for evidence of a delayed hypersensitivity reaction in the form of eczema at the site of application.

Two studies looked at the effects of seasonal and climatic factors on eczema (Vocks, Busch et al. 2001; Kramer, Weidinger et al. 2005). The more recent study by Kramer *et al* was a prospective panel study of 39 children where daily observation of skin status was correlated with environmental and seasonal factors to determine if there was an association (Kramer, Weidinger et al. 2005). This study proposed that there are winter and summer types of eczema where the former flare in cold weather while the latter flare in hot weather with high grass pollen levels.

2.2.4 Discussion

Eczema is a chronic disease with a relapsing and remitting course and, due to frequent and unexplained fluctuations in disease severity, it is difficult to assess the roles of potential trigger factors scientifically. This systematic review has focussed on the evidence to support or refute the roles of commonly quoted "flare factors" on eczema.

Strengths and limitations of this study

This systematic review has critically appraised the evidence on the basis of study design and quality and has included non- English language papers. However, some

relevant papers may have been missed despite a comprehensive search strategy as the data may be concealed within other studies, especially those with a primary focus on asthma or allergy. Another major limitation is that while the main interest of the study is the clarification of evidence for the causes of clinically relevant flares, the included studies focus on disease worsening which is not an equivalent concept (Langan, Thomas et al. 2006). Few if any of the studies have sufficient statistical power to establish definitive conclusions; no author has directly addressed this issue.

Implications for this thesis

Food Food allergy may be important in a subgroup of children with eczema, e.g. those with severe recalcitrant disease with a high suspicion of food allergy. Two caveats need to be mentioned. The first is that the clinical relevance of small changes in severity score is sometimes difficult to interpret. Second, nearly all of the studies have been undertaken on people with severe eczema in a hospital setting, thereby limiting the generalisations to people with milder disease in the community. Many RCTs have assessed the impact of food exclusion in eczema; the level of proof provided by this type of study is not direct evidence of causation since an improvement on removal of an exposure is not the same as flaring following exposure.

House dust mite and aeroallergens The three provocation studies suggest an association between exposure and flares; this evidence is somewhat supported by the patch test studies (Norris, Schofield et al. 1988; Wananukul, Huiprasert et al. 1993; Tupker, De Monchy et al. 1996; Shah, Hales et al. 2002; Bygum, Mortz et al. 2003). Other supportive indirect evidence is derived from atopy patch test (APT) studies, some of which show a correlation between positive test results and eczema in an air-exposed pattern; this association has not been confirmed in other similar studies (Darsow, Vieluf et al. 1996; Bygum, Mortz et al. 2003; Darsow, Laifaoui et al. 2004). These provocation studies may not equate to real life exposure to house dust

mite. A patient's history of flares on exposure to dust mite, which is used as a gold standard in APT studies, may not be a good indicator of the relevance of a factor, particularly if there is a lag period between exposure and reaction and/ or the presence of confounders.

A number of investigators have studied the impact of house dust mite reduction measures in eczema and on the basis of three blinded RCTs, they concluded that there was some evidence that HDM reduction measures might be of benefit in eczema (Hoare, Li Wan Po et al. 2000). Four subsequent double-blind placebo controlled studies have addressed this issue with mixed results (Gutgesell, Heise et al. 2001; Oosting, de Bruin-Weller et al. 2002).

Effects of irritants No study addressing this factor fulfilled the pre-determined criteria for this review, as investigators did not actually study the impact of irritants on severity of eczema. This does not mean that irritants are not an important cause of eczema flares as suggested by clinical anecdotal experience, but simply that the impact of irritants on eczema have not been studied sufficiently using appropriate study designs (Tupker, Coenraads et al. 1995; Seki, Morimatsu et al. 2003).

Seasonality In the study by Kramer *et al*, post hoc analysis was the basis for conclusions regarding seasonality; this seasonality needs to be confirmed in new datasets designed to test an *a priori* hypothesis (Kramer, Weidinger et al. 2005). In the study by Volks *et al*, inferences drawn at a group level cannot be interpreted to be relevant at an individual level (ecologic fallacy) (Vocks, Busch et al. 2001). Some other issues related to this particular study were the selection of a group of inpatients (thereby reducing generalisations of findings) and the frequent population changes within the group. Thus both studies do not allow conclusions to be drawn regarding the impact on individual patients.

Detergents and textiles The studies do not support advocating the use of cotton clothing and enzyme-free detergents to all parents of children with eczema, in the absence of a definite history of worsening following exposure to textiles or detergents (Diepgen, Stabler et al. 1990; Diepgen TJ 1995).

Stress The two case series identified in the review correlated stress, but not life events, with severity of eczema (Gil, Keefe et al. 1987; King and Wilson 1991). Indirect evidence from other types of studies adds weight to this association. Kimata *et al* has studied the impact of road traffic (n=26), video games (n=25) and ringing mobile telephones (n=27) on wheal responses and neuropeptides in eczema (not eczema severity) in two provocation case-control studies. In all three groups, increased wheal responses, substance P, vasoactive intestinal peptide and nerve growth factor was increased in the eczema group but not in controls (Kimata 2003; Kimata 2004).

Ultraviolet radiation The clinical relevance to unselected patients with eczema is not clear (Deguchi, Danno et al. 2002).

Infections Other indirect evidence supporting the importance of bacterial infections is the correlation between the presence of staphylococcal enterotoxin-specific IgE antibodies (SEA and/ or SEB) and severity of eczema. This association has been tested in cross-sectional studies only and not in prospective cohort studies (Bunikowski, Mielke et al. 1999; Breuer, Wittmann et al. 2000; Ide, Matsubara et al. 2004).

Pets Exposure to furry pets is also frequently blamed for causing eczema flares. Such assertions have been based mainly on anecdote, the finding of high serum IgE levels to purified animal allergen in children with eczema and on positive atopy patch

tests. These positive tests may simply be an epiphenomenon of the atopic state. I failed to find any high quality studies addressing the question of whether having furry pets in the home may be responsible for disease flares. Clearly, in clinical scenarios where there is a definite relationship between exposure to pets and severe disease flares, avoidance may be warranted. However, it is likely that exposure to a family pet will lead to tolerance even in those with pet allergy. Therefore, an individual is more likely to react following exposure to an unfamiliar pet. Further high quality studies are required to elucidate this relationship.

2.2.5 Conclusion

Good scientific evidence for the roles of "flare factors" in eczema is limited despite frequent anecdotal lists in review articles and textbooks. Further scientific study is required to elucidate the relative impact of these factors in studies of longitudinal design over longer study periods and whether combinations of factors rather than single factors are important, ideally in unselected groups of people with eczema.

Chapter 3 What are the best outcome measures for eczema?

3.1 Introduction

In Chapters 1 and 2 I have reviewed what is meant by a flare of eczema, I have reviewed the evidence to support the roles of various "flare factors" in eczema. In summary, no consensus exists between investigators regarding the definition of flares in eczema and, despite the high prevalence of the disease there is minimal scientific evidence to support the roles of "flare factors" in eczema. I have proposed recommendations of definitions for flares and totally and well controlled eczema weeks for use in future clinical research in the field. The definition of flares will be used as a secondary outcome for this study. Thus, the identification of a primary outcome measure, a further secondary outcome measure and measures which can assess overall disease control, against which the performance of totally and well controlled weeks can be tested, are essential.

When carrying out epidemiological studies, it is critical that outcome measures which are validated for use in clinical research are utilised. A systematic review of the outcome measures currently used in eczema was therefore carried out (study carried out with Dr Jochen Schmitt (lead author) and Professor Hywel Williams) to determine which measures were adequate to use for the formal study. An outline of this review is described in Chapter 3.

3.2 Background

No laboratory test is available to assess disease severity in eczema (Chren 2000). Therefore clinical outcome measures are relied upon for clinical practice and research. This means that standardized and valid outcome measures are needed.

Charman *et al* in a systematic review of outcome measures used to assess the impact of therapeutic interventions in eczema found that only 27% of the investigators used an "objective outcome measure that had been published before (Charman, Chambers et al. 2003). 56 different objective measures of disease severity were found in 94 trials.

Another issue is the lack of validation of outcome measures. Charman *et al* also identified 13 named outcome measures of disease severity in eczema and reported a lack of validation studies for most of these measures (Charman and Williams 2000). Their review focused on whether published outcome measurements had been tested at all and not whether they performed sufficiently well when tested.

The objectives of this systematic review were to update the review by Charman *et al* and to extend the previous review by assessing the validity, reliability, sensitivity to change, and ease of use of these measures (Charman and Williams 2000).

3.3 Methods

3.3.1 Literature search

A systematic literature review was carried out using multiple search strategies to identify all named outcome measures of disease severity specific to eczema. Searches were undertaken for inauguration articles (i.e., articles in which an eligible outcome measurement was published first), as well as subsequent validation studies of eligible outcome measures.

MEDLINE and EMBASE were searched from inception until July 2006 using different combinations of the medical subject terms "atopic dermatitis," "atopic eczema," "severity of illness index," and "severity". Additional electronic searches were performed in MEDLINE and EMBASE for eligible outcome measures to search for data on validity, reliability, and sensitivity to change. Free internet searches were also performed for psychometrics, sensitivity to change, and acceptability data using

http://www.google.co.uk. The researchers who created the outcome measures were also contacted for additional data relevant to validity. The literature search was restricted to articles with abstracts, articles on human participants, and articles including original data. No language restrictions were imposed. Two reviewers (JS and SL) independently performed the literature search. Independent double assessment of eligibility was performed on a set of randomly chosen abstracts (10% of all abstracts identified). Agreement between the reviewers was 100%. Data abstraction was performed independently by 2 reviewers (SL and JS).

3.3.2 Assessment of psychometric properties from the literature

Before adopting an outcome measurement into clinical practice, it should be tested for reliability, validity, sensitivity to change, and acceptability (Streiner DL 1995). Validity means that the measurement truly measures what it is supposed to, whereas reliability means the confidence with which we can be sure that random error does not affect the measurement.(Kline 2005) Published data was assessed relating to construct validity, internal consistency, interobserver reliability, test-retest reliability, sensitivity to change, and acceptability. Definitions of these properties are summarized in Appendix 4 (Streiner DL 1995; Rosner 2000; Kline 2005). Criteria were also defined for "adequate" and "acceptable" psychometric properties prior to carrying out the literature review or extracting data (Rosner 2000). These criteria are also summarized in Appendix 4.

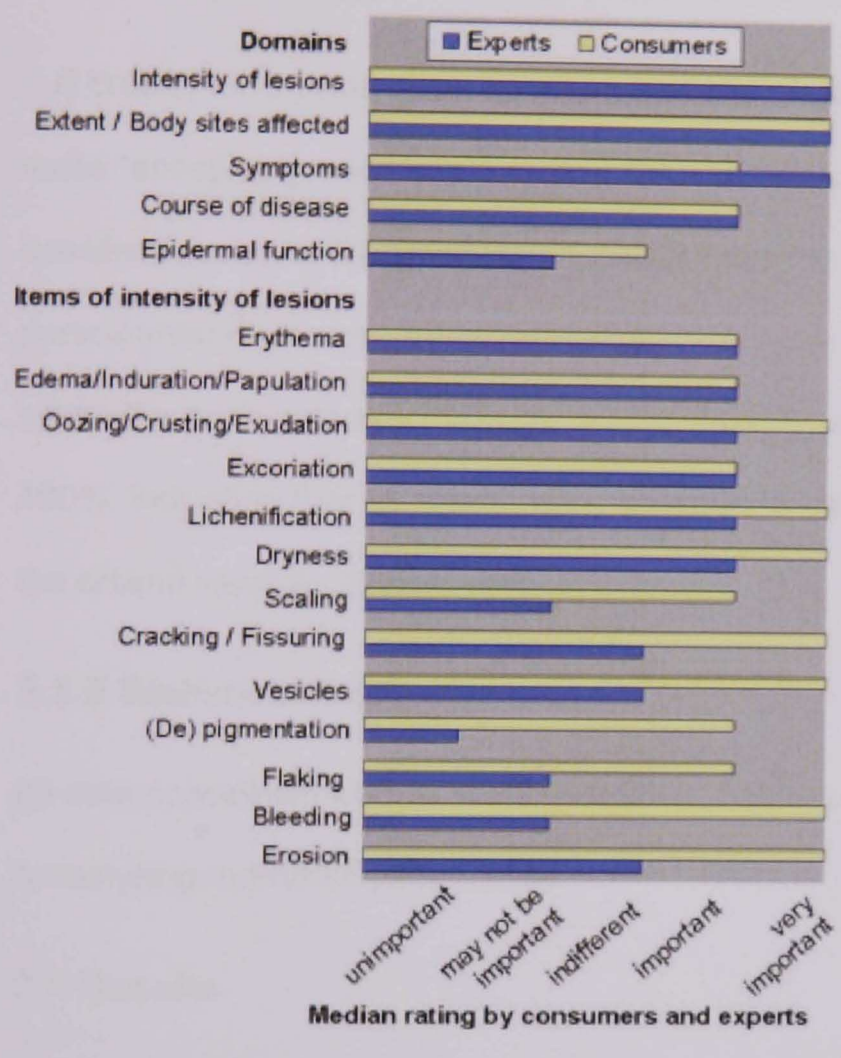
Criterion validity is the extent to which a measurement relates to an external (gold) standard. One of the reasons this study was carried out that there is no gold standard to assess objective disease severity in eczema. Therefore it was not possible to look at criterion validity in this review.

3.3.3 Assessment of content validity of outcome measures

Content validity was not adequately described in the published studies; therefore, this issue was assessed in a separate study. 12 consumers (either individuals with eczema or their parents) were selected from the two centres involved in this study, Nottingham, UK and Dresden, Germany. These comprised 2 patients aged ≥18 years, 2 patients aged 8-14 years and 2 caregivers of patients aged 1-7 years. Six international dermatology experts who were not involved in developing any of the relevant outcome measures scale were also selected.

Experts and consumers rated content validity of all domains (e.g., intensity of lesion and extent of disease) and items (e.g., erythema, papulation, and scaling) included in named outcome measurements on a 5-point Likert scale ("very important," "important," "indifferent," "may not be important," and "unimportant"). Consumers and experts were blinded to the name of the outcome measurement and assessed the individual domains and items without knowing to which measure or measures they belonged. In other words, the name of the scale that the domain was a component of, e.g. SCORAD, was not stated when content validity was assessed. A median score of "important" or "very important" was required to rate a domain or item as adequate. More than 50% of the items used a particular outcome measurement to describe a domain needed to be rated as "important" or "very important" to conclude that the domain was measured adequately (Figure 3-1).

Figure 3-1 Content validity of domains and items used in outcome measures of eczema assessed by consumers (n=12) and experts (n=6)



Legend to figure 3-1

This figure shows ratings of domains of scales assessing eczema severity rated by experts and consumers on a Likert scale. Experts and consumers considered intensity of lesions and extent of disease as "very important" criteria. Course of disease and symptoms were also judged to be "important" or "very important" by both groups, whereas epidermal function was considered as "may not be important" by the experts and "indifferent" by the consumers. Experts tended to rate items that are less specific for eczema as less important when assessing disease severity. Although consumers considered cracking/fissuring, vesicles, bleeding, and erosions as "very important," experts were "indifferent" or judged these items as "may not be important".

3.3.4 Criteria applied for recommendation of outcome measurements

The recommendation on whether to apply an outcome measure is based on the following eight characteristics: content validity by expert, content validity by consumer, convergent construct validity, divergent construct validity, internal consistency, inter-observer reliability, test-retest reliability, and sensitivity to change.

Full credit (100%) was given for characteristics "adequately met," half credit (50%) for those "acceptably met," and no credit (0%) for those "not acceptably met," not assessed, or both. Weighted mean ratings (weighted by the number of study participants) were used for characteristics that have been assessed in more than one study. For each outcome measure, a total relative score was calculated ranging from 100%, indicating that all criteria were adequately met, to 0%, indicating that none of the criteria were acceptably met.

3.3.5 Statistical methods

All data concerning validity and reliability of outcome measures was identified without reanalysing individual patient data.

3.4 Results

A total of 45 eligible articles were found, 21 of which were retrieved by searching MEDLINE and EMBASE, 17 by hand-searching reference lists, and 6 by free internet searches; 1 article was provided by a contacted person (list of references for studies in Appendix 5). The 45 articles reported on 20 different objective outcome measures for severity of eczema.

Most validation studies were performed on the Severity Scoring of Atopic Dermatitis index (SCORAD, n = 14)*, Eczema Area and Severity Index (EASI, n = 5), and Nottingham Eczema Severity Score (NESS, n = 5) (Tofte 1998; Emerson, Charman et al. 2000; Hanifin, Thurston et al. 2001; Hon, Ma et al. 2003; Barbier, Paul et al. 2004; Breuer, Braeutigam et al. 2004; Hon, Leung et al. 2004; Jenner, Campbell et

al. 2004; Belloni, Pinelli et al. 2005; Staab, Kaufmann et al. 2005; Hon, Kam et al. 2006). No data was identified on the validity of 5 published outcome measures (Atopic Dermatitis Severity Index, Four Step Severity Score [FSSS], Skin Intensity Score, Six-area Total Body Severity Assessment, and atopic dermatitis severity score [WAZ-S]) (Kagi, Joller-Jemelka et al. 1992; van Joost, Heule et al. 1994; Van Leent, Graber et al. 1998; Mastrandrea, Pecora et al. 2005; Silny, Czarnecka-Operacz et al. 2005). Appendix 6 describes the study settings and populations of the validation studies for each outcome measure.

*(European Task Force 1993; Kunz, Oranje et al. 1997; Oranje, Stalder et al. 1997; Schafer, Dockery et al. 1997; Wolkerstorfer, de Waard van der Spek et al. 1999; Hon, Ma et al. 2003; Ben-Gashir, Seed et al. 2004; Breuer, Braeutigam et al. 2004; Angelova-Fischer, Bauer et al. 2005; Charman, Venn et al. 2005; Pucci, Novembre et al. 2005; Staab, Kaufmann et al. 2005; Hon, Kam et al. 2006; Hon, Leung et al. 2006)

3.4.1 Domains and items of outcome measures for eczema

Full details of domains studied by the different outcome measures are available in the published paper (Schmitt, Langan et al. 2007). In the 20 outcome measures, five distinct domains were identified: intensity of lesion, extent of disease/body sites affected, symptoms, course of disease, and epidermal function. Substantial heterogeneity between the outcome measures was found for domains being included in the summary score, items used to measure domains, relative weights of the domains, scales used to measure the items, and persons performing the assessment. Disease intensity was assessed in 17 outcome measures using 13 different items. In most outcome measures, physicians are asked to grade intensity on Likert scales, whereas others (e.g., SA-EASI) use visual analog scales marked by the patient or caregiver. Disease intensity contributed 33% to 100% of the summary score (Bahmer, Schafer et al. 1991; Wolkerstorfer, de Waard van der Spek et al. 1999). An assessment of disease extent was included in 16 outcome measures and

contributed between 19% and 100% of the total summary score. A paper by Charman *et al* has recently highlighted the difficulties with measuring body surface area in eczema which leads to problems including this as a component of composite measures.(Charman, Venn et al. 1999) An estimation of the involved body surface area was required by 9 measures and involvement of special body sites by 7 outcome measures. Body surface area is measured heterogeneously, with some outcome measures applying the "rule of nines" (e.g., SCORAD), others using tick boxes (e.g., NESS), and others using a silhouette on which the patient marks involved body sites (e.g., SA-EASI) (European Task Force 1993; Emerson, Charman et al. 2000; Housman, Patel et al. 2002). Disease symptoms like pruritus were assessed in 11 outcome measures attributing up to 33% to the total score. FSSS, NESS, and RL score included an assessment of the course of disease within the past year (Rajka and Langeland 1989; Emerson, Charman et al. 2000; Mastrandrea, Pecora et al. 2005).

3.4.2 Assessment of content validity of outcome measures

Both experts and consumers considered intensity of lesions and extent of disease as "very important" criteria for the assessment of the severity of eczema (Figure 3-1). Course of disease and symptoms were also judged to be "important" or "very important" by both groups, whereas epidermal function was considered as "may not be important" by the experts and "indifferent" by the consumers.

Experts tended to rate items that are less specific for eczema as less important when assessing disease severity. Although consumers considered cracking/fissuring, vesicles, bleeding, and erosions as "very important," experts were "indifferent" or judged these items as "may not be important". Experts and consumers rated content validity on a 5-point Likert scale ("very important," "important," "indifferent," "may not be important" and "unimportant").

3.4.3 Validity of outcome measures and recommendations

Appendix 7 outlines the results of validation studies on all outcome measures identified. Content validity, as assessed by the consumer, is adequate for all outcomes except the OSAAD. Based on the experts' rating, OSAAD, Patient-oriented Eczema Measure [POEM], and WAZ-S do not have acceptable content validity. Only EASI, SCORAD, and the Three Item Severity Score (TISS) have been shown to have adequate convergent and divergent construct validity. Evidence for adequate internal consistency was found only for the POEM. Eighteen outcome measures had either unacceptable internal consistency (n = 4; Atopic Dermatitis Area and Severity Index, SSS, SCORAD, and RL score) or had not been validated for internal consistency (n = 14). There is convincing evidence to conclude that BSCC; NESS; OSAAD; Six Area, Six Sign Atopic Dermatitis severity score [SASSAD]; and SCORAD have adequate inter-observer reliability, whereas adequate test-retest reliability has been shown only for the POEM. For most of the outcome measurements, identified inter-observer reliability and test-retest reliability have not been evaluated adequately yet. Sensitivity to change is adequate for EASI, Investigators' Global Atopic Dermatitis Assessment (IGADA, investigator global assessment with descriptive terms), and SCORAD; acceptable for Leicester index, OSAAD, POEM, SA-EASI, SASSAD, and SSS; not acceptable for the RL score; and has not been adequately assessed for the remaining 10 measures. The time needed to perform disease severity assessment ranges from 1 minute up to 10 minutes.

Based on the existing evidence, none of the 20 outcome measurements can be highly recommended. EASI, POEM, and SCORAD have been shown to meet most validity criteria and are recommended for use. Although the validity criteria are only partly met, IGADA, NESS, SA-EASI, SASSAD, and TIS appear to be acceptable until further validation studies are available. Because of a lack of evidence for their validity, the remaining 12 outcome measurements are not recommended (Appendix 7).

3.5 Discussion

3.5.1 Main findings

Currently, investigators can select from 20 different named measurements of disease severity. Of these, only EASI, POEM, and SCORAD have been validated adequately enough at present to recommend their use in clinical trials and everyday practice.

The reason 17 of the 20 outcome measurements identified are not recommended is primarily that data on their validity is missing. Since the review by Charman and Williams in 2000, 7 new outcome measurements have been introduced (FSSS, IGADA, OSAAD, POEM, SA-EASI, TIS, and WAZ-S) (Charman and Williams 2000; Housman, Patel et al. 2002; Sugarman, Fluhr et al. 2003; Charman, Venn et al. 2004; Mastrandrea, Pecora et al. 2005; Schachner, Lamerson et al. 2005; Silny, Czarnecka-Operacz et al. 2005). Of these, however, only the POEM has been adequately validated (Appendix 7).

Most outcome measurements analyzed are assessed by a physician (e.g., EASI and SASSAD) and are therefore sometimes referred to as "objective," whereas others (e.g., POEM, SA-EASI) are more "subjective" because they are scored directly by the patient or caregiver. In reality, of course, both measurements require subjective judgment of categories within domains by physician and patient. The disadvantage of "subjective" outcome measurements is that reporting bias may be due to coping

strategies, quality-of-life or comorbidity. The advantage of a subjective measurement like the POEM, however, is that it truly measures what is important to the patient (Charman, Venn et al. 2004). Although some of the items included in the POEM were not considered adequate by the experts in this study, the POEM was shown to be highly valid from the consumers' perspective (Appendix 7).

3.5.2 Study strengths and limitations

Based on objective criteria, recommendations were made on which outcome measurements to apply. These were informed by a systematic and comprehensive literature search. The cut-offs used to judge whether the validity criteria studied are "adequate" or "acceptable" are consistent with the literature and were defined *a priori* (Rosner 2000; Kline 2005).

Another potential limitation of this study is that acceptability was not considered (i.e., time needed to perform measurement) in this recommendation. This was not included because the amount of time needed depends on the experience of the person doing the assessment. It was also not clear from most of the articles whether the time needed was actually measured rather than just estimated.

By including content validity from both a consumer's and expert clinician's perspective, content validity has been included twice in the overall grading system. This approach might have given disproportionate weight to content validity. It is likely that consumer and expert perspectives are measuring slightly different elements. Combining both content validity perspectives into one overall composite score did not alter the overall conclusions or choice of instruments in this review (data not shown).

To assess content validity, different consumer groups were surveyed, which raise the question of whether the responses were homogeneous across those groups. The median responses of adult patients, children aged 8 to 14 years, and parents of

younger patients were almost identical (data not shown). This finding provides good evidence for the validity of this approach to assess content validity.

Some authors have used the Investigators' Global Assessment (IGA) as a gold standard and assessed criterion validity of other outcome measurements by correlating them with the IGA. The IGA is not stable enough to be a gold standard as it is influenced by response to treatments, compliance, and the patient-physician relationship. The IGADA is a variant of the IGA in which objective rules on how to rate severity are defined, unlike the IGA. The IGADA gives verbal descriptions for disease severity, such as "almost clear" or "very severe," which seems to be useful for clinical practice. Future research is necessary to evaluate the reliability of the IGADA.

3.5.2 Implications for this research

Substantial heterogeneity was found in the domains included in the different outcomes, the items used to measure the domains, the relative weights of the domains on the summary score, the scales used to measure the items, and the person performing the assessment. This leads to the conclusion that the 20 named outcomes identified do not measure the same aspects. The EASI or (objective) SCORAD are recommended as a valid and unbiased estimate of "objective" disease severity plus the POEM as a measurement of eczema severity from the patient's perspective.

For the purposes of this thesis, two different types of outcome measure were required, a simple daily measure which could be posed as a single question, that would not pose too much respondent burden and monthly standard outcome measures as discussed in detail in this chapter. Two daily measures were selected after intensive debate and discussion, bearing in mind that this literature review has not identified any recommended measure suitable for use on a daily basis that

equates to a single question. The first of these was a "bother" score which is a score derived from the POEM score. The POEM score is a recommended score and has been shown to be valid as previously discussed. The "bother" score assesses how much bother the eczema has caused (0-10) and is a response to a single question. "Scratch" scores were selected as a second primary outcome as this group has experience of its use in the context of clinical trials in eczema and previous research has shown good correlation to scratching as measured using accelerometers.

More guidance on the monthly measures was obtained from this review. The POEM and TIS scores were both selected as the former has been shown to have adequate validity and the latter is considered acceptable pending further research.

Methods

Chapter 4 A pilot study to assess the effects of environmental factors in eczema

4.1 Introduction

A major research gap has been identified in the scientific evidence regarding causes of flares in eczema in Chapter 2. Proposals have been made regarding how flares should be defined in eczema and new concepts including totally and well controlled weeks have been suggested for use in clinical research (Chapter 1). Furthermore, the recent discovery of the high prevalence of filaggrin mutations in children with eczema has led to a hypothesis that patients with filaggrin mutations are more susceptible to environmental trigger factors which may help to explain the heterogeneity between individuals in their response to exposures (Introduction).

Chapters 4 describes in detail how the research gap highlighted in Chapter 2 in relation to the scientific study of possible exacerbating factors for eczema was addressed in this pilot study with a view to planning the methods of the subsequent formal study described in Chapter 5.

4.2 Objectives

This study was designed to assess the feasibility of performing a panel study of exacerbating factors in eczema with the express objective of informing the planning of a focussed study with specific *a priori* hypotheses over a longer duration. In terms of feasibility issues, the main areas to explore were the willingness of parents and their children to take part, the percentage completion of data, the design of the diaries and methods for data analysis.

4.3 Methods

4.3.2 Participants

Parents of 30 children aged 0 to 15 years with eczema fulfilling UK modified Hanifin and Rajka's criteria attending outpatients in the South Infirmary-Victoria Hospital, Cork, Ireland were invited to participate (Williams, Burney et al. 1994).

4.3.3 Study duration

This study took place over four weeks in 2003. Duration was based on allowing sufficient time to assess feasibility.

4.3.4 Severity Assessment

Severity was assessed using the Children's Dermatology Life Quality Index (Lewis-Jones and Finlay 1995) (CDLQI) and the SCORAD (SCORing atopic dermatitis) at baseline and study completion (European_Task_Force 1993) by the lead investigator (SL). Parents or patients recorded daily symptom severity in paper diaries using scratch (1-5) and sleep (1-5) scores. In-depth explanations were given to participants regarding diary completion and severity assessment. Older children completed the diaries themselves (usually >8 years).

4.3.5 Exposures studied

Fourteen variables were included in the analysis based on previously published studies, some of which have been discussed in detail in Chapter 2. These included exposure to dust, exposure to pets, sweating, stress, damp (assessed by patients based on exposure to damp in buildings), central heating, foods, infection, teething (where appropriate), clothing, cleansing products, hot or cold weather and holidays.

4.3.6 Primary outcome

The primary outcome was a daily scratch score (1-5).

4.3.7 Sample size

In the absence of knowledge of the variability and lag times of purported risk factors, a formal power calculation was not realistic in this exploratory study.

4.3.8 Statistical analysis and ethics

A range of analyses were explored. An episode was defined as a day where the patient's scratch score was 4 or greater. At patient level, the total number of episodes were modeled in relation to overall exposure using Poisson regression with correction for overdispersion. Secondly, random-effects ordinal logistic regression was used to model the relation between exposures and scratch scores, with robust variance estimates to account for the error covariance (generalized linear latent and mixed models (gllamm) module in Stata. This relationship was examined on all days whether an "episode" occurred or not with the specific focus being the relationship between exposures and severity of eczema. Gllamm is a Stata program that can fit latent-variable models; the generalized linear mixed model is a special case of latent-variable model) (corporation 2003).The lag time between exposures and worsening was explored (i.e. lag 0=same day, lag 1= one day after exposure etc). Ethical approval was obtained from the local research ethics committee and informed consent was obtained from parents.

4.4 Results

4.4.1 Demographics

25 Irish white children, eleven girls (44%) and fourteen boys (56%) completed the study. Five participants did not complete the one month study or failed to complete the diary. The age range was 2 months to 14 years with a mean age of 4.6±4.26 years. The study period was a 28 day period in June 2003. The average temperatures and relative humidity were 13.3°C and 83.6% respectively and maximum temperature and relative humidity were 20.1°C and 98% respectively.

4.4.2 Disease severity

The initial mean ± SD SCORAD was 20.37±11.94; the final was 22.23±10.62. Most participants/parents attributed worsening to high temperatures. The majority of patients had mild (44%) or moderate (44%) eczema; only 12 % had severe disease (assessed globally at study outset). Mean CDLQI scores before and after were 7.04±3.91 and 7.8±4.72 respectively. Severity scores did not significantly change during the period.

4.4.3 Feasibility objectives

Twenty five of 30 diaries (83%) were available for analysis; the other diaries were either lost (4) or not completed (1). This equates to 83% of participants completing the study. The completeness of recording of exposures ranged from 65% to 83%; measures of outcome were 97% complete in the diaries available for analysis. This highlights differential completion of different aspects of the paper diaries.

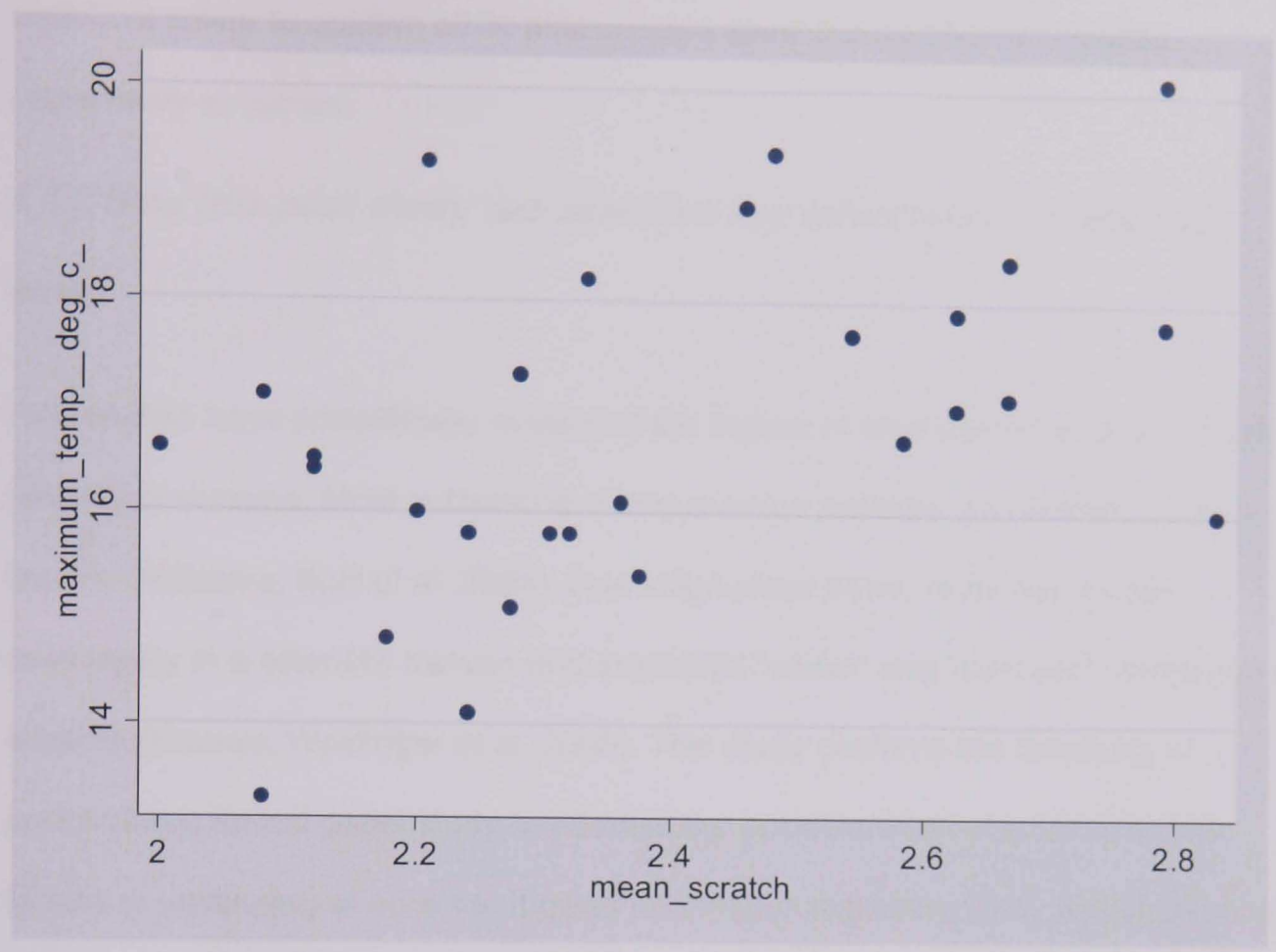
4.4.4 Diary data

12 (48%) experienced flares with an average 3.6 flares per child (range 1 to 8).

Eczema severity using SCORAD ($p=0.025$, $r=0.446$), and CDLQI scores ($p<0.001$, $r=0.734$) at review correlated with the number of flares.

At episode level using random effects logistic regression, on the day of exposure (lag 0), heat (high outside ambient temperatures) correlated to increased scratch scores ($p=0.043$) as shown in Figure 4-1.

Figure 4-1 Correlation between maximum temperature and mean scratch scores



Legend to figure 4.1

This graph shows maximum daily temperatures against mean scratch scores across participants.

At a lag of 2 days, damp (wet outside) was associated with raised scratch scores (p=0.027). Three days after exposure, sweating and stress were associated with elevated scratch scores (p=0.029 and 0.019 respectively). At lag 4, damp outside was associated with elevated scores (p=0.001). Analysis of significant variables using robust variance estimates revealed only damp at lag 4 was significantly associated with disease flares (p=0.039).

4.5 Discussion

4.5.1 Main Findings

Analysis of diary data suggests a temporal association between eczema severity and four variables. These included heat (lag 0), damp (lag 2), sweating and stress (lag 3) and damp (lag 4). Robust variance analysis of the data supported a correlation only

with damp. However, that may be due to the short duration of the study and a lack of statistical power to confirm other associations given the number of possible explanatory variables.

4.5.2 How this pilot study has provided key information for the main study

Few studies have scientifically evaluated the impact of environmental factors on the severity of eczema. Most authors have documented patients' perceptions of "flare factors" (Williams, Burr et al. 2004). One longitudinal panel study has studied seasonality in a scientific fashion and described "winter" and "summer" categories of eczema (Kramer, Weidinger et al. 2005). This study confirms the feasibility of performing a formal panel study to address the possible roles of environmental factors in worsening of eczema. It gives information regarding likely participation and completion rates in order to determine the sample size for the formal study and how best to measure exposures and outcomes. It also suggests that environmental factors may be important in eczema worsening.

In terms of exposures, damp was very crudely measured by asking participants if they had been exposed to damp that day. Previous research suggested that the important component was actually relative humidity rather than household damp. It was therefore decided in the main study to focus on the measurement of indoor and outdoor relative humidity. The main outcome measure in this study was a "scratch" score (1-5). As this scale has only 5 points, it must be analysed using methods for ordinal data and normal distribution cannot be assumed. This makes analysis more complex (requiring ordinal logistic regression rather than normal time series methods) and therefore it was decided for the main study to incorporate "scratch" scores with a greater range (0-10) as a secondary outcome measure and to select a further measure as a primary outcome measure. Data collection for the pilot study

was done using paper diaries which participants completed daily for a one month period. I was suspicious, but unable to confirm, that there was some "parking-lot" compliance based on some respondents showing rows of completed entries with the same colour pen and the same values. This prompted the search for data collection methods which would reduce recall bias which lead to the use of electronic diaries in the main study. In this study, lagged responses were also used assessing the impact of exposures on the study outcomes in the days following exposure. This greatly increases the number of variables in the study, i.e. each variable is included five times if a lag of up to four days is used. The problems with that are the issues of the complexity of the analyses and multiple testing whereby the findings could be significant by chance. I decided for the main study not to include lagged responses for these reasons but to adjust for the fact the response on one day is related to the responses on the surrounding days by using measures to adjust for autocorrelation.

4.5.3 Strengths and limitations of this study

This study prospectively assessed several factors utilising daily recording of exposures and disease severity. This is particularly relevant in a complex disease such as eczema, where several factors may combine to cause flares. The population was well defined and the response rate was very good.

The small sample size, range of variables and weather conditions limit the validity of conclusions, reflecting the exploratory nature of the study. Studying a smaller range of putative flare factors could lead to clearer outcomes but this approach could be associated with the risk of missing a key factor. Finding only one significant variable after robust variance estimates may reflect the duration and low numbers rather than a true lack of association with other variables or indeed this may represent a chance finding due to multiple testing.

4.5.4 Implications for clinical practice and the main study

During consultations with a patient with eczema, health care professionals should ask about environmental factors in order to assess their relevance to the individual patient. In general, studies have suggested that heat may be a major factor in disease flares. Therefore it would appear sensible to advise parents to use simple measures to try to keep children with eczema cool. A larger prospective study over a longer period with independent objective recording of exposures, ideally in a fashion that limits the differential recording of outcomes and exposures is required to definitively establish the impact of these factors on disease status.

Chapter 5

Main cohort/panel study

5.1 Introduction

Chapter 2 and the pilot study results described in Chapter 4 suggest that environmental conditions are likely to influence disease status in children with eczema and may be associated with disease flares. The mechanism underlying environmental triggers of "flares" in eczema is poorly understood. It is not clear why people seem to respond differently to environmental factors. Specifically, some eczema sufferers appear to flare when the weather is hot; others seem to flare during the winter when the outdoor temperature is low and indoor temperature is high with low relative humidity. This Chapter describes the formal study of the effect of environmental factors on eczema severity in a cohort of children with eczema.

5.2 Hypotheses

1. In hot weather, the combination of heat, sweating and grass pollen precipitates increased severity in children with eczema in the UK. This hypothesis is based on a combination of the findings of the study by Kramer *et al* and the discussions of the research team (Kramer, Weidinger et al. 2005).

2. In cold weather, the combination of cold weather, indoor aeroallergen exposure and reduced relative humidity from central heating lead to increased severity in children with eczema in the UK. This hypothesis is based on the clinical experience of investigators and follows intensive discussion of the study by Kramer *et al* (Kramer, Weidinger et al. 2005).

3. Detergents (soap, shampoo) can heighten the propensity to increased severity (triggered by other factors) at all temperatures but possibly more in cold

weather due to impaired skin barrier function. This hypothesis was informed by research which proposed seasonal variation in responses to irritant exposure and clinical experience(Tupker, Coenraads et al. 1995).

4. Patients with filaggrin mutations are more prone to the effects of climatic factors such as cold and heat than individuals who are wild type for filaggrin.

5. Any combination of greater than or equal to three exposures at any time is associated with worsening of eczema. The exposures assessed were: dust, exposure to pets, shampoo, sweating, swimming, nylon clothing next to the skin and a change in mean temperature of more than 3°C from the previous weekly average.

5.3 Methods

5.3.1 Description

Summary of study design

This was a 2 year hypothesis-testing, prospective observational study. Outcome and exposure measures were chosen with the aim of keeping assessments simple, non-invasive yet meaningful.

Study duration

Patients were recruited over a 6 month period and studied for up to nine months. Entry into the study was staggered to analyse seasonal effects.

Primary outcomes:

Primary outcomes (Figure 5-1) were defined by global scores recorded daily in the patient's diary. Global scores were graded from 0 (no bother at all) to 10 (the most bother you can imagine) as a response to the question, "How much bother did your (your child's) eczema cause today? This measure was chosen because it is valid (derived from the Patient Orientated Eczema Measure), sensitive to change and it is

appropriate to use every day as discussed in detail in Chapter 3 (Charman, Venn et al. 2004).

Figure 5-1 Outcome measures for this study

Primary outcome measure

- "Bother" score: Global scores were graded from 0 (no bother at all) to 10 (the most bother you can imagine) as a response to the question, "How much bother did your (your child's) eczema cause today?

Secondary outcome measures

- "Scratch" scores: Scratch was graded from 0 to 10 (0= not scratched at all; 10= scratched all of the time) as a response to the question: "How much did you (your child) scratch today? "
- Disease flares: Binary outcomes were recorded in respect of the question" Have you had to step up your treatment today because your (your child's) eczema was worse?" What is meant by stepping up treatment was defined at the outset for each child

The use of daily itch scores was considered as the primary outcome measure, but flares are composed of more facets than purely itch and, parental perception of a child's itch levels may not be accurate. The use of totally and well controlled weeks (TCW and WCW) was contemplated also but due to the nature of a panel study (intensive study of a relatively smaller group), the loss of statistical power would be too great and these measures would be likely to give a better measure of overall disease control than shorter term disease worsening, as in disease flares. Using flares as defined by the preliminary work (Chapter 1) was deliberated as the primary

outcome measure; however, as this measure has not yet been validated, this was used as a secondary outcome measure rather than the primary outcome and its performance was tested in comparison to "bother" scores.

Secondary outcomes:

Daily scratch scores were recorded in the patient's electronic diaries. Scratch was graded from 0 to 10 (0= not scratched at all; 10= scratched all of the time) as a response to the question: "How much did you (your child) scratch today? ". This measure focuses on day time itching and does not reflect nocturnal scratching. A further secondary outcome was the occurrence of flares as assessed by the need to "step up" treatment. Binary outcomes were recorded in respect of the question" Have you had to step up your treatment today because your (your child's) eczema was worse?" What is meant by stepping up treatment was defined at the outset for each child, e.g. move to potent topical corticosteroid from weak corticosteroid. As this is a patient centred outcome, it needed to be individually defined rather than using a fully standardized approach. If participants responded that they had stepped up their treatment that day, they were asked to specify the site of the flare through a series of follow on questions. Clinical disease severity scoring was assessed monthly using the 3 item score, which is published and validated in eczema and the patient orientated eczema measures (POEM score). All clinical disease severity scoring using the TIS score was done by the lead investigator (SL). Quality of life was assessed using the Children's Dermatology Life Quality Index (CDLQI) (Lewis-Jones and Finlay 1995). Severity scoring was repeated at each monthly review (TIS and POEM) and quality of life (CDLQI) was assessed every three months by an examining dermatologist. The TIS, POEM score and CDLQI provide background data regarding severity and therefore would not be appropriate methods to assess daily fluctuations in severity. This combination of assessments was chosen to reflect on both "objective" and "subjective" outcomes. The TIS score, as discussed in Chapter 3

has not been thoroughly assessed for validity as the criteria defined in Chapter 3, were only partly met. However, this score was selected for its acceptability and ease of use in view of the fact that it was being used to reflect the overall severity rather than relating to the main study outcome measures.

5.3.2 Participants

Setting:

60 patients were recruited consecutively from the Queen's Medical Centre paediatric dermatology outpatient department, Nottingham over a 6 month period. Participants were also recruited from primary care Nurse Consultant lead eczema clinics. Further participants were recruited following a presentation at the Nottingham support group for carers of children with eczema (NSGCCE). Parents and patients were offered the possibility of separately consenting to opt into the genetic arm of the study. No participant was enrolled until informed consent was obtained. All participants were treated in accordance with the Helsinki accord. Nottingham is located 117 metres above sea level and is located in the East Midlands.

Inclusion criteria:

Patients aged 0 to 15 years with moderate to severe eczema, fulfilling UK modified Hanifin and Rajka criteria where parents consented to partake and they/ their parents were able to complete the symptom diary.(Williams, Burney et al. 1994) Baseline severity was determined using the TIS score and the patient orientated eczema measure (POEM score) (Wolkerstorfer, de Waard van der Spek et al. 1999; Charman, Venn et al. 2004). Entry criteria also required that participants must have had a minimum of three significant disease flare ups in the preceding 6 months. The definition of a disease flare up was that proposed in Chapter 1, i.e. escalation of treatment or the need for additional medical advice for increased disease severity.

Exclusion criteria:

Patients 16 or over (These patients have a different disease profile and may not accurately reflect patterns in the childhood eczema cohort); those with diagnoses other than eczema; patients with mild disease; patients/ parents who were either unable to or did not consent to complete the diary; children with concurrent severe asthma requiring oral corticosteroids for treatment of asthma flares.

5.3.3 Procedures

Baseline interview

Avoidance behaviour in relation to types of clothes, detergents and household pets was assessed so that analysis could be stratified by prior belief. Patients/their parents were also asked whether their disease flared more in summer or winter and whether they perceived that cold or hot temperatures played a role in disease flares. Parents and their children were asked some basic questions regarding their housing; including whether there were carpets/ rugs or furry toys in the child's room, frequency of cleaning and use of mattress and pillow covers. These questions were posed discreetly in a standardized questionnaire, avoiding the issue of leading questions which might bias answers (Appendix 8). An investigator was present to clarify any unclear questions. Socioeconomic status was assessed using two methods: parental occupation as assessed using the Standard occupational classification and levels of parental education (Statistics 2002). At the baseline interview, the patient's usual treatment regimen and what they usually do when the eczema worsens (this was defined as "stepping up" treatment for that patient) was established and recorded. The definition of what constituted "stepping up" treatment for their child was agreed at that interview between parents and the investigator.

Diaries

They/ their parents were asked to complete an electronic diary on a daily basis for a 6 to 9 month follow-up period, recording severity of eczema and exposure to potential

exacerbating factors (Appendix 9). Use of the electronic diary was demonstrated to participants at baseline where a trial run was carried out. Participants were requested to complete the diaries in the evening such that exposures from that day (not the previous evening) and eczema severity could be recorded. Participants were also given a booklet designed specifically for the study which explained how the diary functioned, how to respond to questions and also provided troubleshooting advice on the use of the diaries. The electronic diaries did not allow participants to complete the diaries after midnight on the day, neither did they allow partial daily completion. Unless participants answered yes to the question "Are you happy with your answers" and received the response "Your data has been submitted", no information would be stored from that day.

Monthly reviews

Participants were reviewed monthly and clinical assessments were carried out to determine overall disease control. Data from electronic diaries was downloaded monthly. At the end of the study period, a final clinical assessment was performed. These scores allowed correlation of clinically determined severity scores with patient determined "flare" scores in order to assist in their validation.

Filaggrin status

To determine filaggrin status it was necessary to obtain DNA from individuals entering the study. Following written informed consent, participants were asked to provide a saliva sample at enrolment. This was done using standardized techniques; for younger children, a sponge was used for sampling, while older children gave saliva samples into containers following instructions (Oragene). Identification of these containers was limited to the designated study number and date of birth. The containers were shipped to the Human Genetics Unit, University of Dundee. DNA was extracted by standard techniques and *FLG* genotyping for the common null-alleles was carried out according to published protocols (Palmer, Irvine et al. 2006).

FLG genotype status were recorded and returned to the Nottingham-based senior investigators (SL or HW) again using the study number and dates of birth. Correlations between environmental data, filaggrin status and eczema flares were determined.

Detailed personal data was kept by the lead researchers (SL and HW) and was not transferred to the laboratory researchers. It was therefore not possible for the study laboratory to link genotyping data back to participant's personal details. A single hard copy of the database linking genotype to phenotype was securely kept under the direction of the data controllers/senior investigators (SL and HW). Electronic databases were anonymous and did not contain any identifying data.

Measurement of exposures:

Eleven variables were included in the study (temperature, relative humidity, sun exposure, sweating, clothing, cleansing products/ washing, outdoor pollen level, extent and nature of exposure to household pets, dusty environments and swimming) which have been proposed to flare eczema (Table 5-1) Season was an additional variable; this was included as the study by Kramer *et al* demonstrated strong associations between seasonality and eczema flares. The seasons were defined using the UK Meteorological office guidelines as follows: spring (March 1- May 31), summer (June 1-August 31), autumn (September 1-November 30) and winter (December 1-February 28). These differ slightly from the definitions used for spring (March 11-May 15) and summer (May 16-September 14) in the German study (Kramer, Weidinger et al. 2005).

Selection of the exposures for inclusion in the formal study was difficult; including too many variables would result in reduced precision and increased standard error. It would also be technically impractical to assess for interactions. It was equally important to include all the relevant exposures likely to contribute to disease flares.

I have described the justification for the exposures recorded in Table 5-1. A number of factors suspected of causing disease worsening have been excluded.

Stress also appeared to play a role in the pilot study, however to study the impact of this factor accurately on a daily basis would require too many daily questions. The burden on respondents would be too great and would be likely to reduce compliance. In order to analyse the relevance of this factor accurately, a formal study of stress in eczema would be required. Similarly, examining the role of foods would require in depth study which would preclude the examination of a range of factors and would merit a study on its own.

Table 5-1 Rationale for choice of variables for cohort study and methods of measurement of exposure

Variable	Rationale for choosing variable	Variables to be analysed	Methods of measurement	Frequency of measurement
Environmental temperature	1. Weiland *et al* (ISAAC phase 1.(Weiland, Husing et al. 2004) Worldwide questionnaire study. 6-7y and 13-14y olds. Negative association between eczema symptom prevalence and mean annual temperature 2. Pilot study findings as outlined in Chapter 3 demonstrated disease worsening with heat.(Langan, Bourke et al. 2006) 3. Tupker *et al.* Influence of season on weal and flare responses in eczema. More pronounced weal and flare reactions in winter (n=16).(Tupker, Coenraads et al. 1995) 4. Uter *et al.*(Uter, Gefeller et al. 1998) Irritant hand dermatitis increased in cold weather in large group of hairdressers	Daily maximum and minimum temperature, weekly change in mean temperature	Outdoor temperature and relative humidity measured by environmental monitoring centre, University of Nottingham, Sutton Bonnington campus Electronic data loggers- (iButton, Maxim, Dallas). Measures temperature and humidity	Hourly
Humidity	1. Weiland *et al* (ISAAC phase 1. Tendency towards negative association between indoor relative humidity and eczema.(Weiland, Husing et al. 2004) 2. Sato *et al.*(Sato, Fukayo et al. 2003) Questionnaire study comparing 200 adults working in ultra dry room compared to other workers. Higher prevalence of eczema in ultra-dry room workers. 3. Denda *et al.*(Denda, Sato et al. 1998) Extremes of humidity contribute to disease flares	Minimum indoor relative humidity	Measurements as for temperature.	Hourly

Variable	Rationale for choosing variable	Variables to be analysed	Methods of measurement	Frequency of measurement
Sweating with exercise	1. Williams *et al.*(Williams, Burr et al. 2004) Questionnaire study. 42% exacerbated by sweating with exercise. n=225 2. The pilot data- 56% reported exacerbations. n=25. Questionnaire study 3. Itch when sweating reported by between 23 and 78% in previous questionnaire based studies	Amount of sweating	Question regarding sweating. Did you/ your child sweat today? Modified Likert score with a range from 0 (no sweating) to 4 (dripping sweat, had to change clothes). **Not relevant in infants**	Daily
Clothing	1. Diepgen *et al.*(Diepgen TJ 1995) RCT diff fabrics. Synthetic shirts increased irritative capacity, cotton best tolerated. Rougher fabrics more irritating. 55 eczema, 31 controls 2. Ricci *et al.*(Ricci, Patrizi et al. 2004) Study of silk fabric in 31 children with eczema. Improved eczema severity. 4 children, mean age 2 3. Williams *et al.*(Williams, Burr et al. 2004)Questionnaire study. Fabrics reported to worsen eczema in 39% children, wool in 17%. N=225 4. The pilot study, eczema reported to flare with fabrics as follows: 48% wool, 24% fleece, 16% nylon. Questionnaire data from 25 patients	Clothes worn directly against the skin	Participants were asked daily if they wore wool or nylon clothing that day. If they responded affirmatively, they were asked if they had worn that fabric directly against their skin. This was then converted into a binary exposure variable whereby the exposure was only positive if the fabric was worn directly against the skin	Daily

Variable	Rationale for choosing variable	Variables to be analysed	Methods of measurement	Frequency of Measurement
Detergents	1. Williams *et al.* Cleansing products felt to induce flares in 24.9%, of which washing powder freq listed (% not stated).(Williams, Burr et al. 2004) Questionnaire study 225 p 2. Sherriff *et al.*(Sherriff, Farrow et al. 2005) Increasing "hygiene scores" associated with increased prevalence of eczema. ALSPAC study	Shampoo exposure. Direct exposure of the skin to shampoo daily.	Participants were asked daily if they had washed their hair that day. If they responded affirmatively, they were asked if they washed their hair at the same time as their bath or shower. If this was positive, exposure to shampoo was recorded that day.	Daily
Pollen count	1. Burr *et al.*(Burr, Emberlin et al. 2003) ISAAC phase one. No association between high pollen counts and eczema prevalence. (28 centres, 11 countries. 13-14 year olds. Questionnaire 80,050 children) 2. Darsow *et al.*(Darsow, Vieluf et al. 1996) Correlation between +PT, raised serum IgE to same and +ve SPT. 79 patients eczema, 20 controls 3. Lewis *et al.*(Lewis, Corden et al. 2000) Grass pollen not birch pollen related to asthma flares and A+E attendances	Grass and birch pollen levels	Midlands Asthma and Allergy Research Association. Measures daily pollen using standardized techniques. This measuring centre is located in Leicester and previous studies have demonstrated that there is sufficient lack of variation for these measures to be applied to the whole of the East Midlands region.	Daily

Variable	Rationale for choosing variable	Variables to be analysed	Methods of measurement	Frequency of measurement
Other aeroallergens-house dust mite	1. Shah *et al.*(Shah, Hales et al. 2002) In vivo challenge in 20 adult pt. Suggest that clinically relevant HDM hypersensitivity present in 1/3 adult atopics studied. 2. Gutgesell *et al.*(Gutgesell, Heise et al. 2001) 20 adults 1 year HDM avoidance no reduction in severity scores 3. Ricci *et al.*(Ricci, Patrizi et al. 2000) 41 children, HDM measures reduced severity scores over 1 yr.	HDM avoidance measures recorded Record of exposure to dusty environments	Record at baseline of house dust mite reduction measures, i.e. avoidance of furry toys and frequency of cleaning. Daily recording of exposure to dusty environments	Daily
Other aeroallergens-animals	1. Williams *et al.*(Williams, Burr et al. 2004) Cats and dogs reported to induce flares in 8% and 5% respectively. Questionnaire study 2. The pilot study, 36% reported flares on exposure to dogs and 32% to cats respectively. Horses perceived to cause flares in 28%. Questionnaire study	Exposure to animals- type and duration	Patients/ parents record their contact with animals in their diaries, specifying the type of animal and whether the pet was the family's pet or an unfamiliar pet. Pet exposure recorded as a binary variable positive with an unfamiliar pet only.	Daily
Sun exposure	1. Deguchi *et al* reported worsening of facial erythema in adult patients following UV exposure.(Deguchi, Danno et al. 2002) 2. Tajima *et al* report photoexacerbation of eczema with abnormal UV responses.(Tajima, Ibe et al. 1998) 3. Russell *et al* reported photoexacerbation in 7 patients with photosensitivity dermatitis/actinic reticuloid on a background of atopic eczema.(Russell, Dawe et al. 1998) 4. UV therapeutically used for treatment of severe atopic eczema	Sun exposure	Retrospective meteorological data of UV levels from University of Nottingham environmental monitoring site, Sutton Bonnington	Daily

Variable	Rationale for choosing variable	Variables to be analysed	Methods of measurement	Frequency of measurement
Swimming	Seki *et al* demonstrated sensitivity to lower chlorine concentrations in individuals with eczema compared to those with normal skin with reduced water holding capacity. (Seki, Morimatsu et al. 2003)	Swimming in chlorinated swimming pool	Question in daily electronic diary	Daily
Seasons	1. Vocks *et al* studied a cohort of individuals in Davos and demonstrated an inverse relationship between increasing outdoor temperature and levels of itch (Vocks, Busch et al. 2001) 2. Kramer *et al* showed seasonal variations in a panel of children with eczema and proposed as a post hoc hypothesis that winter and summer types of eczema existed (Kramer, Weidinger et al. 2005)	Seasons of the year	Seasons: spring, summer, autumn and winter	Quarterly

Temperature and humidity

Objective data of the temperature and relative humidity of the micro-environment to which the child was exposed were obtained by supplying each child/ parent with an ibutton© data logger (Maxim, Dallas, USA) on a keyring. This measured the daily maximum, minimum, mean and standard deviation of both the temperature and relative humidity. Data was downloaded from these devices every month, processed and then added to the study database by the accompanying software. Outdoor data from the local environmental monitoring centre in Sutton Bonnington was used for the outdoor data. Other measures were considered, e.g. twice daily recording of household temperature and humidity as used by Kramer *et al* (Kramer, Weidinger et al. 2005). However, this method is likely to be associated with missing data and is not an accurate measure of the individual's microenvironment, i.e. does not record temperature and humidity exposures when the child is in school.

Sweating

Patients/ parents were asked to score the amount of sweating on that day using a modified Likert score with a range from 0 (no sweating) to 4 (dripping sweat, had to change clothes).

Clothing and shampoo

Patients and their children recorded the duration and nature of exposure to clothing including wool and nylon and if this clothing was worn directly against the skin. Exposure was only considered positive if the fabric was worn directly against the skin. Parents were also asked to record whether they washed their child's hair that day and if so, whether this was at the same time as the child's bath or shower. Usual washing practices and products used were recorded at the baseline interview. This

posed less of a burden on participants than daily recording of washing products and was selected to be pragmatic.

Household pets

Patients/ their parents recorded exposures to household pets (type of pet, own pet or infrequent exposure) in the daily diary. This is a relatively weak way to measure exposure to pets. The ideal way to measure pet allergen exposures would be with personal air samplers, however this would be cumbersome, expensive and would pose too much of a burden on respondents. Static sampling, i.e. measuring pet allergen from dust samples is not an accurate way to assess actual exposure as it does not reflect air levels of pet allergen. Exposure to pets is also behaviourally driven so a portable personal sampler would be the only truly accurate was to assess this. Exposure to pets was only considered positive if it was not the patient's own pet, as tolerance to family pets is well recognised.

Dusty environments and pollen counts

Patients were asked to record exposure to dusty environments on a daily basis in their diaries. Pollen levels were measured daily by a local aerobiology pollen monitoring centre using an automatic volumetric Burkard trap. This device was situated on the roof of the University of Leicester campus at a height of 12 metres. Leicester is an urban city with tree lined roads in the local vicinity, position reference 52°38'N 1°5'W, with an altitude of 60 metres. The methodology used for collecting pollen used the standard methods of the National Pollen Monitoring Network described in the British Aerobiology Federation (BAF) guide. Pollen counts are expressed in grains/metre cubed and represent a daily average. A previous year long study examining pollen data in Derby and Leicester showed that both sets were comparable and that one can be used to forecast the other (Pashley CH 2007). As Nottingham is the same distance from Leicester as Derby, it is assumed that the pollen data will be representative for the local region.

Sun exposure

Sun exposure was assessed using retrospective data from the environmental monitoring site, University of Nottingham at Sutton Bonnington. One option considered was to ask a subset of patients (15) to wear personal dosimetry UV badges one per week for 4 weeks at the onset of the study to quantify their UV exposure over that period. In terms of additional information gained, this measure would not add much to the accuracy of the study.

Maintenance of a high response rate

Loss to follow up was minimised by initial fortnightly telephone reminders (120 calls), giving the patents/ parents an opportunity to discuss queries about diary completion. This approach, combined with review of diaries and guidance on how to complete them at monthly reviews, allowed maximization of data collection.

5.3.4 Sample size

There was no formal sample size justification for this study because of its exploratory nature. What was needed was sufficient data relating episodes of eczema to a range of putative exposure variables. There needed to be sufficient data for these exploratory analyses to give protection against misleading results arising from chance. Large numbers of participants were also needed to explore the interaction between risk factors.

In the pilot study of 30 patients and 18 variables over a 28 day period, the completeness for pre-specified exposures ranged from 65% (holidays) to 83%, while measures of outcome were about 97% complete. 25 children (83%) completed the study.

Based on the pilot study, the proportion of days on which an episode is recorded is 0.23.The definitive study would prudently require 20 events/variable thus needing 18x20/0.23 =1565 person-days. This would be achieved with only 5 individuals if data were complete (6 to 9 months follow-up is required to assess seasonal

effects). However, around 50 participants would still be needed for the patient to patient random effect reflecting differing susceptibility to be measured with a coefficient of variation of 20% and for cluster analysis of eczema types.

In practical terms, the study numbers were restricted by resources, including the study duration, the numbers of children eligible for entry into the study, of which half were likely to agree to participate and the requirements to follow up participants through a long follow-up period. Bearing these constraints in mind, 60 children was a realistic number and was likely to give us sufficient numbers to allow for a contrast between winter and summer groups. Two previous studies, the pilot study and the study by Kramer *et al* managed to show some significant effects despite smaller numbers, 25 and 39 respectively, than the planned study and shorter follow-up periods, 28 days and 6 months respectively (Kramer, Weidinger et al. 2005; Langan, Bourke et al. 2006). The formal statistical analysis methods are discussed in detail in Chapter 7.

5.3.5 Data management

Data was extracted monthly from the dataloggers and electronic diaries to the study laptop. No patient identifiable data accompanied this data. At the end of the study, a second data extraction was done from each electronic diary by the manufacturers. This double-data entry and the automated nature of data extraction should prevent data errors. I performed interim data tabulations and analysis and carried out range and consistency checks to ensure data was accurate. Data from the baseline interviews was stored on the laptop in a separate Excel spreadsheet. All databases were married towards the end of the study and the results of filaggrin mutation analyses were added to this data to allow formal analysis.

5.3.6 Ethics

Written informed consent was obtained from the parents of all participants. Children's assent was also sought, when they were old enough to understand, using appropriate information sheets.

Testing for filaggrin mutations involved obtaining a separate written informed consent, in other words, parents could consent to participate in the study with or without providing consent for mutation analysis. Saliva samples were anonymised and tested using published protocols.

Confidentiality was maintained at all times. No personally identifiable data was stored on the study laptop. Identification of data was through identification numbers; the list of participants was secured separately in a locked filing cabinet.

Chapter 6 The use of electronic diaries

6.1 Background

Diary data collection methods are a well established method of collecting patient reported outcomes (PROs) in clinical research. Their main advantage is that proximate data collection, for example on a daily basis, is associated with reduced recall bias.

Traditional diary methods use pen and paper diaries to record PROs. However, recent studies and systematic reviews of their performance have highlighted important flaws which may be an important cause of bias. Issues include "backfilling" of paper diaries, sometimes termed "parking lot compliance". This is often suspected when paper diaries are completed with a row of identical outcomes for categorical outcome measures. Similarly, "forward filling" of paper diaries is well described. These issues were highlighted in a study by Stone *et al* comparing paper diaries with electronic diaries (Stone, Shiffman et al. 2003). The study compared actual compliance with reported paper diary compliance (measured using a concealed electronic device) and with electronic diary completion. In that study, participants reported completion of paper diaries per protocol 90% of the time compared to actual compliance of only 11%. Indeed for 32% of the study days where diary completion was reported as 90%, the diaries had in fact not been opened.

6.2 Comparisons of electronic and paper diaries

Electronic diaries are a recent development in research. There is some evidence to support their use over paper diaries in clinical studies. Dale and Hagen reviewed this issue in a recent systematic review (Dale and Hagen 2007). They included only randomised controlled trials (RCTs) or quasi-randomised studies with direct comparisons of the two data collection methods. Their comparisons included the following fields: feasibility, protocol compliance, data accuracy and participant

acceptability. Nine studies were included in the review. In terms of feasibility, five studies reported technical problems including malfunction and problems with power leading to a loss of data in three of the five studies (Tiplady B 1997; Gaertner, Elsner et al. 2004; Lauritsen, Degl' Innocenti et al. 2004; Nyholm, Kowalski et al. 2004; Palermo, Valenzuela et al. 2004). One study reported an 80% reduction in the time needed for data handling with electronic devices (Tiplady B 1997). Five studies reported improved compliance using electronic diaries, while one study in adults reported better compliance with the paper diary method (Rabin, McNett et al. 1993; Rabin, McNett et al. 1996; Stone, Shiffman et al. 2003; Nyholm, Kowalski et al. 2004; Palermo, Valenzuela et al. 2004). Four of five studies reported "falsification" using the paper diary method (Tiplady B 1997; Stone, Shiffman et al. 2003; Gaertner, Elsner et al. 2004; Lauritsen, Degl' Innocenti et al. 2004). Three studies reported fewer errors using electronic diaries (Tiplady B 1997; Quinn, Goka et al. 2003; Palermo, Valenzuela et al. 2004). Of seven studies assessing participant acceptability, four reported a preference for electronic diaries while three showed no difference (Rabin, McNett et al. 1993; Rabin, McNett et al. 1996; Tiplady B 1997; Quinn, Goka et al. 2003; Gaertner, Elsner et al. 2004; Lauritsen, Degl' Innocenti et al. 2004; Palermo, Valenzuela et al. 2004). Other significant differences highlighted by the authors include the increased costs of purchase of the devices and the increased set up times required.

6.3 Choosing and piloting the electronic diaries

Electronic diaries were chosen to record exposures and outcomes to increase compliance, reduce data errors and reduce the possibility of bias (Chapter 7). This method was also more likely to appeal to children more than paper diaries. This methodology represented a novel use of electronic PROs in dermatology, although they have been used for similar studies in respiratory medicine and rheumatology settings. Smart Patient Diary Cards (SPDC, Logos Technologies, Lymington, UK)

were used in this study. These were selected in preference to personal digital assistants (PDAs) due to concerns about the risk of loss of these devices. Other alternatives considered for this study included the use of mobile phones and the internet; two issues were a concern with these methods; firstly, the issue of data encryption and protection and secondly a concern that restriction to participants with access to these resources would incur selection bias. Other portable diaries were either less attractive interfaces or more expensive to source. The SPDC is a device specifically designed to record diary data. It has a small screen and a series of numbers and arrows which is suited to categorical responses and the use of visual analogue scales (Figure 6-1).

Figure 6-1 The Smart patient diary card (SPDC)

Legend to figure 6-1

This figure shows an example of the type of electronic diary used in the study. Participants use the numbers top and bottom to answer the questions which use Likert scales and the keys on either side to go foreward.

Set up stages involved designing a questionnaire which could be used on a daily basis to record relevant exposures and outcomes. This questionnaire was piloted amongst staff and volunteers from the paediatric eczema clinic, both adults and children. Subsequently, questions were uploaded onto a test device. This highlighted problems with the format of a number of questions, some of which needed to be abbreviated to fit on the screen. Piloting of the revised questions was carried out using the same panel. A series of further revisions followed before the final question series was completed (Appendix 9). Formatting "bugs" were uncovered when pilot testing the "final" series which took ten revisions to resolve; these included problems with non-functioning "skip" questions and ease of reading of the interface. The next step involved trial data downloading from the test device using a smart card. A training booklet was prepared to accompany the devices which complemented an initial training session on their use. The training booklet was given to all participants. A "smart card" for data download was maintained for each participant and this was used to download information from electronic diaries at each monthly review. A final data download was also carried out by Logos technologies.

6.4 Electronic diary experience

The SPDC was user-friendly and participants had no problems using the devices. However, despite installation of special long-life batteries to allow the devices to last for the length of the study, battery failure was a significant problem. Battery failure occurred in the event of either genuine battery failure or displacement of batteries. 39 (65%) of participants required replacement diaries on at least one occasion; of these, 25(42%) were replaced once, 13(22%) twice and 1(2%) three times. Due to delays incurred by getting the devices reprogrammed and reissued to the participant, a pragmatic solution was reached whereby a replacement diary was issued when battery failure occurred. The disadvantage of that was that this resulted in participants having multiple diary numbers. A strict log of participant and diary

numbers was maintained to avoid error. On a few occasions, multiple diaries failed simultaneously leading to delays and lost data. Data extraction was a smooth process using smart cards; this was duplicated by the final diary download carried out by the manufacturers. There were no data entry errors or skipped questions as the diary format made this impossible. As responses were pre-coded and downloading was automated, transcription errors were not possible.

In summary, the diaries were a user-friendly interface which allowed easy data download and avoided data errors. However, devices were expensive and associated with significant technical problems which lead to their use being more cumbersome than planned. Comparison with paper diaries is not possible in this study. Power failure is a frequently reported problem with the use of electronic diaries and this study is testament to that.

On balance, the increases in data accuracy associated with the use of electronic diaries and reduction in recall bias merits the extra costs and technical difficulties incurred by their use. The reduction in bias and data errors is of critical importance in an observational study setting.

Chapter 7 Statistical methods

7.1 Environmental factors

The mean, standard deviation and range for all environmental variables were calculated for different environmental factors and examined graphically. High outdoor temperature was defined as greater than 22°C, which is equivalent to the 95th centile. Low outdoor temperature was defined as less than 1°C, which is equivalent to the 5th centile. Similarly low relative humidity was defined as <40%, or the 5th centile.

7.2 Missing data

As this was an observational study requiring completion of electronic diaries daily for long periods of time, there was likely to be a substantial proportion of missing data. Kramer *et al* carried out a similar panel study in a group of children in Germany and excluded 14 children out of 56 (25%) due to poor completion of diary data.(Kramer, Weidinger et al. 2005) The researchers highlighted major differences between participants with missing data and those with higher degrees of compliance. Children with missing data were systematically different with lower parental school education (23% vs. 37% having at least one parent with a university degree) and had a slightly lower prevalence of acute eczematous lesions (50% vs. 57%). As a similar or higher degree of missing data was expected, a strategy was planned to assess missing data to try to minimise selection bias and the loss of power which would be incurred by case exclusion. A recent paper by Burton and Altman highlighted the poor quality of observational studies in terms of dealing with missing data and proposed guidelines for the reporting of missing covariate data (Burton and Altman 2004). These guidelines recommend that investigators should quantify the amount of missing data in the study (by case and by variable), outline the approaches used to handle the

missing covariate data and explore the missing data comparing the characteristics of those with missing data to those with complete data.

After considering the options, a pragmatic approach to the missing data was chosen highlighting the amount of missing data and comparing good responders to poor responders in terms of baseline characteristics to identify obvious sources of selection bias. As each individual's observations were being collected over long periods and all the data are correlated for each participant, losing a data point loses much less information than for independent data. Therefore after considering the use of imputation techniques such as multiple imputation by chained equations (ICE, available as a downloadable add-on for Stata. This program performs imputations using a model based approach based on chained regression equations), and obtaining independent statistical advice from an independent senior statistician (Professor Mike Campbell, Sheffield) with expertise in time-series analysis, it was concluded that it was reasonable to proceed with analysis using the Kalman filter option in Stata in order to handle missing data. The Kalman filter skips missing values, then obtains maximum likelihood estimators of the model parameters and then applies a smoothing process. ARMA will still fail however if there is substantial missing data and may lead to exclusion of some participants from analysis.

7.3 Autoregressive moving average (ARMA) model

The following autoregressive moving average (ARMA) model was used in which the error terms are allowed to be autocorrelated.

Equation 7-1 ARMA model

$$y_t = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_n x_n + e_t$$
$$e_t = ARIMA(p,q)$$

Legend for equation 7-1

=outcome, β_n=regression coefficient associated with *n* exposure variables, x_n=exposure variables, e_t=error term

For this model ante-dependence of the response is entirely subsumed in the autocorrelations. An AR (1) structure was used, i.e. an ARMA (1,0,0) model, assuming that the error terms have a first order autocorrelation. The choice of model was determined by comparing the Akaike Information Criteria (AIC) for different model specifications; a first order specification was associated with a lower AIC than a second order autocorrelation for all but three individuals and therefore this was the preferred model. This model was used to assess the impact of variables on "bother" and "scratch" scores. The model generated regression coefficients and standard errors for each patient in relation to the different exposure variables. One patient's data was entirely excluded from analysis as the poor quality data made regression impossible.

7.4 Analysis for the primary and secondary outcome measures

Comparison of regression coefficients between patients on exposure to different variables was done using standard meta-analysis methods, i.e. treating each participant as a separate "study". The data was first examined for the primary outcome measure "bother" and then examined for the secondary outcome "scratch scores". If heterogeneity between participants was established, this indicated variation in individual susceptibility to exposures.

Der Simonian & Laird's approach was used to pool estimated coefficients on the basis of a random effects model and to estimate the between-participant variance. If heterogeneity was demonstrated for different exposure variables, these variables were entered into a multiple regression model and coefficients estimated using the multiple regression model were likewise combined using the Der Simonian and Laird method to determine whether the association seen in univariate models may have been explained by a confounding variable, assuming that the confounding variable was included in the regression model. Examination of the association between the secondary outcome measure, "stepping up" of treatment was carried out using a

different technique as the binary nature of this outcome measure (yes/no) means that it does not meet the assumptions of the ARMA model (which assumes a Normal distribution for the errors). The technique used was a logistic regression with inclusion of lagged responses in the regression model, thus generating autocorrelated responses rather than autocorrelated errors as in ARMA. This was done by generating lagged responses for the outcome measure and including the lagged term within the regression model (Equation 7-2).

Equation 7-2

$$Logit(y)=\alpha+\beta_1 x_1+ \beta_n x_n+\beta y_{t-1}$$

Legend for equation 7-2

y=outcome, β_n=regression coefficient associated with n exposure variables, x_n=exposure variables, βy_{t-1}=lagged response variable

The issue of multiple testing was also explored in relation to main study findings by exploring the impact of using 99% confidence intervals on associations with increased "bother" scores significant using 95% confidence intervals. The site-specificity of reactions was also examined. Analysis was carried out to see whether exposure to aeroallergens such as grass, exposure to pets and dust was associated with worsening of facial and hand eczema and whether clothing exposure (wool or nylon worn next to the skin) was associated with worse eczema on the trunk and limbs. This was done by examining the data for associations between regression coefficients for responses to exposures and site-specific worsening as recorded in the electronic diaries as a follow-on question if the participant had stepped up their treatment that day.

7.5 Testing of hypotheses

Hypotheses were tested by generating point and interval estimates of regression coefficients corresponding to specific exposures. If the 95% confidence interval did

not include zero this was equivalent to a significance test performed at a two-tailed 5% level. Testing the hypotheses required construction of three composite variables A (high outdoor temperature, >22°C, sweating and high grass pollen levels), B (dust exposure, low outdoor temperature, <1°C, and low indoor relative humidity, <40%) and C (shampooing hair at the same time as the bath or shower and low outdoor temperature). The main effects of the composite variables A, B, and C were assessed, followed by estimation of the interaction between temperature and these variables if the main effect showed statistical significance. Power for the latter is likely to be low (as it nearly always is in studies not specifically designed to detect interactions).

The final hypothesis was that combinations of exposures rather than individual exposures might be the important aspect in disease worsening and flares. This hypothesis was based on Rothman's "pie" model of causation, whereby disease causation or worsening may relate to several factors acting in concert rather than an individual factor.(Rothman KJ 1998) This theory is based on factors being sufficient to cause or, in the scenario of this study, to worsen disease. Sufficient causes can comprise a number of component causes which are not themselves necessary for disease causation or worsening. To test this hypothesis, a binary variable was created which was defined as being present if any three or more of the following exposures was experienced: dust, exposure to pets, shampoo, sweating, swimming, nylon next to the skin and a change in mean weekly temperature of greater than or equal to 3°C, and absent if this was not the case. The selection of change in mean temperature of greater than 3°C was an arbitrary point chosen following discussion with parents of children with eczema and colleagues with expertise in the management of eczema as being sufficient to trigger disease worsening. The association between the combined variable and the primary outcome measure was assessed using meta-analysis techniques as described previously. I also explored

the impact of each additional exposure contained within the combined variable, by treating the components of the variable as categorical, to determine graphically whether the relationship between worsening of disease and number of exposures at the level of the episode was linear. This was done using regression for one, two and three exposures and combining the regression coefficients using meta-analysis combining across patients as previously described. A line graph was then created and examined graphically with the hypothesis that each additional exposure would be associated with a linear increase in eczema severity.

7.6 Comparing the performance of totally and well controlled weeks to monthly outcome measures

The performance of the proposed definitions of disease control, totally and well controlled weeks (TCW and WCW) was examined by assessing the association between these measures and the measures of objective and subjective disease severity measured at monthly and three monthly intervals throughout the study, the three item severity score (TIS), the patient orientated eczema measure (POEM) and the children's dermatology life quality index (CDLQI) respectively. This analysis was done at the level of the patient rather than the level of the episode as in time-series analysis. All of the regular measurements were converted into binary measures at arbitrary points as there are no clear guidelines on their correlations with clinical severity to define more and less severe disease. The cut off points to define more severe disease used were as follows: a POEM score of greater than 14, CDLQI of greater than16 and a TIS score of greater than five. These scores were calculated for each individual by calculating an average of the monthly and three monthly scores taken throughout the study. The mean number of totally and well controlled weeks was calculated and compared amongst those with more and less severe disease for each score to determine whether there was a statistically significant difference between the groups. TCW and WCW were defined as in Figure 7-1.

Figure 7-1 Proposed definitions of totally and well controlled weeks in eczema

Totally controlled week (TCW)

Treatment not "stepped up"

Plus

Zero days with scratch score >4

Well controlled week (WCW)

Treatment "stepped up" for ≤2 days

Plus

≤2 days with scratch score>4

The average number of flares was also calculated for each individual to determine if this varied between groups with differing severity of eczema, using the same outcome measures to determine severity.

7.7 Correlation between baseline perceptions and worsening on exposure

The relationship between perceived worsening on exposure to an environmental factor as assessed in the baseline interview by parental perception of avoidance of exposure and observed worsening on exposure was assessed. This was done by examining regression coefficients for bother scores following specific exposures at the patient level and comparing this outcome between participants who had given a history or worsening or avoidance of specific exposures and those that had not.

7.8 Exploratory analysis to assess the validity of "summer" and "winter" types of eczema

The hypothesis proposed by Kramer *et al* that winter and summer types of eczema exist where one group worsens in winter when the weather is cold and the other in summer when the weather is hot was also examined (Kramer, Weidinger et al. 2005). I used cluster analysis to assess whether distinct groups existed who responded in a different fashion during summer and winter. Two methods were used to generate the clusters, Ward's method and the complete linkage method. Clustering of patients was carried out using each patient's regression coefficients for "bother" scores in summer and winter. Dendrograms were then produced for both methods and examined visually to determine whether the summer and winter differentiation was valid and whether similar clusters were identified with each methodology. Dendrograms are two dimensional diagrams whereby the degree of similarity between individuals is used to group participants by response to both summer and winter.

Results

Chapter 8 Demographic details of participants

8.1 Description of participants

Sixty children completed the study. 146 participants were given information about the study of which 52 did not respond, 16 had insufficient eczema, one was not within the study age category, ten could not complete the diary and seven were not keen to participate. The baseline demographic details of participants are described in Table 8-1. The median age for participants was 6.5 years (interquartile range (IQR) = 8.5 years); the age range was 0.4-15.9 years. There were 32 boys (53.3%) and 28 girls (46.7%). The majority of participants, 38 (63%) were white European, the next largest proportion were Indian, n=8 (13%) with smaller numbers from other ethnic groups. Social classes 1 and 2 (assessed by parental occupation) were in the majority, n=26 (43%) and similarly, when social class was assessed by parental education, n=23 (38%) had a parent/carer with a university degree or higher level of education (Statistics 2002). Median study duration was six months (IQR= 0.5 months). At baseline, the median POEM score was 13 (IQR=10) with a range from 2-28. The median CDLQI was 9 (IQR=8, range 1-25). Median baseline TIS score was 3 (IQR=2, range 1-8). As shown in Table 8-1, 15 (25%) had either previous systemic (azathioprine, cyclosporine or oral prednisiolone) or phototherapy treatment. 46 children (77%) were recruited from hospital clinics while 14 were recruited from community clinics. However, many of the patients recruited from community clinics may have originated in the hospital clinic in the first instance. Average baseline TIS scores were 3.3 in the hospital cohort and 2.6 in the community clinic cohort (p=0.12). 40 children (67%) were from urban areas while 20 were from rural regions.

9.2 Baseline beliefs

I also determined parental perceptions and avoidance behaviour at baseline to determine if there was any determinable correlation with worsening on exposure. Parental perceptions as assessed at baseline were as follows: 42 (70%) were avoiding clothes (wool or synthetic), 51 (85%) of parents were avoiding cleansing products including shampoos and washing powders and 29% (48.3%) were avoiding furry pets as these were believed to worsen eczema. 31 (51.7%) believed that their child's eczema was worse in cold weather, while 6 (10%) felt the eczema was better in cold weather. Similarly for hot weather, 37 (61.7%) gave a history of worsening in hot weather and 9 (15%) described an improvement in eczema severity in hot weather.

8.3 Filaggrin mutations

Mutations in *FLG* were detected in ten of 54 children who had saliva tests (18.5%). Six opted not to have filaggrin tests done. Six children were heterozygous for the r501x null mutation, of whom four were white European and two were mixed race. 2282del4 mutations were detected in four white European children of whom three were heterozygous and one was homozygous. No compound heterozygotes were identified and no *FLG* mutations were in children from other ethnic groups. The proportion of white European children with *FLG* mutations was 8/38 (21%).

Table 8-1 Demographic details of participants in cohort study

Characteristic	Frequency	Percentage (%)
Age group (years)		
<2	8	13.3
2-5.9	19	31.7
6-11.9	18	30
>12	15	25
Gender		
Boy	32	53.3
Girl	28	46.7
Ethnicity		
White	38	63.3
Indian	8	13.3
Black Caribbean	4	6.7
Mixed race	4	6.7
Pakistani	3	5
Chinese	3	5
Social class by parental occupation		
1-2	26	43.3
3-4	8	13.3
5-7	11	18.3
8-9	15	25
Parental education		
None	6	10
GCSE	22	36.7
A level	2	3.3
Higher education below degree	7	11.7
Degree or higher	23	38.3
History of asthma		
Yes	30	50
No	30	50
History of hayfever		
Yes	36	60
No	24	40
Previous systemic or phototherapy		
Yes	15	25
No	45	75
Total	60	100

Chapter 9

Results of statistical analysis

9.1 Environmental factors

Temperatures during the study period ranged from -6.1 to 28.7°C. The daily mean temperatures for each season (Figure 9-1) were as follows: spring 10.2°C (range -1.8 to 23.1), summer 15.5°C (range 5.8 to 28.5), autumn 11.7°C (range -1.7 to 28.7) and winter 6.6°C (range -6.1 to14.5). The daily mean outdoor relative humidity was 83.8% (range 61.1 to 100.0) with mean relative outdoor humidity by season as follows: spring 79.7% (range 61.1 to 100), summer 81.4% (62.1 to 86.5), autumn 85.1% (61.2 to 100) and winter 85.6% (62.0 to 97.9). Mean solar radiation level during the study was 230.8 MJ/m^2 (range -17.2 to 2496), Figure 9-2. Examining mean solar radiation by season, in spring mean radiation was 546.7MJ/m^2 (86.5 to 1063.5), in summer 662.7 MJ/m^2 (124.2 to 1139.6), autumn 311.1 MJ/m^2 (-3.8 to 744.4) and winter 119.0 MJ/m^2 (16.6 to 355.8). Mean grass pollen level was 7.9 grains/m^3 (range 0 to 229), Figure 9-3. The grass pollen season lasted from May 18th 2007 to August 11th 2007 with a peak on June 9th of 229.0 grains/m^3 (Figure 9-3) The mean birch pollen level was 2.7 grains/m^3 (range 0 to 223.6) (Figure 9-4). The birch pollen season was shorter, lasting from April 5th 2007 to May 1st 2007 with a peak on April 15th of 223.6 grains/m^3.

Figure 9-1 Mean temperature during study period

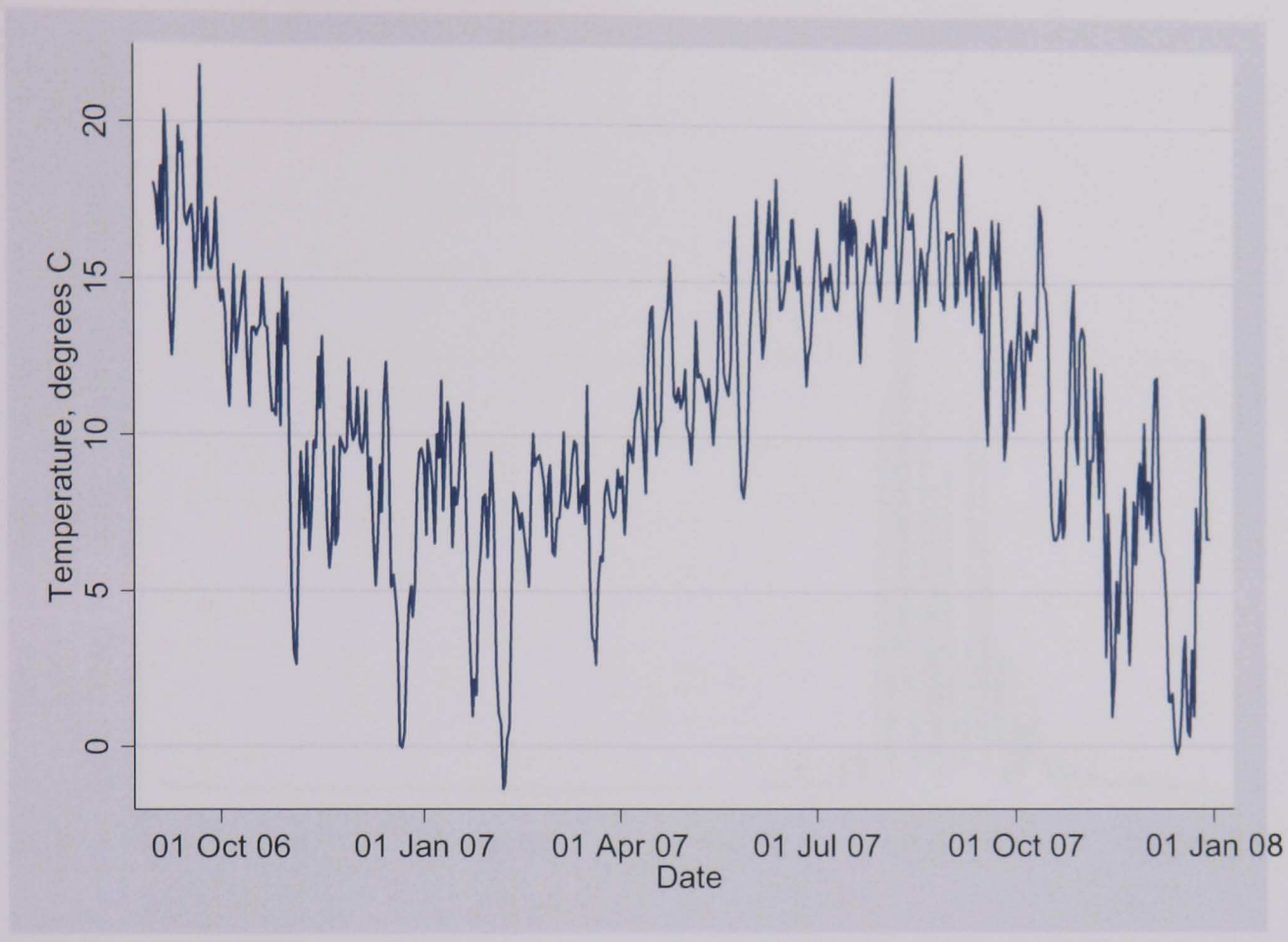


Figure 9-2 Mean radiation during the study period

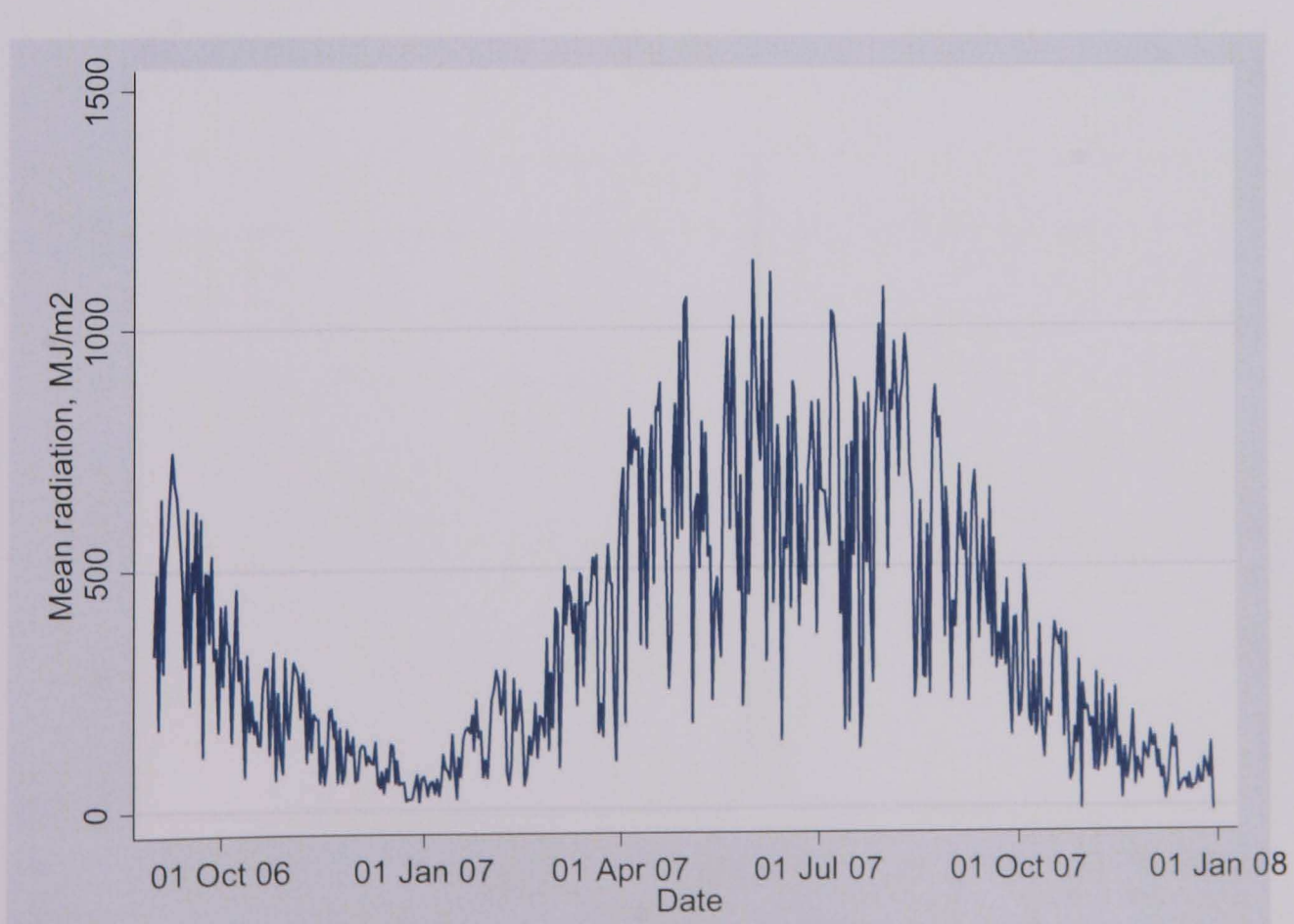


Figure 9-3 Grass pollen level during study period

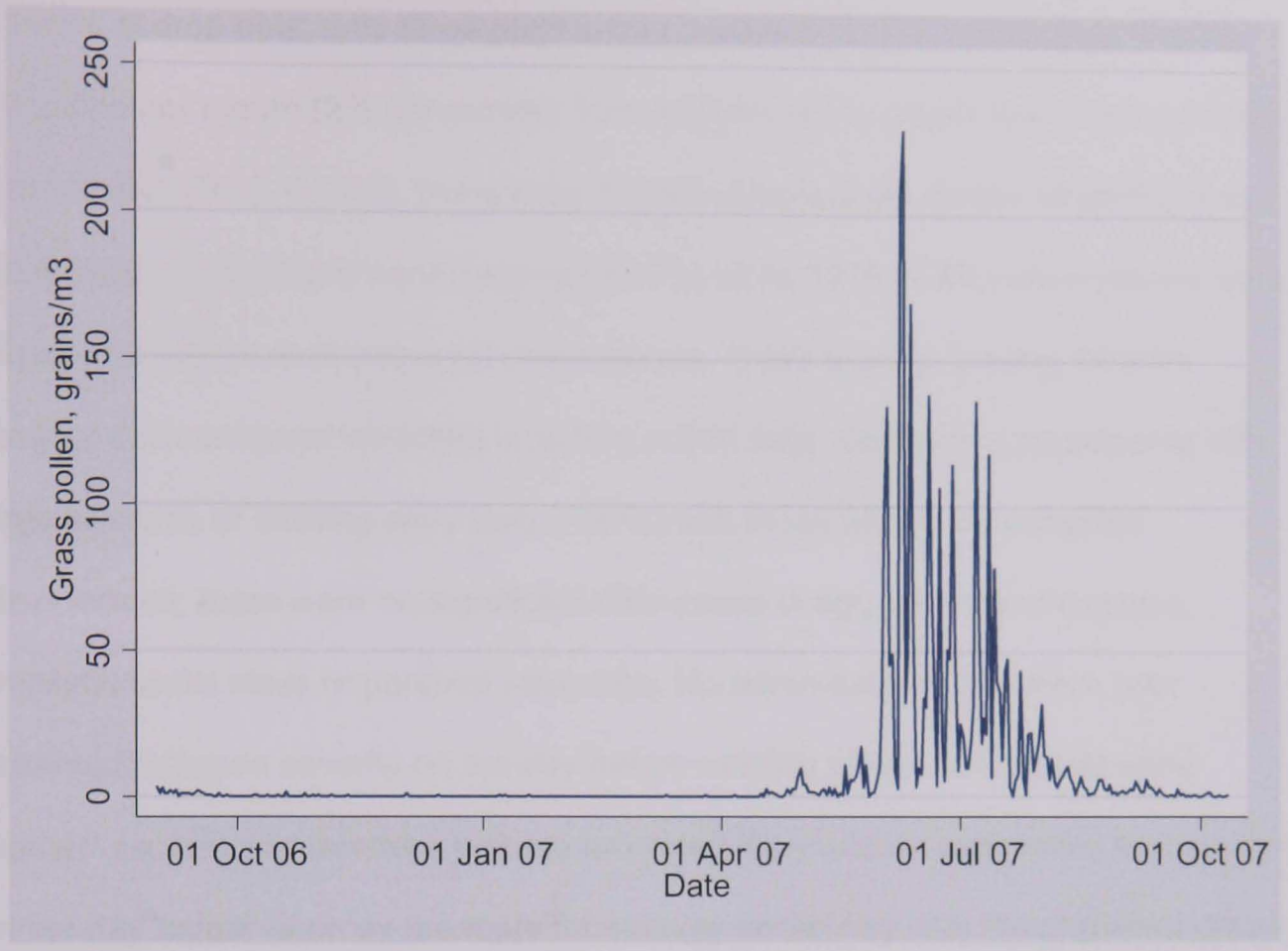
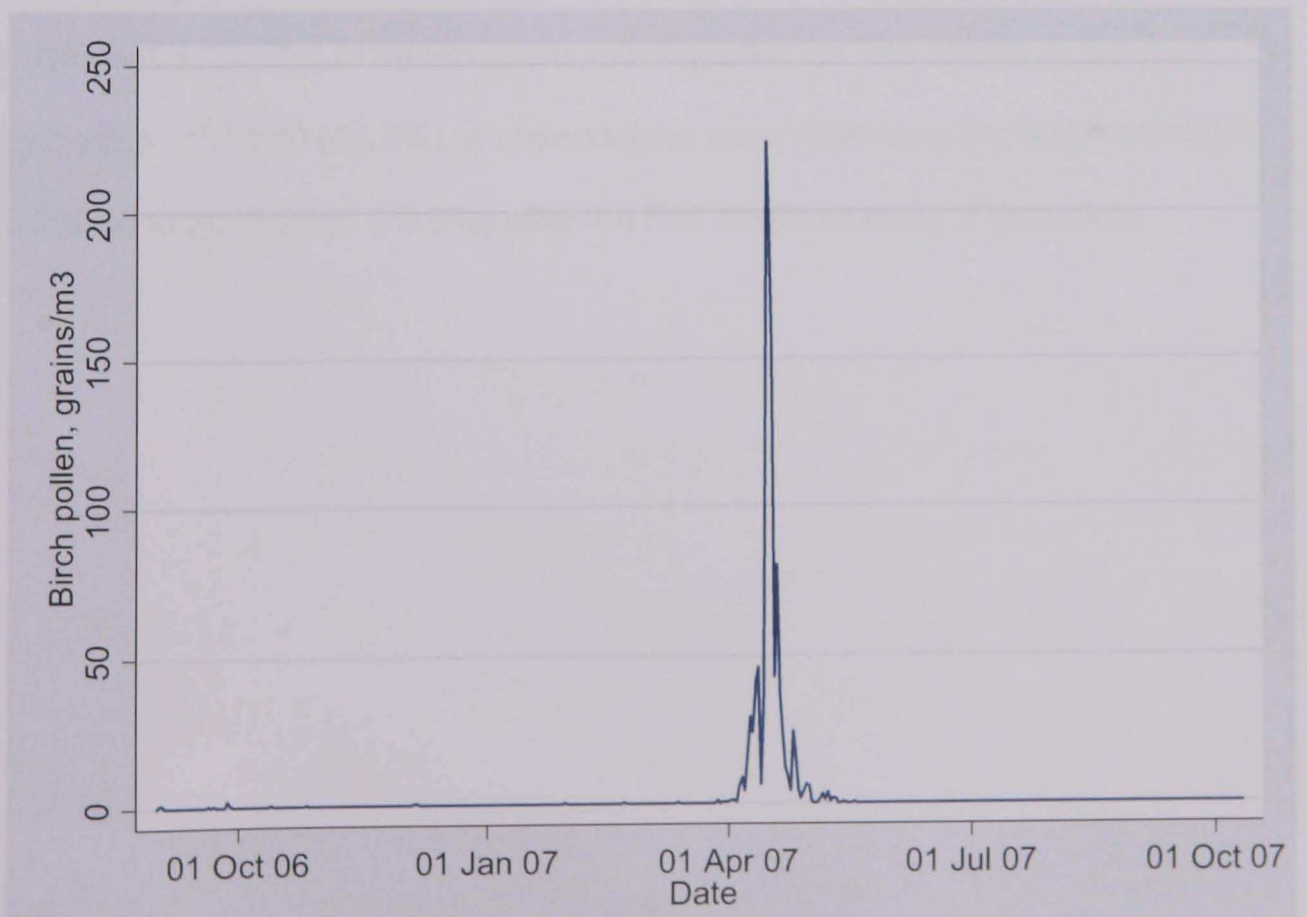


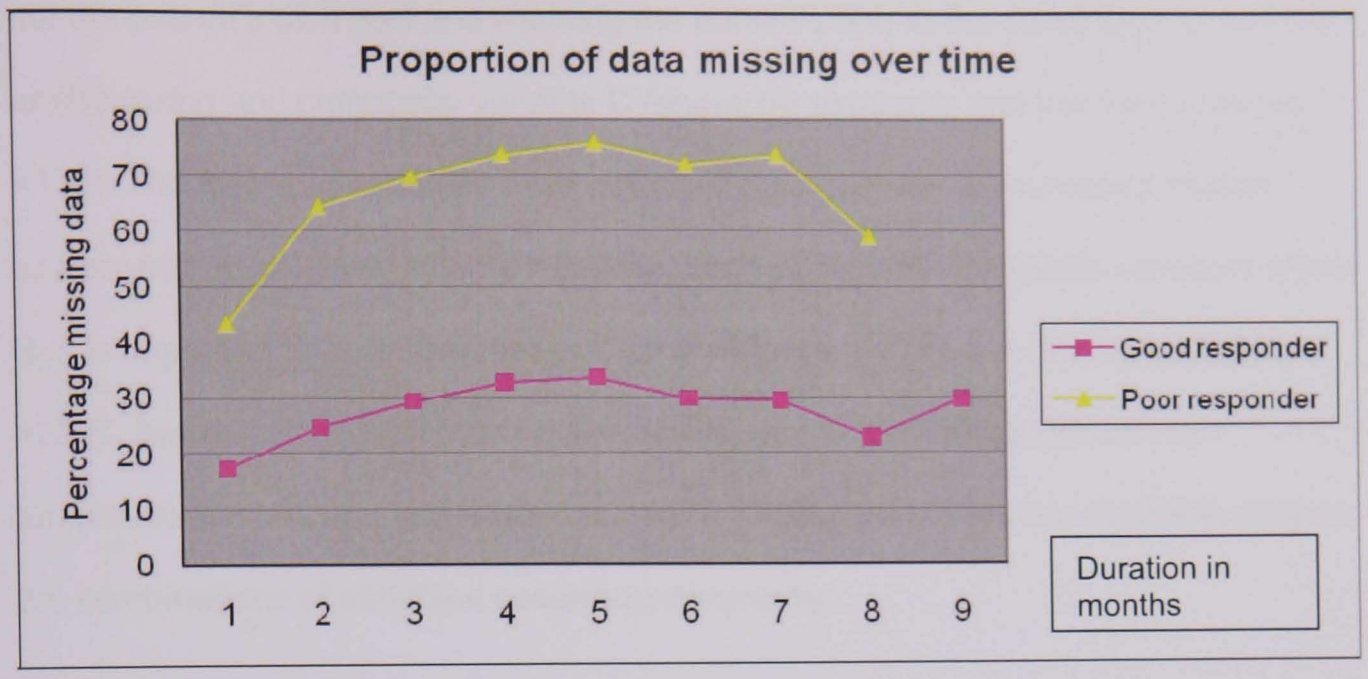
Figure 9-4 Birch pollen levels during study period



9.2 Missing data

In terms of drop outs, only three participants dropped out in the first three months (6%), one per month (2% per month); four dropped out in month four (7%) and three in month five (5%). Overall, there were 10,940 observations across all participants. 4354 diary observations were missing (39.8%) while 1079 (9.8%) observations were missing for indoor environmental observations. There was no missing data for outdoor environmental variables including pollen data. Comparing participants with large amounts of missing diary data (>50%) with those with more complete observations, there were no significant differences in age, severity of eczema, ethnicity, social class or parental education. No within-subject difference was observed between severity on the day before missing values (measured using "bother" scores) and the days before completed diary entries suggesting that severity on the day before (a proxy measure for severity on the day with missing diary entries) was not a good predictor of missing values (p=0.17). In good responders, there was 199/1153 (17.3%) missing data in the first month of study across patients compared to 1889/6363 (29.7%) of observations missing after the first month. In the poor responders, 251/580 (43.3%) of observations were missing in the first time month compared to 2015/2844 (70.9%) after the first month of study (Figure 9-5).

Figure 9-5 Proportion of missing data in "good" and "poor" responders over the study period



Legend for figure 9-5

This figure shows the percentage of data missing over time (months) in responders. Responders are divided into "good" and "poor" responders. "Poor" responders were defined as those with more than 50% of diary data missing through the study duration. Both groups demonstrated fatigue after month 1 but this was more pronounced in the "poor" than in the "good" responders.

9.3 Results of relationship between environmental factors and eczema severity as measured using "bother" score

9.3.1 Univariate analysis

Table 9-1 shows the results of meta-analysis for the primary outcome measure "bother". In univariate analysis, heterogeneity was detected for the following variables: dust, swimming, maximum outdoor temperature, mean radiation, wool exposure next to the skin, sweating, grass pollen, spring, summer, autumn, winter exposure (shown in the forest plot Figure 9-6) and change in mean weekly temperature.

No statistically significant heterogeneity was detected for the other variables and therefore it is reasonable to use the pooled estimates. Increased bother scores were

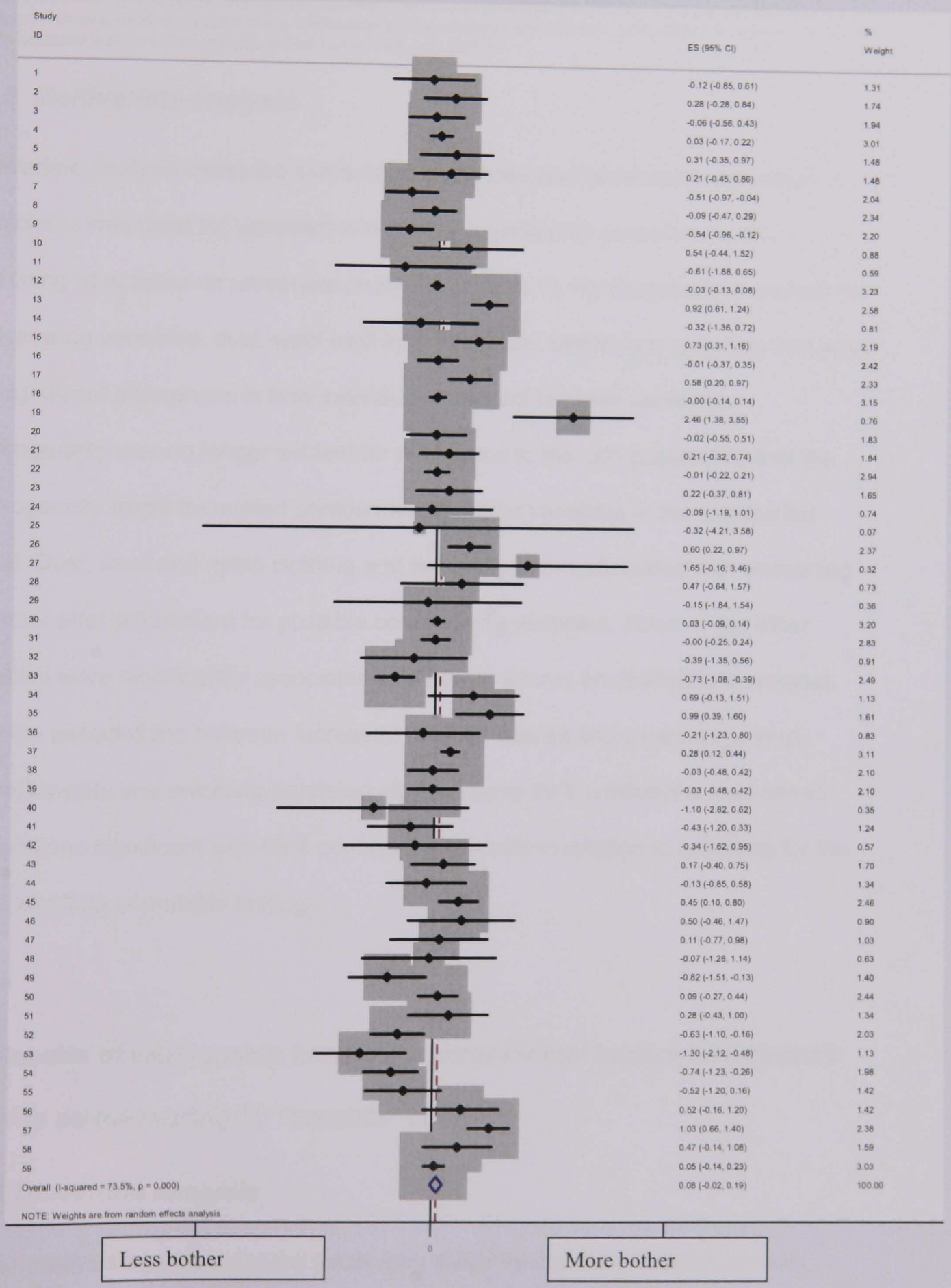
detected relating to wearing nylon next to the skin, exposure to unfamiliar pets (i.e. not the patient's own pet) and washing the patient's hair at the same time as bathing or showering and composite variable C (shampoo exposure and low temperatures, <1°C). The following variables were not significantly related to increased "bother" scores: minimum indoor relative humidity, birch pollen and composite variables A and B. It is important to note however that for composite variables A (hot temperature, >22°C, sweating and high grass pollen levels) and B (dust exposure with low temperature, <1°C and low relative humidity, <40%) there were few available data as the combinations of variables occurred infrequently.

Table 9-1 Results of univariate and multivariate analyses for primary outcome "bother" using meta-analyses to assess heterogeneity

Factor	Summary regression coefficient	Confidence interval	Results of heterogeneity Chi-squared test	Tau squared	Coefficient of variation
Univariate analysis					
Dust	**0.344**	**0.046 to 0.642**	**<0.001**	**0.375**	**1.780**
Swim	0.081	-0.119 to 0.281	0.002	0.112	0.872
Minimum relative humidity	-0.003	-0.007 to 0.001	0.632	<0.001	0.657
Maximum outdoor temperature	0.001	-0.016 to 0.017	<0.001	0.002	0.549
Mean radiation	0.000	-0.000 to 0.000	0.009	<0.001	0.482
Wool next to skin	**0.463**	**0.101 to 0.825**	**<0.001**	**0.304**	**0.434**
Nylon next to skin	**0.342**	**0.143 to 0.540**	**0.05**	**0.094**	**0.398**
Pets	**0.221**	**0.099 to 0.343**	**0.469**	**<0.001**	**0.370**
Sweating	**0.178**	**0.039 to 0.316**	**0.03**	**0.057**	**1.340**
Shampoo	**0.067**	**0.005 to 0.129**	**0.994**	**0.000**	**0**
Grass pollen	0.06	-0.034 to 0.154	<0.001	0.056	3.944
Birch pollen	0.001	-0.006 to 0.008	0.742	<0.001	0
Composite variable A	0.035	-2.508 to 2.578	1.0	<0.001	0
Composite variable B	-0.330	-1.468 to 0.808	0.982	<0.001	0
Composite variable C	**0.303**	**0.039 to 0.566**	**0.188**	**0.093**	**1.006**
Spring	-0.049	-0.279 to 0.181	<0.001	0.431	-13.398
Summer	0.220	-0.006 to 0.445	0.001	0.185	1.955
Autumn	-0.144	-0.552 to 0.233	<0.001	0.738	5.966
Winter	0.082	-0.137 to 0.300	<0.001	0.199	5.440
Change in temperature	0.057	-0.117 to 0.231	<0.001	0.158	6.974

Factor	Summary regression coefficient	Confidence interval	Results of heterogeneity Chi-squared test	Tau squared	Coefficient of variation
Multivariate analysis					
Dust	**0.531**	**0.230 to 0.832**	**<0.001**	**0.291**	**1.016**
Wool next to the skin	**0.421**	**0.061 to 0.782**	**<0.001**	**0.291**	**1.281**
Nylon next to the skin	**0.232**	**0.034 to 0.430**	**0.101**	**0.074**	**1.173**
Pet	0.110	-0.058 to 0.278	0.110	0.054	2.113
Sweating	**0.237**	**0.086 to 0.388**	**0.023**	**0.065**	**1.076**
Shampoo	0.070	-0.005 to 0.144	0.917	<0.001	0
Composite variable C	0.228	-0.053 to 0.508	0.172	0.113	1.474

Figure 9- 6 Forest plot of the effects of grass on individual patient's "bother" scores in those with reasonably complete data (n=59) (univariate analysis)



Legend to figure 9-6

The left side of the forest plot lists the individuals. The results for each individual are shown as squares centred on the regression coefficient. A horizontal line runs through the square to show its 95% confidence interval. On the right hand side the regression coefficient and its confidence interval are given as are the weights given to each individual. The overall estimate from the meta-analysis and its confidence interval are represented by the diamond. The centre of the diamond represents the pooled regression coefficient, and its horizontal tips represent the confidence interval. A vertical line representing no effect is also plotted.Significance is achieved at the set level if the diamond is clear of the line of no effect. In this figure, the diamond overlaps the line of no effect and therefore the pooled estimate is not significant. Heterogeneity is evident in the distribution of responses around the line of no response and the results of the Chi-squared test for heterogeneity shown bottom left, $p<0.001$.

9.3.2 Multivariate analysis

Multivariate analysis using the same ARMA methods and generating regression coefficients was used for variables which were significantly associated with worsening of eczema on univariate analysis (Table 9-1). Heterogeneity remained for the following variables: dust, wool next to the skin and sweating suggesting that there are significant differences in how individuals respond to these variables. Heterogeneity was no longer evident for nylon next to the skin suggesting that the heterogeneity might be related confounding by other variables in the unadjusted model. Dust, wool and nylon clothing and sweating were associated with worsening of bother after adjustment for possible confounding variables. None of the other variables were significantly associated with bother scores on multivariate analysis. Only the associations between increased "bother" scores and exposure to dust, unfamiliar pets and sweating persisted after applying 99% confidence intervals to associations significant with 95% confidence intervals in relation to adjusting for the possible effect of multiple testing.

9.4 Results of relationship between environmental factors and eczema severity as measuring by "scratch" scores

9.4.1 Univariate analysis

Similar analysis was done for the secondary outcome variable, "scratch" scores (Table 9-2). Significant heterogeneity was detected for the following variables: dust,

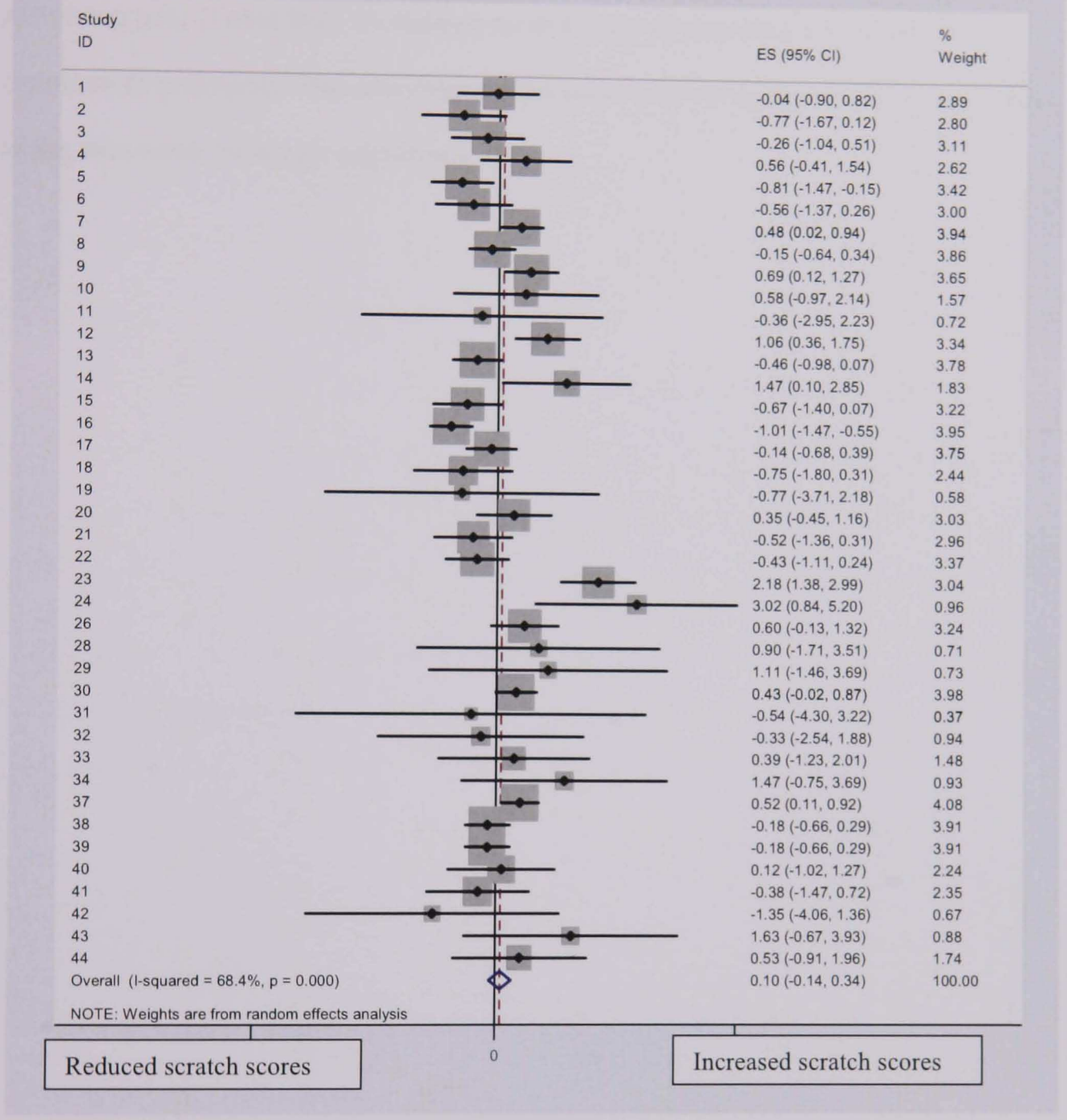
maximum outdoor temperature, mean radiation, wearing nylon against the skin, pet exposure, shampoo exposure, grass pollen, the four seasons (Figure 9-7 shows the heterogeneity in response to winter exposure) and composite variable C. No significant heterogeneity was detected for the other variables. Pooled estimates for the variables not showing heterogeneity show no significant associations between minimum relative humidity, change in mean weekly temperature, birch pollen exposure, composite variables A and B and scratch scores. Significant increases in scratch scores were seen for the following variables: swimming, wearing wool next to the skin, sweating and shampoo exposure.

Table 9-2 Results of univariate and multivariate analyses for secondary outcome "scratch" using meta-analysis to assess heterogeneity

Factor	Summary regression coefficient	Confidence interval	Results of heterogeneity Chi-squared test	Tau squared	Coefficient of variation
Univariate analysis					
Dust	0.087	-0.202 to 0.375	<0.001	0.361	6.906
Swim	**0.142**	**0.004 to 0.280**	**0.246**	**0.021**	**1.020**
Minimum relative humidity	0.002	-0.002 to 0.006	0.533	0.000	0
Maximum outdoor temperature	-0.005	-0.021 to 0.011	0.001	0.001	-6.324
Mean radiation	-0.000	-0.000 to 0.000	0.001	0.000	0
Wool next to skin	**0.283**	**0.113 to 0.453**	**0.834**	**0.000**	**0**
Nylon next to skin	0.232	-0.100 to 0.564	<0.001	0.620	3.394
Pets	0.123	-0.083 to 0.329	0.001	0.177	3.420
Sweating	**0.147**	**0.037 to 0.258**	**0.300**	**0.013**	**0.776**
Shampoo	**0.068**	**0.007 to 0.129**	**0.587**	**0.000**	**0**
Grass pollen	0.012	-0.069 to 0.092	<0.001	0.035	15.590
Birch pollen	0.005	-0.012 to 0.023	0.12	0.000	0
Composite variable A	0.113	-2.526 to 2.751	1.0	0.000	0
Composite variable B	-0.498	-1.493 to 0.497	0.413	0.081	-0.571
Composite variable C	0.326	-0.043 to 0.694	<0.001	0.446	2.048
Spring	-0.019	-0.256 to 0.219	<0.001	0.505	-37.402
Summer	0.138	-0.089 to 0.366	0.001	0.192	3.175
Autumn	-0.018	-0.361 to 0.324	<0.001	0.569	-41.907
Winter	0.104	-0.137 to 0.345	<0.001	0.282	5.106
Change in weekly temperature	0.104	-0.009 to 0.218	0.808	0	0

Factor	Summary regression coefficient	Confidence interval	Results of heterogeneity Chi-squared test	Tau squared	Coefficient of variation
Multivariate analysis					
Swim	0.175	-0.038 to 0.388	0.033	0.106	1.860
Wool	0.116	-0.049 to 0.281	0.498	<0.001	0
Sweat	**0.190**	**0.060 to 0.321**	**0.153**	**0.032**	**0.941**
Shampoo	**0.085**	**0.011 to 0.160**	**0.588**	**<0.001**	**0**

Figure 9-7 Forest plot of the effects of winter on individual patient's "scratch" scores (regression coefficients) in those with reasonably complete data (n=44) (univariate analysis)



Legend 9-7

In this figure, the diamond overlaps the line of no effect and therefore the pooled estimate is not significant. Only 44 individuals (of 60) had sufficient data to be included in the analysis. Heterogeneity is evident in the distribution of responses around the line of no response and the results of the Chi-squared test for heterogeneity shown bottom left, $p<0.001$.

9.4.2 Multivariate analysis

Multivariate analysis of the variables which were significantly associated with increased scratch scores on univariate analysis showed residual heterogeneity for swimming only (Table 9-2). Increased scratch scores persisted for sweating and exposure to shampoo. The associations between swimming and wearing wool next to the skin were no longer significant.

9.5 Results of analysis for effects of environmental factors on disease flares as defined by the need to "step up" treatment

9.5.1 Univariate analysis

Similar analysis was done for the other secondary outcome variable, "stepping up" treatment (Table 9-3). Univariate analysis showed heterogeneity between individuals for the following variables: dust, minimum relative humidity, maximum outdoor temperature, nylon next to the skin, shampoo, spring, summer and autumn. For the variables not showing heterogeneity, an association was detected between "stepping up" treatments and swimming. No association was detected for the other factors. It was however not possible to assess a possible relationship between composite variables A and B and "stepping up" treatment as the use of regression with lagged responses resulted in the loss of data. Multivariate analysis was not carried out for this outcome as only one of the exposures was associated with worsening of eczema on the univariate analysis.

Table 9-3 Results of univariate analyses for secondary outcome "treat" using meta-analysis to assess heterogeneity

Factor	Summary regression coefficient	Confidence interval	Results of heterogeneity Chi-squared test	Tau squared	Coefficient of variation
Univariate analysis					
Dust	0.420	-0.191 to 1.030	0.012	0.686	1.972
Swim	**0.420**	**0.046 to 0.795**	**0.589**	**0**	**0**
Minimum relative humidity	0.280	-0.670 to 1.237	<0.001	9.51	11.014
Maximum outdoor temperature	0.003	-0.031 to 0.037	0.028	0.03	57.735
Mean radiation	-0.000	-0.001 to -0.000	0.444	0	0
Wool next to skin	-0.205	-0.661 to 0.251	0.692	0	0
Nylon next to skin	0.051	-1.292 to 1.393	<0.001	7.428	53.440
Pet	0.299	-0.108 to 0.707	0.353	0.063	0.839
Sweat	-0.132	-0.457 to 0.193	0.489	0	0
Shampoo	0.074	-0.664 to 0.813	<0.001	3.604	25.564
Grass pollen	0.054	-0.144 to 0.252	0.136	0.059	4.498
Birch pollen	-0.002	-0.016 to 0.012	0.136	0	0
Composite variable C	-0.170	-0.680 to 0.340	0.988	0	0
Spring	-0.060	-0.399 to 0.280	0.03	0.220	-7.817
Summer	-0.115	-0.676 to 0.447	0.003	0.607	-6.775
Autumn	-0.03	-0.400 to 0.341	0.02	0.263	-17.094
Winter	0.269	-0.011 to 0.549	0.238	0.064	0.940

9-6 Comparison of associations between eczema severity using primary and secondary outcome measures

The primary outcome measure "bother" and the secondary outcome measure "scratch" show many similar associations between exposure and eczema severity and also some unique associations (Table 9-4). Some similar findings were detected for the secondary outcome "stepping up" treatment, although due to methodological differences and the need to use measures other than ARMA for this outcome measure, true associations may have been missed. In the first two analyses, minimum indoor relative humidity, birch pollen levels and composite variables A and B showed no association with eczema severity for bother and scratch scores. Relative humidity and birch pollen also showed no association with the secondary outcome measure "stepping up" treatment. Dust, shampoo and exposure to wool were associated with increased severity for the outcome measures, bother and scratch but not for the other secondary outcome measure.

Table 9-4 Comparison of associations using primary and secondary outcome measures

Primary outcome measure "bother"		
	Associated with increased severity	**No effect**
Univariate analysis	Dust	Minimum relative humidity
	Wool next to the skin	Birch pollen levels
	Nylon next to the skin	Composite variable A[1]
	Exposure to pets	Composite variable B[2]
	Sweating	Change in temperature
	Shampoo	Maximum outdoor temperature
	Composite variable C[3]	Mean radiation
		Grass pollen
		Birch pollen
		Seasons
		Swimming
Multivariate analysis*	Dust	Exposure to pets
	Wool next to the skin	Shampoo
	Nylon next to the skin	Composite variable C[3]
	Sweating	
Secondary outcome measure "scratch"		
	Associated with increased severity	**No effect**
Univariate analysis	Swimming	Minimum relative humidity
	Wool next to the skin	Birch pollen
	Sweating	Composite variable A[1]
	Shampoo	Composite variable B[2]
		Change in temperature
		Dust
		Maximum outdoor temperature
		Mean radiation
		Nylon exposure next to skin
		Exposure to pets
		Grass pollen
		Composite variable C[3]
		Seasons
		Change in temperature
Multivariate analysis**	Sweating	Swimming
	Shampoo	Wool next to the skin
Secondary outcome measure "stepping up" treatment		
Univariate analysis	Swimming	Mean radiation
		Wool next to skin
		Pets
		Sweating
		Grass
		Birch pollen
		Maximum outdoor temperature
		Nylon next to the skin
		Shampoo
		Grass pollen
		Seasons
		Dust
		Minimum relative humidity

Legend for table 9-4

*Factors associated with residual heterogeneity: dust, sweating and wool next to the skin

**Factors associated with residual heterogeneity: swimming

[1]Composite variable A: high outdoor temperature (>22°C), sweating and high grass pollen levels

[2]Composite variable B: dust exposure, low outdoor temperature (<1°C), and low relative indoor humidity (<40%)

[3]Composite variable C: shampooing the hair at the same time as shower or bath and low outdoor temperature (<1°C)

9.7 Site specificity of associations

I hypothesised that specific exposures would cause site-specific flares. In particular, aeroallergens would be associated with flares of "air exposed" skin while clothing would be associated with flares of covered skin. The site-specificity of exposures was clearly demonstrated for a number of possible triggers (Table 9-5). No association was seen between dust or grass exposure and eczema of "air-exposed" sites. Exposure to pets was associated with flares of hand ($p<0.001$) but not face eczema ($p=0.149$) implying that direct contact may be relevant for disease flares. Looking at clothing, nylon contact with skin was associated with flares of both trunk ($p=0.02$) and limb eczema ($p=0.03$) while an association was only seen for wool contact of the trunk and not the limbs.

Table 9-5 Site-specific reaction to exposures

Exposure	Site	Regression coefficient	P value
Dust	Face	0.048	0.08
	Hands	0.024	0.31
Pet	Face	0.017	0.24
	Hands	0.078	<0.001
Grass	Face	-0.002	0.39
	Hands	-0.000	0.87
Wool	Trunk	-0.066	0.03
	Limbs	0.013	0.62
Nylon	Trunk	0.031	0.02
	Limbs	0.09	0.03

9.8 Correlation to perceptions

There was no correlation between perceived worsening on specific exposures or specific avoidance as recorded in the baseline interview and worsening on exposure to these factors as assessed during the study at the patient level (Table 9-6).

Table 9-6 Correlation of responses to exposures to parental perceptions of "flare factors"

Association	Regression coefficient	Confidence interval
Perceived worsening in hot weather/ regression coefficient for maximum outdoor temperature	-0.013	-0.046 to 0.207
Perceived worsening in summer/ regression coefficient for maximum outdoor temperature	-0.047	-0.108 to 0.013
Perceived worsening in hot weather/regression coefficient for worsening in summer	-0.284	-0.720 to 0.153
Perceived worsening in summer/regression coefficient for worsening in summer	-0.403	-1.090 to 0.284
Perceived worsening in cold weather/regression coefficient for worsening in winter	0.250	-0.040 to 0.539
Perceived worsening in winter/regression coefficient for worsening in winter	-0.021	-0.632 to 0.589
Pet avoidance/regression coefficient for pets	0.165	-0.461 to 0.790
Shampoo or wash product avoidance/regression coefficient for shampoo	0.178	-0.368 to 0.724

9.9 Results of hypothesis testing

Hypothesis 1

In hot weather, the combination of heat, sweating and grass pollen precipitates increased severity.

Composite variable A was created to test this hypothesis. Neither the primary outcome "bother" not the secondary outcome "scratch" was associated with composite variable A (Table 9-1 and Table 9-2) and it was not possible to test this hypothesis for the other secondary outcome measure "stepping up" treatment. There is therefore no evidence to lead to rejection of the null hypothesis of a lack of

association between this combination of factors and worsening of eczema. However only five participants experienced this combination of exposures.

Hypothesis 2

In cold weather, the combination of cold weather, indoor aeroallergen exposure and reduced relative humidity from central heating lead to increased severity.

This hypothesis was tested by the creation of composite variable B. Composite variable B was not associated with significant increases in either bother or scratch scores and it was not possible to test this hypothesis for the other secondary outcome measure "stepping up" treatment. There is therefore no evidence against the null hypothesis that there is no association between this combination of factors and worsening of eczema. However only ten participants experienced this combination of exposures.

Hypothesis 3

Detergents (soap, shampoo) can increase the propensity to increased severity (triggered by other factors) at all temperatures but possibly more in cold weather due to impaired skin barrier function.

This hypothesis was tested by looking at whether washing the child's hair at the same time as the bath or shower was associated with significant increases in scratch or bother scores when outdoor temperature was low, <1°C. An increase in both scratch and bother scores was observed with shampoo exposure. Composite variable C (shampoo and low outdoor temperature) was created to test this hypothesis. For the primary outcome measure, this variable was associated with increased severity of eczema without heterogeneity in responses providing evidence against the null hypothesis of no association.

Hypothesis 4

Patients with filaggrin mutations are more prone to the effects of climatic and environmental factors such as cold and heat than individuals who are wild type for

filaggrin.

This hypothesis was tested by carrying out regression using the response to the exposure (regression coefficient) as the outcome variable and the filaggrin status as the explanatory variable.

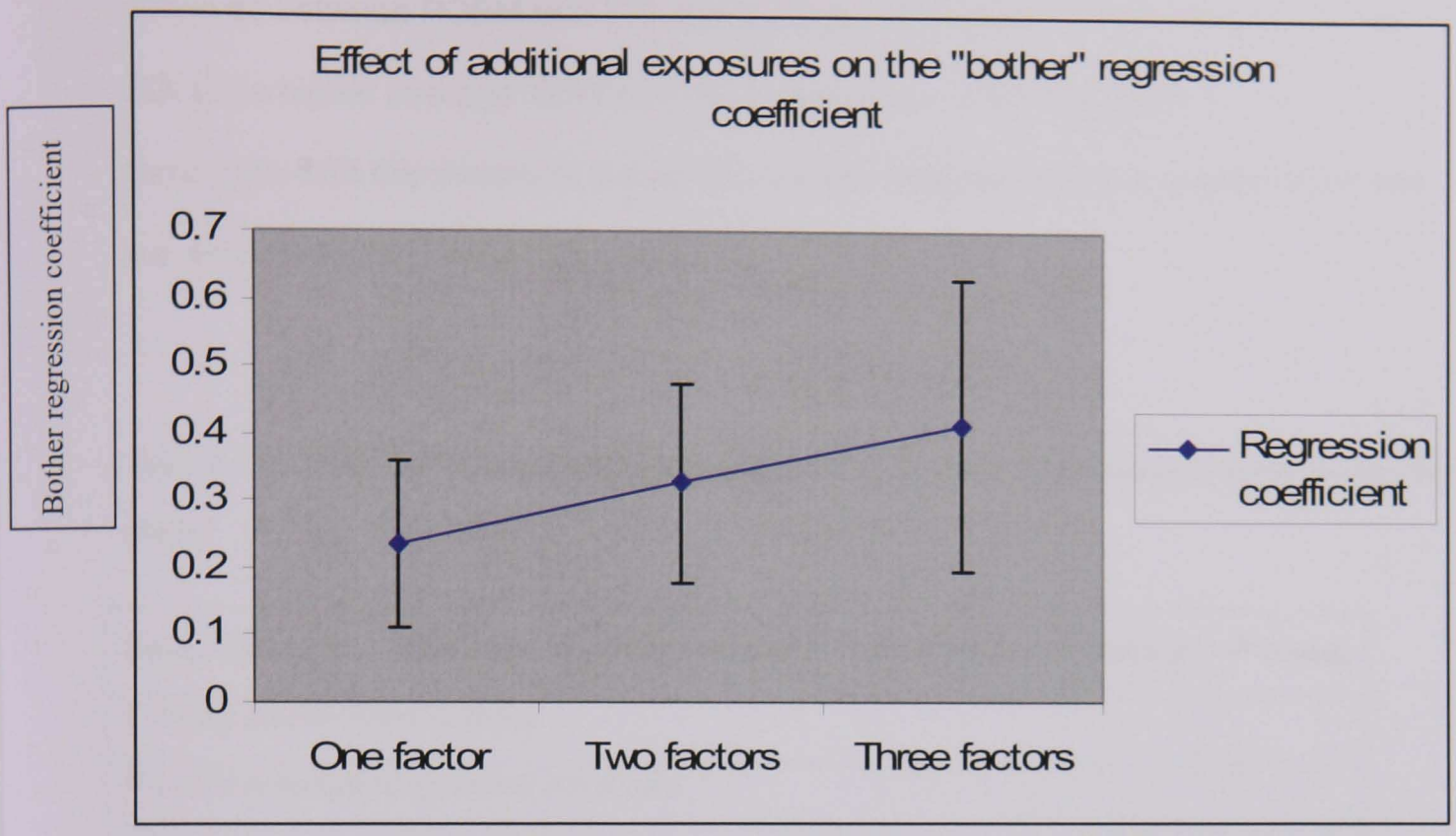
Only worsening in summer (p=0.01) was associated with the 2282del4 mutation. No associations were seen with the r501x mutation. There is insufficient evidence to reject the null hypothesis as these associations may have occurred due to chance as a result of multiple testing. However, associations are also difficult to detect due to the low numbers of filaggrin mutations seen.

Hypothesis 5

Any combination of greater than or equal to three exposures at any time is associated with worsening of eczema. The exposures assessed were: dust, exposure to pets, shampoo, sweating, swimming, nylon clothing next to the skin and a change in mean temperature of more than 3°C from the previous weekly average.

The hypothesis that *any* combination of greater than or equal to three of certain exposures would be associated with worsening of eczema was also explored. A clear association was seen with any of these combinations and worsening of eczema as assessed using the primary outcome, regression coefficient 0.159 (95% confidence interval 0.034 to 0.283). No heterogeneity was seen in responses, p=0.296, Tau squared=0.016. A linear association was also seen when data was analysed for the effect of each additional exposure as shown in Figure 9-8 below. This hypothesis will require further study as an *a priori* hypothesis looking at the impact of different exposures in different study populations.

Figure 9-8 Effect of additional cumulative exposures on "bother" scores



Legend to figure 9-11

This graph shows the effect of each additional exposure on the "bother" regression coefficients with a linear trend. The bars represent the confidence intervals.

9.10 How TCW and WCW perform in comparison to monthly outcome measures

The definition of flares proposed was intuitively well understood by children and their parents. However, as this is a binary definition where flares are either present or absent, the sensitivity to detect change is lower than the primary outcome used and than the other secondary outcome (both 11 point scales).

The number of totally and well controlled weeks (TCW and WCW) were also compared between those with less and more severe eczema during the course of the study at the level of the patient. Individuals were divided into two groups each for average CDLQI, TIS and POEM during the study based on arbitrary cut offs of

greater than 16, greater than 5 and greater than 14 respectively. Associations were observed between POEM and TIS and number of TCW and WCW (Table 9-7). For CDLQI, a higher average TCW and WCW was seen, which suggests a poor correlation with this measure, but as the former measure relates to quality of life and not disease control, this is not surprising.

Table 9-7 Relationship between totally and well controlled weeks and average severity during the study

Severity score	**Average number of weeks**	**Confidence interval**	**P value**
Totally controlled weeks			
Patient orientated eczema measure			
≤14	0.006	0.005 to 0.007	<0.001
>14	0.001	0.000 to 0.001	
Children's Dermatology Life Quality index			
≤16	0.004	0.004 to 0.005	<0.001
>16	0.008	0.006 to 0.011	
Three item severity score			
≤5	0.005	0.004 to 0.006	<0.001
>5	0	0	
Well controlled weeks			
Patient orientated eczema measure			
≤14	0.051	0.049 to 0.053	<0.001
>14	0.007	0.006 to 0.009	
Children's Dermatology Life Quality index			
≤16	0.041	0.040 to 0.043	0.008
>16	0.048	0.042 to 0.054	
Three item severity score			
≤5	0.045	0.043 to 0.047	<0.001
>5	0.001	0.000 to 0.002	

Similarly the relationship between average numbers of flares, as defined by the need to step up treatment, and the average of the severity scores, CDLQI, TIS and POEM was assessed. This again showed clear associations with more flares in individuals with higher TIS and POEM scores (Table 9-8). No association was seen between higher CDLQI scores and number of flares suggesting that this may be measuring a different aspect of eczema.

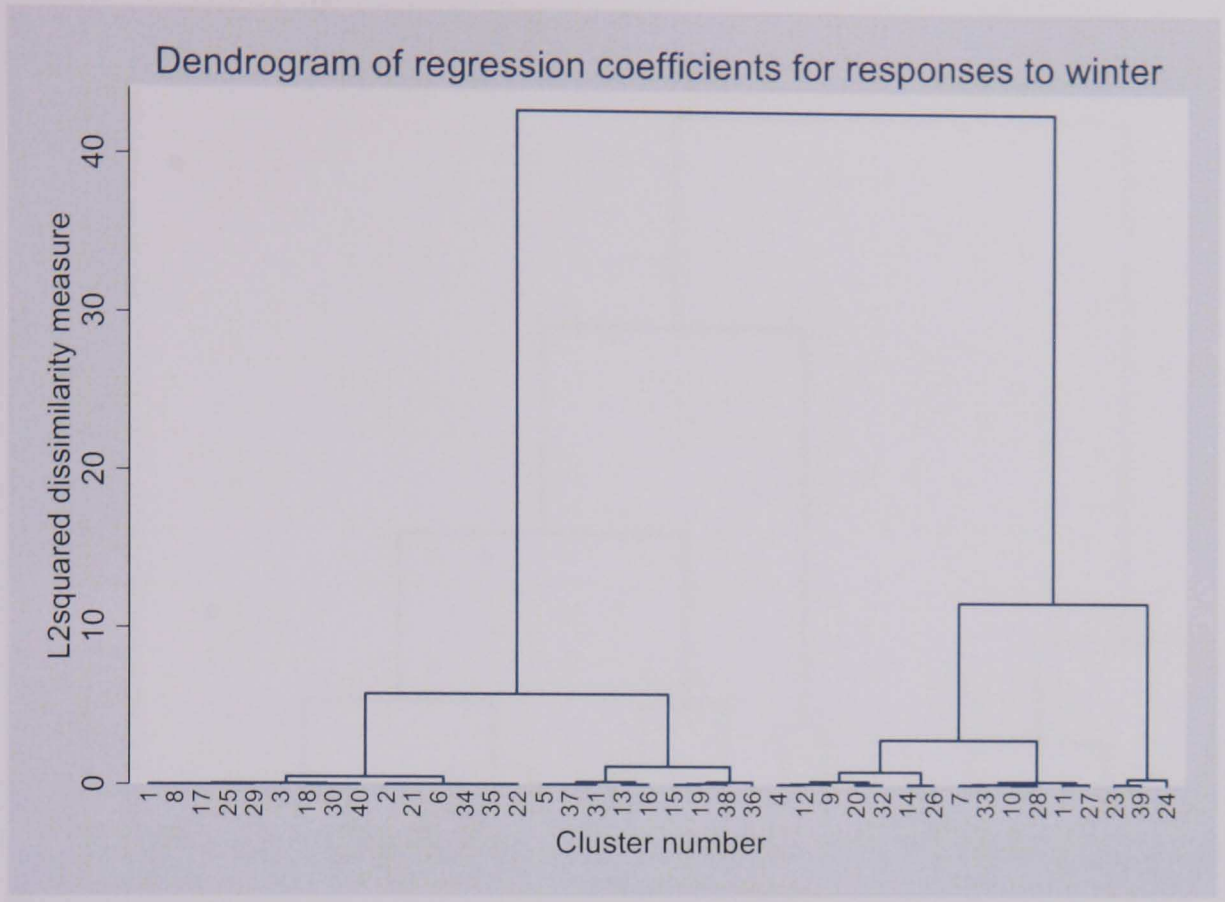
Table 9-8 Relationship between mean number flares per individual per day and average severity during the study

Severity score	**Average number of flares per individual per day**	**Confidence interval**	**P value**
Patient orientated eczema measure			
≤14	0.168	0.165 to 0.170	<0.001
>14	0.314	0.306 to 0.321	
Children's Dermatology Life Quality index			
≤16	0.198	0.195 to 0.200	0.683
>16	0.196	0.185 to 0.207	
Three item severity score			
≤5	0.168	0.165 to 0.170	<0.001
>5	0.314	0.306 to 0.321	

9.11 Exploratory analysis to assess the validity of "summer" and "winter" types of eczema

The regression coefficients for the effect of summer and winter on the primary outcome measure "bother" were used to form clusters using Ward's and the complete linkage method. Cluster analysis was used to group participants into categories based on their responses to winter and summer. Ward's method uses an analysis of variance (ANOVA) approach to evaluate the distances between clusters. The complete linkage method by contrast determines the distances between clusters by the greatest distance between any two participants in the different clusters. Dendrograms were then used to displaying relationships among the clusters. A dendrogram shows the distances between participants in a tree-like structure. Dendrograms were produced for the response of eczema in winter and summer (Figure 9-9, Figure 9-10, Figure 9-11, Figure 9-12, Figure 9-13). The diagrams show individual responses to the seasons at the bottom of the diagram clustered by their similarity of responses. Dendrograms looking at both winter and summer responses show two major categories for responses to the seasons but this is much less clear when the complete linkage method is used than when Ward's method is used suggesting that this apparent clustering is not robust to the method used. This suggests that while there may be some validity in dividing participants into two groups for responses to seasons, more evidence is required to substantiate this clustering.

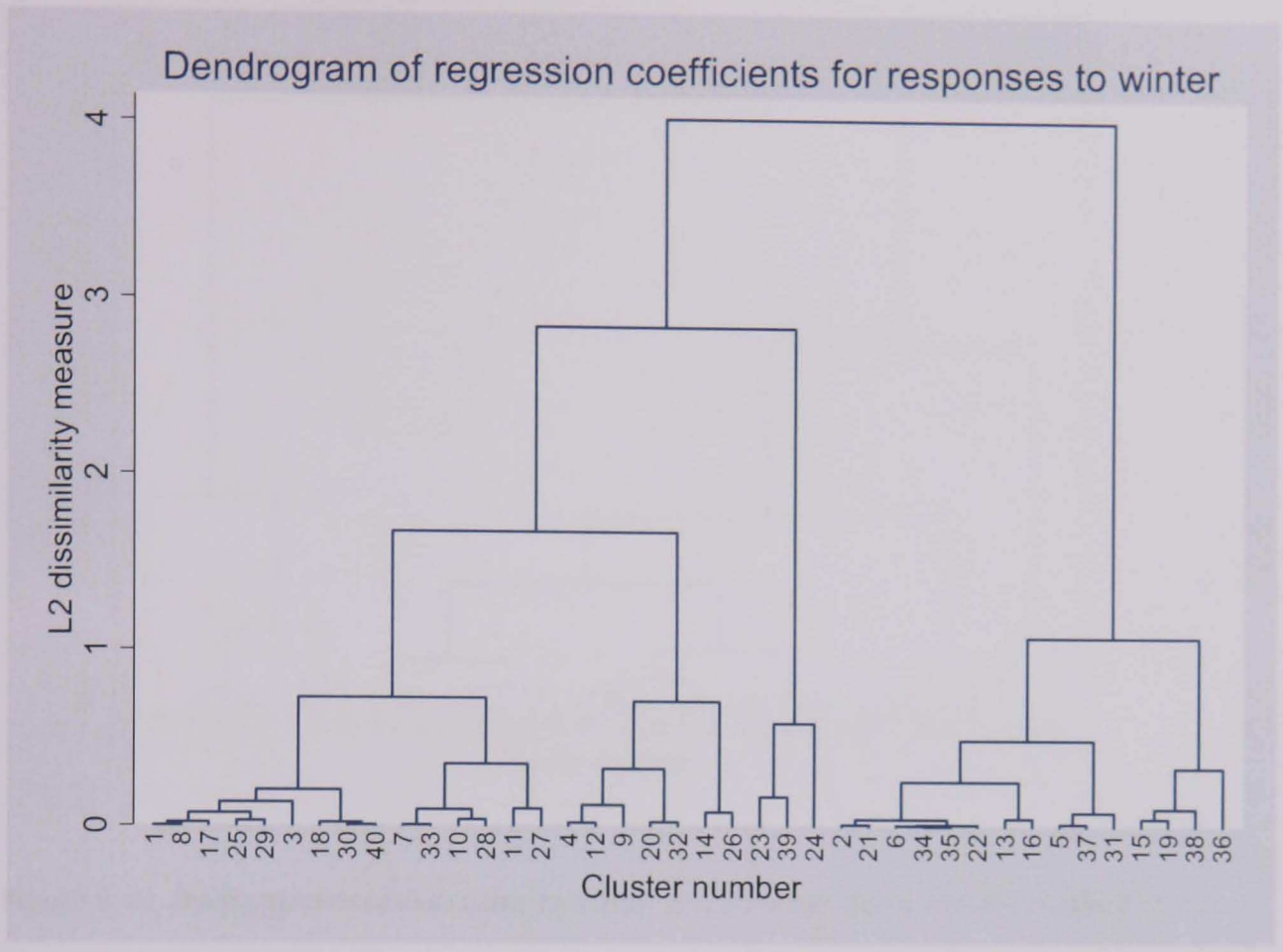
Figure 9-9 Dendrogram for response to winter using Ward's method



Legend to figure 9-9

The dendrogram graphically presents the information concerning which participants responses are grouped together at various levels of dissimilarity in their regression coefficients for bother relating to the exposure winter. The clustering in this dendrogram was generated used the Ward's method which attempts to minimise the sum of squares of any two clusters. At the bottom of the dendrogram, each individual is considered its own cluster identified by a generated cluster identification number. The height of the vertical lines and the range of the dissimilarity axis give visual clues about the strength of the clustering. Long vertical lines indicate more distinct separation between the groups as in this dendrogram.

Figure 9-10 Dendrogram for response to winter using the complete linkage method



Legend to figure 9-10

This dendrogram was created using the complete linkage method of clustering which determines the distance between clusters by the farthest neighbour within each cluster. The dendrogram shows much less distinct separation between groups.

Figure 9-11 Dendrogram for response to summer using Ward's method

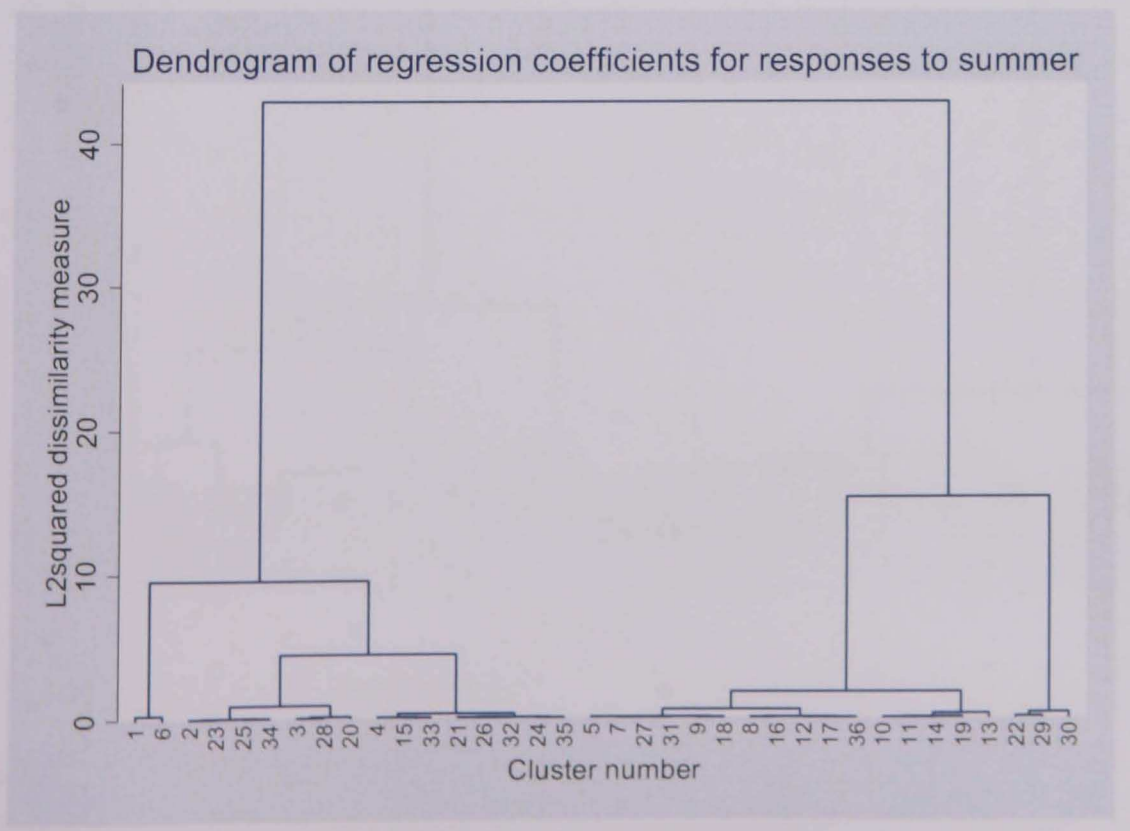
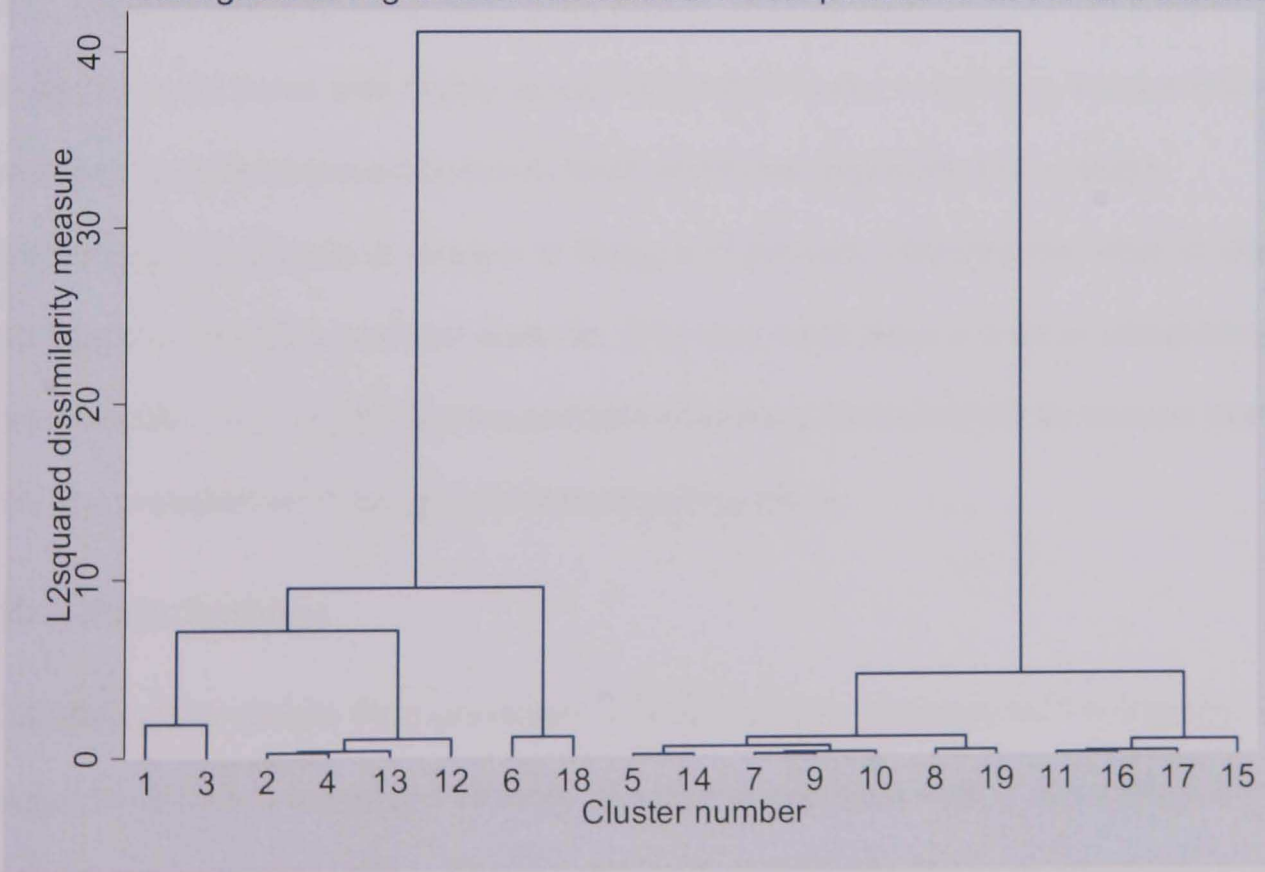


Figure 9-12 Dendrogram for response to summer using the complete linkage method

Figure 9-13 Dendrogram for response to winter and summer using Ward's method



Chapter 10

Discussion

10.1 Summary of main findings

Worsening of eczema was seen with exposure to nylon and wool clothing next to the skin, exposure to unfamiliar pets, shampoo, sweating and swimming. No association with worsening of eczema was seen for either minimum indoor relative humidity or birch pollen. Heterogeneity of responses between individuals was detected for many of the other exposures assessed including dust, grass pollen, maximum outdoor temperature and the four seasons. Site specificity was detected for responses to exposure to pets, wool and nylon clothing. In relation to the specific hypotheses tested, the null hypothesis that combined exposure to shampoo and cold outdoor temperatures was not associated with worsened eczema could be rejected. Analysis also showed that any concurrent combination of three or more of seven exposures likely to cause flares was highly associated with disease worsening. Indeed a linear relationship was observed between each additional exposure and eczema worsening. Specifically in relation to filaggrin mutations, only summer season showed an association with worsened eczema. This may have been a chance association or alternatively, other significant interactions may have been missed by chance due to the low prevalence of filaggrin mutations in the cohort.

10.2 Main findings

Combining the results from univariate and multivariate analyses for the primary outcome "bother", increased severity of eczema was observed in association with the following exposures: dust, wearing nylon and wool next to the skin, exposure to pets, shampoo exposure, the composite variable C (shampoo and cold weather) and sweating (Table 10-1).

Table 10.1 Summary of main study findings

	Outcome measures		
	Primary	**Secondary**	
	"Bother" score	**"Scratch" score**	**Flares of eczema**
Factor			
Dust	**Increased**	No change	No change
Swim	No change	**Increased**	**Increased**
Minimum relative humidity	No change	No change	No change
Maximum outdoor temperature	No change	No change	No change
Mean radiation	No change	No change	No change
Wool next to skin	**Increased**	**Increased**	No change
Nylon next to skin	**Increased**	No change	No change
Pet	**Increased**	No change	No change
Sweat	**Increased**	**Increased**	No change
Shampoo	**Increased**	**Increased**	No change
Grass pollen	No change	No change	No change
Birch pollen	No change	No change	No change
Composite variable A	No change	No change	No change
Composite variable B	No change	No change	No change
Composite variable C	**Increased**	No change	No change
Spring	No change	No change	No change
Summer	No change	No change	No change
Autumn	No change	No change	No change
Winter	No change	No change	No change

Footnote to explain table 10-1:

"Increased" means that the exposure was associated with increased disease severity

"No change" means that disease severity was unchanged with the exposure

"Reduced" means reduced disease severity was associated with the exposure

Persistent heterogeneity was observed for responses to dust, swimming, grass pollen, wearing wool next to the skin, sweating, maximum outdoor temperature, the four seasons and change in weekly average temperature of greater than or equal to 3°C. No association was seen for minimum indoor relative humidity, birch pollen and composite variables A and B.

For the secondary outcome "scratch", increased severity was detected on exposure to swimming, wearing woollen clothing next to the skin, sweating and shampoo exposure. Persistent heterogeneity was detected for dust, maximum outdoor temperature, mean radiation, wearing nylon next to the skin, exposure to pets, grass pollen, composite variable C and seasons. No association was detected for dust, minimum relative humidity, maximum outdoor temperature, wearing nylon next to the skin, pet exposure, grass pollen, birch pollen, composite variables A, B and C, change in mean weekly temperature, seasons and mean radiation. For the other secondary outcome "stepping up" treatment, increased severity was seen only for swimming. No association was seen for dust, mean radiation, minimum relative humidity, maximum outdoor temperature, wearing wool or nylon next to the skin, exposure to pets, sweating, shampoo, birch and grass pollen and seasons. Persistent heterogeneity of response was detected for dust, minimum relative humidity, maximum outdoor temperature, wearing nylon next to the skin, shampoo exposure, spring, summer and autumn. A summary of the factors shown to have associations with worsening of eczema across all outcome measures is shown in Table 10-2.

Table 10-2 Summary of factors associated with worsening of eczema

Dust
Exposure to unfamiliar pets
Grass pollen
Wool exposure
Nylon exposure
Sweating
Swimming
Shampoo
Shampoo and cold weather

Site specificity of a number of the associations was also seen. Exposure to pets was associated with flares of hand eczema while nylon exposure was associated with flares of eczema of the trunk and limbs and wool exposure was associated with worsening of truncal eczema.

For the five hypotheses, only two null hypotheses could be rejected. Firstly the null hypothesis that shampoo exposure at the same time as the bath or shower in cold weather was not associated with eczema could be rejected. In regard to the final hypothesis, a combination of any three of seven likely variables was associated with worsening of eczema with no heterogeneity of responses between individuals. This

strongly suggests that the combination of a number of variables may be the key to disease flares. However this hypothesis requires further testing looking at different exposures in different study populations to see if this relationship is robust.

Only summer season was associated with worsened eczema in people with 2282del4 filaggrin mutations. This may be a chance association with multiple testing or associations may have been missed due to the low prevalence of filaggrin mutations.

The performance of the proposed definitions for flares of eczema and totally and well controlled weeks (TCW and WCW) was also tested against the general control of eczema as assessed using monthly TIS and POEM scores and three monthly CDLQI scores. Average TIS and POEM scores correlated well with the average number of flares and TCW and WCW. No association was seen between average CDLQI and the average number of flares. Higher CDLQI scores were associated with greater numbers of TCW and WCW, which suggests that CDLQI may measure a different aspect of disease control than TCW and WCW.

10.3 Coherence with previous studies

10.3.1 Aeroallergens

In Chapter 2, I reviewed the published literature on what causes worsening of eczema. Previous experimental studies of the impact of house dust mite show associations between topical and inhaled dust mite and worsening of eczema in adults (Norris, Schofield et al. 1988; Tupker, De Monchy et al. 1996; Shah, Hales et al. 2002). In this study, dust exposure was associated with heterogeneous responses suggesting that individual children with eczema respond differently to dust exposure. The evidence for other aeroallergens from the literature is mainly from atopy patch test studies which have shown that eczema can be induced through topical application of aeroallergens. However, the associations between this experimentally induced eczema and clinical history and location of eczema are not clearly established (Bygum, Mortz et al. 2003). In this study, grass was associated with heterogeneous responses; worsening of eczema was seen using the secondary outcome measure "scratch" after multivariate analysis but not with the other two outcome measures. The responses to grass pollen did not show site specificity for air exposed sites. Birch pollen showed no association with worsening of eczema.

10.3.2 Clothing

In relation to clothing and worsening of eczema, previous studies by Diepgen *et al* in adults with eczema have shown the weave of fabrics is more important that whether the fabric is cotton or synthetic (Diepgen, Stabler et al. 1990; Diepgen TJ 1995). In this study, nylon clothing was associated with worsening of eczema that was site specific. In other words, nylon clothing was associated with worsening of eczema on the trunk and limbs. Wool exposure was associated with worsening of eczema of the trunk but not the limbs. Wool exposure was associated with increased bother scores on univariate analysis but this disappeared after adjusting for possible confounding

factors. Wool exposure was associated with increased disease severity using the secondary outcome "scratch" scores with no heterogeneity between individuals. Diepgen's study differed from this study in that it was an experimental study involving the use of specially constructed ponchos and assessment of disease severity under experimental rather than "real-life" conditions. The authors also did not study eczema in children.

10.3.3 Seasons

In terms of the impact of seasonal factors on eczema, Vocks *et al* have shown a reduction in itch scores with increased mean daily temperature (Vocks, Busch et al. 2001). This study has shown that the response to maximum daily temperature is heterogeneous and varies between individuals. Kramer *et al* have proposed a specific model of disease heterogeneity to environmental factors in eczema, specifically that there are winter and summer types of eczema which respond differently to outdoor temperature (Kramer, Weidinger et al. 2005). In this study, variation has been demonstrated in people's responses to outdoor temperature and the seasons. The dendrograms used to examine responses to different seasons lend some support to the model proposed by the aforementioned authors, but are not sufficient to confirm these associations. This possible association was not tested as a pre-specified hypothesis.

10.3.4 Irritants

A number of other important factors included in this study were the impact of irritants, specifically shampoo, swimming and sweating. There is some previous evidence that irritants may be important in eczema severity and that these factors might show seasonal variation (Tupker, Coenraads et al. 1995; Tupker, Coenraads et al. 1995; Seki, Morimatsu et al. 2003). However, the previous studies were not eligible for inclusion in *Chapter* 2 as they did not assess the impact of irritants on eczema

severity. The study by Seki *et al* showed that individuals with eczema could tolerate lower levels of chlorine exposure than individuals without eczema. This study indicates associations between eczema worsening and irritant exposure. Specifically, associations were seen between washing a child's hair at the same time as the bath or shower and worsening eczema. It was also possible to demonstrate interactions between this response and low environmental temperature, which is an anecdotally and clinically reported association. Swimming in chlorinated pools was associated with disease worsening as assessed using daily scratch scores and the need to "step up" treatment. It was associated with heterogeneity of response when the primary "bother" score was the outcome used.

10.3.5 Exposure to pets

Worsening of eczema on exposure to pets has been inadequately studied in the past as I noted in Chapter 2. Specifically no-one has studied the association between exposures to pets other than the family pets and worsening of eczema. This is relevant as patients develop tolerance to family pets, which may not extend to unfamiliar or infrequently exposed pets. In this study, an association was observed between exposure to unfamiliar pets and worsening of eczema. Furthermore, site-specificity was seen for this association, whereby exposure to pets was associated with worsening of hand but not facial eczema.

10.3.6 Filaggrin mutations

Interactions were observed between worsening of eczema in summer season and one of the filaggrin mutations, the 2282del4 mutation. No interactions were observed between the r501x mutations and worsening of eczema with exposures. No previous study has assessed the impact of filaggrin mutations and worsening of eczema on exposure to environmental factors and therefore it is not possible to compare the

results with those from other research. The low prevalence of filaggrin mutations in the cohort will mean that this study is not powered to adequately assess interactions.

10.4 Strengths and limitations

10.4.1 Originality

This is an original study addressing a highly important issue, the role of environmental factors in eczema. The study has been carried out in a methodical fashion, with a pilot feasibility study, systematic reviews to identify research gaps, proposals of definitions of flares in eczema and followed by a formal planned study.

This study has a number of novel components which will have improved the quality of the information. These include the use of specially programmed electronic diaries which are likely to have reduced data entry errors and recall bias, improved compliance and removed data download errors. Electronic dataloggers were also used to record climatic factors accurately. This is a novel concept, which allows recording of indoor climatic factors and study of the child's microenvironment. A previous study has assessed the impact of indoor temperature and relative humidity in the home, but as children spend a large proportion of their time in school and other indoor settings, these environmental factors have not been captured by previous study designs.

This study also assessed the importance of filaggrin mutations in regard to responses to environmental factors. These possible gene-environment interactions have not previously been studied. Although the low prevalence and relatively small sample size precluded full assessment of the role of these mutations, this study did afford the opportunity to explore environmental interactions with filaggrin mutations for the first time.

10.4.2 Study duration

One of the further advantages of this study is the long study period, which due to staggered entry allowed study of the seasonal effects of environmental variables across participants. No previous similar study has had a similar duration or incorporated all of the seasons. This therefore was a unique opportunity to study the impact of environmental factors on eczema.

10.4.3 Study design and analysis

The prospective observational study design allowed observation of time course of eczema and temporal associations between exposure and worsening of disease. It was also possible to test site-specificity of the effect of exposures to determine whether particular exposures were associated with worsening at specific sites. Individuals effectively acted as their own controls as the ARMA regression was carried out on an individual basis before meta-analysis. This reduced the impact of confounding factors and made it was possible to examine inter-individual variation in response to exposures. Although there was some missing data, an inevitable occurrence in any study of long duration, the quality of data collected was high and the fact that the data is not independent means that missing data at a single time point is less important. All of these factors combined lead to the conclusion that this study is likely to be associated with good internal validity.

10.4.4 Hypothesis testing

The use of a cohort design meant that it was possible to test and examine multiple hypotheses. A number of pre-specified hypotheses were tested including the possible gene-environment interactions of filaggrin mutations.

10.4.5 Possible sources of bias

One of the main problems with long duration cohort or panel studies is the possibility of selection bias if there are differential losses to follow up between different groups.

Similarly, selection bias may arise in this study if there are differential completion rates between groups who differ in important ways. This issue was also explored in relation to baseline characteristics of "poor" responders (<50% diary completion rates) and "good" responders and also in relation to exposures predicting the likelihood of missing data. No important differences were seen in terms of age, gender, social class, parental education or the baseline severity of eczema. The only exposure associated with missing data was maximum outdoor temperature. This may well be a chance finding from multiple testing. If this were due to poorer diary completion during vacations, one would also expect an association with mean solar radiation. A further source of selection bias relates to differences between persons who were screened and did not participate and those who participated in the study. This may have lead to over-representation of individuals of higher socioeconomic status. The issue of multiple testing was also explored in relation to main study findings by exploring the impact of using 99% rather than 95% confidence intervals for associations with increased "bother" scores as it was not possible to use statistical methods such as the Bonferroni correction in this *post hoc* situation. The associations between increased "bother" scores and dust, exposure to unfamiliar pets and sweating persisted; other associations no longer persisted but this criterion may be too stringent given the relatively small sample size.

Fatigue is a major problem in panel studies, where overall completion rates reduce with time. This phenomenon has been clearly shown in this study where in both "poor" and "good" responders, response rates reduced after the first month. This was much more markedly seen for the "poor" responders than the "good responders" but was evident in both groups. This suggests that for future observational studies, consideration should be given to the use of a month "run in" period to identify participants with good compliance.

In terms of information bias, observer bias is not likely to be a major problem as the primary analysis was based on self-assessment of the severity of eczema. Responder bias is more likely, if parents perceive associations between exposures and worsening of eczema and are thus more likely to record worsening of eczema. I believe this is unlikely to be a major problem as diary completion was undertaken daily over a long follow up period. Parental bias is also unlikely to be the only explanation because no association was seen between parental perceptions of flare factors or avoidance factors determined at the baseline interview and associations observed during the study. Another possible source of information bias relates to the use of proxy respondents. For young children, aged 8 years or less, parents completed the diaries on behalf of the children. This may lead to poor recording of some exposures. For example, if children are in a nursery during the day, parents may not be aware of all daily exposures. Every effort was made to reduce this element by clear explanations to parents and by requesting diary completion by the person most likely to be aware of all exposures. Another possible issue relates to measurement of exposures for factors such as dust exposure. No direct measure was taken of household dust or dust mite levels; it is likely therefore that the question will only detect individuals in very dusty environments and therefore extreme levels of exposure rather than day-to-day house dust mite exposure.

10.4.6 Confounding

A confounder is a factor which is associated with the exposure and the outcome and may be responsible for either observed associations or missing real associations. In this study, the roles of factors which may cause worsening or flares of eczema were assessed. Some possible confounders not studied are the effects of exposures such as stress or bacterial infections previously reported to cause worsening of eczema. It was decided not to include these factors as stress can only be adequately studied by asking multiple relevant questions; such a requirement would have increased

respondent burden significantly and is likely to have an associated reduction in compliance rates. Study of bacterial infections was not the main focus of the study and would have required laboratory testing in addition to the study procedures. This would have complicated the study without significantly enhancing it, as detecting Staphylococcus Aureus from the skin of people with eczema is not specific for clinical infection (Leung, Schiltz et al. 2008). I also did not differentiate between whether individuals were from urban or rural locations as the study would have been inadequately powered to examine this and it was not one of the study primary objectives.

10.4.7 Random error

Random error is always a possible source of chance associations or missed associations. For example in relation to environmental interactions with the filaggrin 2282del4 mutation, multiple testing may have led to the observed worsening with summer season as a chance phenomenon. However, equally, as only ten of the participants had filaggrin mutations, significant interactions may well have been missed due to low numbers.

10.4.8 Specification of the wrong hypothesis

It is possible that the five hypotheses tested as *a priori* hypotheses in this study may not have been the key hypotheses in relation to worsening of eczema. However, two of the null hypotheses could be rejected. The other null hypotheses may either have been the wrong choice of hypotheses or the low prevalence of exposures may have lead to missing significant associations by chance. It is acknowledged that hypothesis 1 and 2 may have been too complicated thus leading to low prevalence of the specified combined exposures. Specifying simpler hypotheses in these cases may have shown different results.

10.4.9 Methodological issues

One of the issues affecting this study was a methodological issue precluding the use of ARMA for analysis of the binary variable, "stepping up" treatment as the binary nature of responses cannot be assumed to be normally distributed. This required the use of logistic regression on an individual basis followed by meta-analysis of the regression coefficients across individuals which was not the ideal means to study time-series data. This process may have impacted on the ability of this outcome measure to show associations between exposures and disease worsening.

One of the disadvantages of panel studies is that they are slow to carry out and the investment of time can lead to them being relatively expensive. However, it would be very difficult to study associations between exposures such as seasonal associations and worsening of eczema using shorter studies. This issues was highlighted in the study by Kramer *et al*, whereby, the non-inclusion of the winter season in their study (study period March to September) meant that it was difficult to truly infer "winter" types of eczema (Kramer, Weidinger et al. 2005). A longer study period was essential to study these associations in detail and this was weighed against the increased costs incurred.

10.5 Clinical importance of findings

Causation is never possible to prove in the context of an observational study although it is possible to demonstrate associations and then to determine if these are likely to be clinically relevant. The findings of this study imply that parents don't often correctly guess what makes their child's eczema worse. The findings of this study suggest that nylon clothing, dust, exposure to unfamiliar pets and shampoo use need to be enquired about and minimised. The data also implies that children with eczema respond in different and clinically relevant ways to certain exposures such as dust, grass pollen and hot outdoor temperature. The data do not support a very important

role for filaggrin mutations in how people react to external exposures, but the study is not sufficiently statistically powered to assess this fully and hence, important interactions may have been missed by chance. Data also suggests that it is the combination of concurrent exposures which is associated with disease worsening rather than individual exposures.

An issue which determines the generalisations of the findings is that of external validity. The study population may not be representative of the population attending general practitioners with eczema. By definition, if participants are recruited from hospital and community outpatient clinics, they may have more severe eczema and may be more susceptible to the effects of environmental exposures. However, in order to effectively study flares without too long a study duration, the study population needed to have sufficient disease severity to experience flares during the study period and therefore this decision was made pragmatically prior to the onset of the study. Another issue related to external validity is the issue that participants who agree to participate in a study for between six and nine months which involves daily diary completion and monthly assessments may be different to the general population and this may reduce the external validity. Again, this was believed to be essential to study these associations effectively and worth the reduction in external validity.

10.6 Recommendations for future research

The findings of this study highlight the need for further research in a number of key areas. A larger gene-environment study is required to look at possible gene environment interactions with filaggrin mutations. These studies will require larger number of participants to ensure that there is sufficient statistical power to look at these possible interactions. Further study is also required of the theory that multiple concurrent exposures are critical to disease flares in eczema. Specifically, it would be useful to assess this in different populations with different combinations of exposures.

A key area highlighted by this research is the possible role of shampoos in eczema worsening, particularly in cold weather. More research is required into the impact of different formulations using a clinical trial for example. If this is a generic association with all available shampoos, more work will be required in conjunction with the pharmaceutical industry to create a more suitable product for use in eczema.

10.7 Conclusions

This study suggests that the proposed definitions of flares and totally and well controlled weeks perform well in comparison to other measures of disease severity. The following factors were shown to be associated with disease worsening in children with eczema in this UK study: clothing (wool and nylon), sweating, shampoo, swimming, dust, contact with unfamiliar pets and high grass pollen levels. The implications of the findings of this study for clinical practice are that that worsening of eczema may be more complicated in that multiple exposures acting in concert may be associated with worsening of disease. This study strongly suggests that parental perceptions of the causes of flares may not be reliable for use in clinical practice. This study has also shown for the first time that shampoo exposure may be associated with eczema worsening and that this is more pronounced in cold weather. There was insufficient evidence to support the other hypotheses tested in this study but this may be explained by low prevalence of these exposures.

Chapter 11 Lessons learned from this research

11.1 Writing

Medical papers:

I have published five papers from this study. A further two papers are being preparation and submitted. The project I completed for my MSc project has been accepted as an original publication by the British Medical Journal. My writing has improved significantly since commencing research. For example, in the first paper I wrote, I had less clarity about what should go in each section and had "mini-reviews" within my introduction and discussion sections. I am much clearer now about the division of papers using the standard IMRAD (introduction, methods, results and discussion) format.

Protocol and ethics submissions:

The discipline of writing my own protocol and preparing the ethics submission were useful to improve the study design and to obtain independent peer review of the proposal. The process obliged me to address specific issues such as how I would explain my study to a lay audience, what exposure and outcome variables I would collect and why I had chosen them. The peer review process gave a fresh perspective on the protocol and highlighted potential weaknesses and important omissions. For example, one of the peer reviewers noticed that sunlight was not included as an exposure variable and suggested that this was a key exposure variable. The protocol was subsequently modified to include this variable. The COREC form was quite a challenge to complete, but the process did improve the preparatory stages of the study as outlined above.

Choosing study instruments:

The use of novel electronic diaries is advantageous in terms of improving compliance and the accuracy of the data collected (Hyland, Kenyon et al. 1993; Jamison, Raymond et al. 2001; Palermo, Valenzuela et al. 2004). The disadvantages are the lack of control over the timing of the project due to dependence on external programmers to prepare the devices. An additional disadvantage is the cost incurred, approximately £250 per device. In comparison, paper diaries are easier to prepare and produce; there is a wealth of experience in their design and use and they are relatively inexpensive. A major concern, however is that the information in paper diaries does not accurately reflect exposures and outcome status (discussed in detail in Chapter 6). This is due to a number of factors: missing data, poor compliance, retrospective data entry (thus incurring recall bias), and poor handwriting leading to erroneous conclusions. The main advantage with the electronic devices is improved compliance and the prevention of retrospective data entry.

Using electronic dataloggers gives highly accurate individual data representing the temperature and humidity in the child's micro-environment. This is a much more accurate representation than, for example, measuring household climatic conditions twice daily (Kramer, Weidinger et al. 2005; Langan, Bourke et al. 2006). Using the latter approach, even with full parental compliance, only household conditions will be taken into account. As children spend large proportions of time outside the home, for instance at school or outdoors, the data would poorly reflect exposures thus compromising the validity of the data. These electronic devices have potential uses for future clinical research in a variety of areas.

Designing study instruments:

Designing the electronic diary questions was an entirely new process for me. I had assumed that as I had experience designing paper diaries and a clear idea of what I

wanted to study, that this would be a straightforward process. It is much clearer to me now that the use of high technology equipment in a study requires learning completely new skills. These skills include adapting questions to suit the electronic format; questions must be closed-ended, must fit on the screen and be legible and must be readable and "user-friendly". I also had to intensively study the tool to look for "bugs". The initial pilot device did not use the skip-format I had requested and when buttons were repeatedly pressed (as children will do!), the machine gave unreadable responses. I therefore had to intensively re-test the diaries and developed a close working relationship with the company preparing the device. In this case, using electronic diaries delayed the start by several months and required a lot of persistence to bring the tool to perfection. In terms of the "ibutton" dataloggers, I tested these in a variety of settings. This type of testing showed me that humidity readings were unreliable when the devices were kept in my pocket and that the "ibuttons" were easy to lose when they were kept loose. As a result of this, I ordered key ring holders for the ibuttons so that they could be worn externally and thus reduce the chance of loss of the dataloggers.

11.2 Attitudes and approach

Patience and persistence

The research processes are associated with significant delays at all stages, including securing funding, applying for ethical approval and designing and preparing tools to use in the project. I am satisfied that I have learned patience and persistence through these experiences.

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Appendix

Appendix 1 How investigators have defined disease flares in eczema

Author (year)	Intervention (s)	Follow up	Single or multiple relapses	Primary outcome	Severity of AD	Definition of flare used	Symptoms	Signs	Treatment	Duration	Comment
Composite Scales											
Papp 2004	Double blind RCT pimecrolimus 1% cream vs. vehicle	1 year	Multiple	Days of treatment with pimecrolimus1% or 1% CS	Moderate or severe	IGAS ≥4. Corticosteroid (CS) 3 days. 7 days CS free	No	Yes	Yes	Yes	Same methods as Kapp and Wahn
Kapp 2002	Double blind RCT pimecrolimus 1% vs. vehicle (CS for flares)	1 year	Multiple	Incidence of flares at 6 months	Majority moderate disease	IGAS ≥4. Corticosteroid (CS) 3 days. 7 days CS free	No	Yes	Yes	Yes	
Wahn 2002	Double blind RCT pimecrolimus 1% vs. vehicle (CS for flares)	I year	Multiple	Ranked flares of AD in 6 months	Majority moderate disease	IGAS ≥4. Corticosteroid (CS) 3 days. 7 days CS free	No	Yes	Yes	Yes	

Author (year)	Intervention (s)	Follow up	Single or multiple relapses	Primary outcome	Severity of AD	Definition of flare used	Symptoms	Signs	Treatment	Duration	Comment
Thomas 2002	Double blind RCT 0.1% betamethasone valerate for 3 days vs. 1% hydrocortisone ointment for 7 days	18 weeks	Multiple	Number of scratch free days and number of relapses	Mild and moderate AD	Scratch score>2 for 3 consecutive days	Yes	No	No	Yes	Assessed steroid usage but not used in definition of flare
Arbitrary score thresholds											
George 1993	Open study 12 weeks baseline, 12 weeks TL-01 3/week, 24/12 F/Up	48 weeks	Single	Modified Costa severity score. Visual analogue score (patient)	Severe	Severe relapse 70% pre-phototherapy Costa score	No	Yes	No	No	Assessed patient symptoms but not in definition of relapse
Granlund 2001	Open randomised parallel group trial. Compared 8 week cycles of either cyclosporine or UVAB	1 year	Multiple	Number of days in remission	Severe	SCORAD> 50% baseline	Yes	Yes	No	No	

Author (year)	Intervention (s)	Follow up	Single or multiple relapses	Primary outcome	Severity of AD	Definition of flare used	Symptoms	Signs	Treatment	Duration	Comment
Bunikowski 2001	Open-label study of cyclosporine A	12 weeks	Single (discontinued in case of relapse)	SCORAD Cytokines IL-6, IL-8 and TNF-α	Severe	SCORAD≥80 % baseline	Yes	Yes	No	No	
Atakan 1998	Open-label study of Sandimmun Neoral®	36 weeks	Single	Disease severity score	Severe	SCORAD≥75 % baseline	Yes	Yes	No	No	
Ehlers 2001	Double blind sugar challenges	10 days	Single	SCORAD	Moderate	SCORAD> 15 points above baseline	Yes	Yes	No	No	
Berth-Jones 2003	Double-blind RCT twice weekly fluticasone propionate vs. placebo base	20 weeks	Single	Time to relapse	Moderate to severe	TIS≥4	No	Yes	No	No	
Granlund 1995	Open study: Two treatment periods of 6 weeks cyclosporine	32 weeks	Multiple	Length of remission	Severe	Disease activity score>75% baseline	No	Yes	No	No	Symptoms and steroid use recorded but not in definition

Author (year)	Intervention (s)	Follow up	Single or multiple relapses	Primary outcome	Severity of AD	Definition of flare used	Symptoms	Signs	Treatment	Duration	Comment
Hanifin 2002	Open-label stabilisation followed by double-blind maintenance RCT study of twice weekly fluticasone propionate 0.05% cream vs. vehicle	48 weeks	Single (withdrawn from study)	Risk of relapse in maintenance phase	Moderate to severe AD	IGAS ≥3 and score 2 to 3 for any 2 of erythema, itch, papulation/ induration/ oedema	Yes	Yes	No	No	Steroid use recorded but not in definition of relapse
Siegfried 2006	Double-blind randomized vehicle-controlled parallel group study of pimecrolimus 1% cream with topical corticosteroids for flares	6 months	Multiple	Primary efficacy variable was the number of individuals who remained flare-free	Mild to severe AD affecting at least 5% of body surface area	IGAS≥4	No	Yes	No	No	Flares are not specifically defined although the authors define use of a "major flare regimen"
Behavioural scales											
Meurer 2002	Double blind RCT of pimecrolimus cream 1% vs. vehicle	24 weeks	Multiple	% of days on which topical CS was received	Moderate to severe	Disease state requiring CS use for ≥3 days	No	No	Yes	Yes	Symptoms assessed but not used in definition

Author (year)	Intervention (s)	Follow up	Single or multiple relapses	Primary outcome	Severity of AD	Definition of flare used	Symptoms	Signs	Treatment	Duration	Comment
Zaki 1996	Open case series treated with cyclosporine	12 weeks max	Single	Response to treatment	Severe	Need to use potent topical CS/ further systemic treatment	No	No	Yes	No	Some children part of multicentre study
Meurer 2004	Double blind RCT of pimecrolimus 1% vs. vehicle	24 weeks	Multiple	% of days on which topical CS used	Moderate	≥3 days in which CS considered necessary by investigator	Yes	No	Yes	Yes	
Gollnick 2008	Double blind RCT of pimecrolimus 1% cream vs. vehicle	26 weeks	Multiple	Number of study days without topical CS use for major flare	Mild or moderate	≥3 days in which CS considered necessary by investigator	Yes	No	Yes	Yes	Cut off on IGA not clearly defined but authors references previous studies

CS = corticosteroid; F/Up = follow-up; SCORAD = Severity Scoring of Atopic Dermatitis; TIS = Three Item Severity score; IGAS = Investigator Global Assessment Score

Appendix 2 Search strategy for systematic review of flare factors for eczema

1. exp Dermatitis, Atopic/
2. atopic dermatitis.mp.
3. atopic eczema.mp.
4. exp NEURODERMATITIS/
5. neurodermatitis.mp.
6. infantile eczema.mp.
7. childhood eczema.mp.
8. Besniers' Prurigo.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. environment$.mp. or exp ENVIRONMENT/
11. climate.mp. or exp CLIMATE/
12. weather.mp. or exp WEATHER/
13. exp METEOROLOGICAL FACTORS/ or meteorological.mp.
14. temperature.mp.
15. humidity.mp. or exp HUMIDITY/
16. seasons.mp. or exp SEASONS/
17. wind.mp.
18. exp ALTITUDE/ or altitude.mp.
19. air temperature.mp.
20. (damp or wet).mp.
21. $allergen$.mp. or exp ALLERGENS/
22. irritant$.mp. or exp IRRITANTS/
23. sunlight.mp. or exp SUNLIGHT/
24. ultraviolet.mp. or exp ULTRAVIOLET RAYS/
25. wool.mp. or exp WOOL/
26. exp Clothing/ or cloth$.mp.
27. pollen.mp. or exp POLLEN/
28. exp Animals, Domestic/
29. *CATS/ or cat$.mp.
30. *DOGS/ or dog$.mp.
31. house dust mite.mp. or *Pyroglyphideczema/
32. *HOUSING/
33. exp Food/
34. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 9 and 34
36. flare$.mp.
37. exacerbation$.mp.
38. relaps$.mp.
39. remission$.mp.
40. worse$.mp.
41. *RECURRENCE/
42. 36 or 37 or 38 or 39 or 40 or 41
43. 35 and 42
44. review.pt.
45. 43 not 44

Appendix 3 Summary of results of the evidence for factors being associated with eczema flares by "flare factor"

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
FOODS							
Sampson 1985 USA (Sampson and Ho 1997)	DBPCFC. Randomised order No washout	113 severe eczema	4 mo to 24.5 years	Elimination diet for 1-2 weeks prior to admission (up to six allergens, based on history, SPT or RAST test) DBPCFC: Two challenges given daily, one active, one placebo in randomized order	Symptoms, severity and duration assessed using standardized scoring sheet	56% children challenge +ve (101 challenges positive in 63 patients), of which 84% had rash. All symptomatic within two hours of ingestion. Results for placebo challenge not given. 42% of positive reactions to egg, to peanut in 19% and milk in 11%; other allergens accounted for lower percentages	Unclear if skin symptoms equated to a flare of eczema

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Pike 1989 UK(Pike, Carter et al. 1989)	Individualised few food diet (n=65) followed by serial reintroduction of foods in diet responsive children (n=20). DBPCFC in subset (n=10). Randomised order of active and placebo challenges. Washout (1 week)	66 children with severe eczema, 54% of whom had previous dietary intervention	0.6-16.8 years, mean age 4.2 years	Few food diets (based on commonly allergenic substances, history from parents and foods frequently ingested) for median of 26 days (range 19-44), serial reintroduction (n=20). Parental recording of "exacerbating foods". DBPCFC (n=10) of foods described as exacerbating eczema by parents.	Visual eczema score (unvalidated) Diary cards (itch, redness and sleep disturbance 0-3)	DBPCFC all negative despite 12 (18%) having long term benefit from dietary exclusion.	Parental identification of provoking foods is unreliable

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Van Bever 1989 Belgium (Van Bever, Docx et al. 1989)	DBPCFC to food and food additives and food additives (tartrazine, sodium benzoate, sodium glutamate, sodium metabisulfite, acetylsalicylic acid and tyramine) Randomised order. No washout	25 children severe eczema	5 months to 13.8 years	Elemental diet via nasogastric tube for 1-2 weeks as inpatient. DBPCFC given via nasogastric tube (19 challenged with food, 5 with food and additives and 1 with food additives only). Two challenges per day, one active and one placebo.	Clinical scoring <4 hours after challenge. Symptom score (redness, hives, swelling, itching)	All improved during elemental diet phase. Food 46.8% of challenges +ve, 51% skin reactions Food additives 39% +ve. Most developed rashes. No reactions to placebo	Authors state no exacerbation of eczema after challenge (all resolved <4 hours).

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Sloper 1991(Sloper, Wadsworth et al. 1991)	DBPCFC with washout (1 week)	64 children with eczema recruited from outpatient clinics and advertisement in eczema magazine. Varying severity	0.5-15 years	Elimination diet (milk, eggs and foods implicated in history) for >3 weeks (median length of avoidance 4.6 months) followed by DBPCFC (194 challenges given, range 1-11). Challenges given as 1 tin daily for 1 week of specific food type followed by 1 week washout.	Daily symptom score (0-3). Unpublished clinical scoring system. A reduction of skin core of 3 (range 0-80) considered significant.	74% improved during elimination period. Cow's milk median itch score increase 1.4 (-2 to 12.5), $p<0.01$, median sleep score increase 9 (-6 to 9), $p<0.05$; Egg median itch score increase 0.8 (-4 to 12) NS. Significant association between positive challenge and improvement on elimination diet, $p<0.001$. No relationship between history of food-induced eczema and positive challenge.	Authors report worsening with cow's milk and tomato (actual results not given). No worsening with egg but 36% incomplete. Questionable if change in score of 3 points clinically significant.

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Oranje 1992 Netherlands (Oranje, Aarsen et al. 1992)	Case control study of food provocation using skin application food tests (SAFT) to trigger food immediate contact hypersensitivity (FICH). No randomisation	91 patients with eczema (severity not given) and 16 healthy controls	0-5 years	Skin application food tests (SAFT) using food allergens applied on gauze in Finn chambers (milk, egg, soy, peanut butter and other foods if clinically suspected). Oral food challenge tests in patients with inconclusive SAFT results	Unvalidated severity score	67% FICH +ve of whom 33% had flared during or shortly after SAFT. FICH +ve to eggs in 44 (72%), to milk in 29(47%) and peanut in 21(34%) of FICH +ve individuals. Placebo responses not given. No positive responses in controls	No definition of what change in score constituted a flare. The authors state that most flares were urticarial. Eczematous flare ups were seen in 33% of FICH +ve individuals.
Oranje 1992 Netherlands (Oranje, van Toorenenbergen et al. 1992)	Case control study of food provocation using skin application food tests (SAFT). No randomisation	52 eczema, 22 control	0-5 years	Skin application food tests (SAFT) where foodstuffs applied to back of patient using pieces of gauze, oral food challenge tests in patients with inconclusive SAFT results	Unvalidated severity score	Contact urticaria in 25/52 (egg), 16/52 milk and 11/52 peanut. 10.5% (4/38) exacerbation of eczema after SAFT. Placebo responses not given. No positive responses in control group.	50% had correlation between food contact or ingestion and eczema worsening.

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Devlin 1992 UK(Devlin and David 1992)	Double-blind placebo controlled challenges with tartazine. Randomised order. No washout	12 children severe eczema and parental history of tartrazine worsening eczema.	1.9 to 6.9 years	Three tartrazine 50mg and glucose challenges comprising weeks in random order.	Change in unvalidated score. Severity was assessed before and 24-48 hours after the challenge. Positive challenge was where tartrazine weeks had highest scores or greatest increase in scores	Median eczema symptom score tartrazine weeks (216) vs. placebo weeks (154), median change in score (+4) vs. (-6); not statistically significant, p>0.1	1 worsened during three weeks of tartrazine exposure. P=0.46 for possibility of result arising from chance. Small study

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Beyer 1998 Germany (Beyer, Renz et al. 1998)	DBPCFC No randomisation No washout	17 children with eczema with suspected allergy to egg or cow's milk 9 controls	1-10 years	Milk and egg free diet for 5 days followed by DBPCFC. Increasing doses of hens egg (up to 30ml); cow's milk allergen (up to 200ml) or placebo given at 30 minute intervals until clinical symptoms or the maximum dose was reached.	Clinically determined exacerbation of eczema within 48 hours after challenge. Lymphocyte populations assessed by flow cytometry.	41% +ve challenge 18% worsening of eczema. Placebo challenges all negative	Authors demonstrate change in lymphocyte subpopulations with reduction in total number and percentage lymphocytes (activated T cells and B cells) after challenge in food-sensitised children independent of outcome of food challenge.
Reekers 1999 Germany (Reekers, Busche et al. 1999)	Elimination diet followed by DBPCFC Randomised order. No washout	37 outpatients eczema and hypersensitivity to birch pollen and no history of food hypersensitivity	17-64 years	Elimination diet excluding all birch pollen-related food for 4 weeks followed by DBPCFC (one active challenge only) with 60g of carrots, 20g of hazelnuts and 60g of apple and a placebo challenge	SCORAD (increase of 15 points significant) Proliferation assays before elimination diets using birch pollen. Observation period of 2 hours after challenge	17/37 worsened (median increase in SCORAD 21 in responders). Results for placebo challenge not given.	Polyclonal T cells with Bet v1 in responsive and non-responsive patients. Increased CLA+ve lymphocytes only in responder group. Authors suggest that CLA positivity in responsive patients may explain skin homing

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Vieluf 1999 Germany (Vieluf, Wieben et al. 1999)	Part 1 Open oral provocation tests (OPT) to foods, part 2 Double-blind placebo-controlled OPT to food additives Not randomised	Part 1. 64 moderate to severe eczema Part 2. 30 people with eczema with a history of reactions to additives	Part 1. 1-66 years Part 2. 3-68 years	Part 1. Series of foods including "provocation diet" on day 6 with additive rich foods Part 2. Food additives in gelatine capsules in increasing doses for up to 8 hours with observation for 16 hours. Challenge given to people with a history of adverse reactions to food additives or to additive-rich foods on day 6	Change in SCORAD, not given in detail	96 positive reactions in 44 patients to foods in part 1. 23 flare ups of eczema with food additives in part 1, first symptoms occurring 30 minutes after provocation. 7 reacted to 1, 9 to two , 1 to three and 2 to 4 FAs in part 2 Results for placebo not given	Unclear what degree change in SCORAD significant

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Worm 2000 Germany (Worm, Ehlers et al. 2000)	Elimination diet, open challenge, DBPCFC with food additives. Randomised order Washout 48 hours after each provocation	50 outpatient eczema (multiple SPT +ve), 15 responders to low pseudo-allergen diet underwent DBPCFC	18-72 years	Low pseudoallergen diet for 6 weeks followed by open challenge (n=26) in responders, then by DBPCFC (n=15) in responders to open challenge. Challenge with food additives combined in one administration or placebo. Observation for 48 hours after.	Worsening of modified Costa >10 points. Fall of >35% improvement.	Elimination diet: 63% improved (26/41 who completed diet) Open challenge: 19/24 +ve; DBPCFC: 6/15 +ve, 1/15 +ve response to placebo. No immediate responses.	Only 6 +ve DBPCFC. No long term F/up
Ehlers 2001 Germany (Ehlers, Worm et al. 2001)	Elimination diet (sugar-free diet for 1 week prior to challenges and continued during challenges), DBPCFC Randomised order Washout	30 outpatient eczema	2-47 years	Sugar elimination diet for 1 week followed by DBPCFC with either sucrose or placebo in random order	SCORAD (>15 increase) ECP levels Pruritus levels	No change in SCORAD or pruritus levels active vs. placebo challenge	No control group

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Breuer 2004 Germany (Breuer, Wulf et al. 2004)	Elimination diet followed by DBPCFC Randomised No washout	12 children moderate to severe eczema	3-9 years	Elimination diet for 4 weeks excluding all birch pollen-related foods followed by DBPCFC (n=9). Challenge with either verum containing birch pollen related food or placebo; successive doses given until full dose or reaction with 10 minute intervals between doses on day 1. On day 2, the full dose was given together. Washout period of 1 day	SCORAD, IgE to birch pollen and birch pollen related foods. Clinical assessment for up to 6 hours after last dose.	4 had worsening of eczema P=0.018. No relation to specific IgE in responders vs. non-responders. No +ve placebo challenge	Challenges varied. 3 patients had immediate reactions requiring oral steroids, these patients did not develop eczematous reactions

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Worm 2006 Germany	DBPCFC in people identified as having eczema with either a history or investigation suggestive of allergy to that food	Questionnaire sent to 13,300 individuals in population. 13% (1739) responders of whom 28 had active eczema. Tests done in 9 patients	18-65 years	DBPCFC in people with history, SPT or RAST suggestive of food allergy. Active challenge with 50g of vegetables and fruit, 10g of hazelnut and peanut, 20g of fresh flour, 200ml of cow's milk and 1 egg	SCORAD (>15 increase) with a negative placebo response	1/9 showed worsening of eczema	Poor response to questionnaire but study suggests that food allergy is not an important cause of exacerbations of unselected adults in the population.
HOUSE DUST MITE							
Tupker 1996 Netherlands (Tupker, De Monchy et al. 1996)	Double-blind randomised placebo controlled study	20 patients with eczema and positive SPT to HDM	18-30 years	Inhalant challenge with HDM over 80 minutes. Interval of 1 week between random order active and placebo challenges	Costa score, Itch score 1-4 Changes in severity or localization of eczema noted. FEV1	Worsening 9/20 (scores not given in results), 4 <8 hours of challenge, 5 sustained. Preceded by fall FEV1>15% (n=8). 1 response to placebo	Unclear if worsening constituted flare of eczema. Costa and itch scores not given (description only: 3 exacerbation existing areas only, 3 new areas only and 3 combination)

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Norris 1998 UK (Norris, Schofield et al. 1988)	Double-blind placebo-controlled exposure tests to Dermatophagoides pteronyssinus (Dp) solution. Not randomised	34 eczema 12 atopic, 6 endogenous eczema	16-65 years	Dp and control solution to alternate antecubital or popliteal fossae twice daily for 5 days	Clinical grading system, measurement of area, VAS itch	1/3 deterioration score. Significant difference compared to placebo only seen for mildly, not uninvolved skin, $p<0.01$	Only one site tested
Shah 2002 UK (Shah, Hales et al. 2002)	Double-blind placebo-controlled exposure tests to Dp solution Randomised to different sides	20 outpatients with eczema of varying severity	17-62 years	Dp and control solution to antecubital fossae twice daily for 4 days	SASSAD score in antecubital fossae VAS Itch (0-100) PBMC proliferation assays	6 patients increased SASSAD and VAS scores. Stimulation indexes challenge positive vs. challenge negative ($p=0.004$). No response to placebo	Blinding may not have been complete (different coloured solutions). Only one site tested
OTHER AEROALLERGENS							
Wananukul 1993 Thailand (Wananukul, Huiprasert et al. 1993)	Double-blind placebo controlled atopy patch test (APT) series. Not randomised	30 eczema 30 controls (respiratory atopy)	2-14 years	SPT, APT aeroallergens: house dust mite, cockroach, mold mix and grass mix on tape stripped skin	Clinical severity assessment (subjective)	90% APT +ve in eczema group 3 patients in eczema group had flare of eczema (antecubital and popliteal fossae). No reaction to placebo	No severity assessment tool used. Eczema in other sites may not be related

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Bygum 2003 Denmark (Bygum, Mortz et al. 2003)	Case control atopy patch test study. Randomised	23 moderate to severe eczema 25 healthy non-atopic controls	19-29 years (cases) 18-30 years (controls)	APT various potential allergens including Dp, grass, cat, milk and pityrosporum ovale.	Reading of tests and correlation to prospective history. Clinical severity (subjective)	No convincing relationship between +ve APT, history and distribution of eczema. 2 patients flare up of eczema during APT. No reaction to placebo	Trigger for flare up unclear
WASHING POWDER							
Andersen 1998 Denmark (Andersen, Bindslev-Jensen et al. 1998)	Randomised double-blind crossover trial of washing detergents enzyme vs. non-enzyme containing detergents	25 mild to moderate eczema involving clothing covered body sites	17 to 59 years	Randomised double blind crossover; each period one month duration	SCORAD, Corticosteroid quantity Patient record itch and intensity using arbitrary scale (0-3)	No difference between eczema severity in either study period, p>0.99	Authors comment on low numbers and short duration
SUNLIGHT							
Deguchi 2002 Japan (Deguchi, Danno et al. 2002)	Case series. No placebo, no control group	74 patients facial eczema (>50% surface) indurated erythema for >6 mo	15 to 47 years	UVB and UVA phototests (n=36) on unexposed skin of back	Measurement of erythema and papules Histological assessment	14 patients (39%) abnormal papular response to UVB with normal or reduced minimal erythema doses. Histology confirmed eczema	Improvement with sunscreen 1-2 weeks in patients with abnormal UVB response

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
TEXTILES							
Seymour 1987 USA (Seymour, Keswick et al. 1987)	Randomised controlled trial, 26 weeks. Three types of nappy: home laundered cloth nappies, conventional cellulose core and cellulose core containing absorbent gelling material	85 infants with eczema and 87 controls were recruited from advertisements and physician referral. Varying degrees of severity	<20 months	Cloth vs. cellulose core nappies vs. cellulose nappies with absorbent core	Scoring system for eczema modified from Queille. Score for nappy rash (0-4). Graded every two weeks for 6 weeks and then monthly	Significant difference in nappy rash score cellulose with absorbent core vs. cloth nappies at 5 of 8 visits. Significant correlation between nappy rash and eczema severity outside the nappy area only in those wearing cloth nappies.	Change in nappy rash only not eczema severity
Diepgen 1990 Germany (Diepgen, Stabler et al. 1990)	Randomised controlled trial of poncho-like shirts in 4 different materials: cotton and synthetic fabrics of different fibre structure	55 eczema, 31 controls (severity not given)	Mean age 24.8y	Cotton, 3 synthetic textiles varying roughness. Repeated wearing of ponchos	Comfort score (1-10), maximum comfort=10, maximum discomfort= 1	Comfort 8.4 cotton vs. 7.3, 3.66 (S), 3.3 (S). Difference between cotton and synthetic fabrics with coarser weave with reduced comfort in the coarser fabrics for those with eczema compared to controls.	Only significant difference for fabric roughness.

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
Diepgen 1995 Germany (Diepgen TJ 1995)	Randomised controlled trial comparing ponchos in seven different fabrics.	20 eczema, 20 patients with psoriasis vulgaris and 20 control participants with no skin disease	Mean age 25.3 (eczema), 27.2 years (psoriasis) and 28.4 years (controls)	Seven different types of fabrics: three jersey knits (one cotton, two polyester) and four warp knit polyester fabrics. Each individual underwent an 100 Watt stress on an ergometric bicycle wearing the ponchos	Visual analogue scale: very comfortable, comfortable, slightly uncomfortable and very uncomfortable (4 categories in each).	More discomfort with rougher weave fabric (warp vs. jersey, $p<0.01$). Reduced comfort with sweating in all groups ($p<0.0001$), worst at maximum sweating. Ponchos made from polyester with similar fineness to cotton were tolerated as well as cotton in eczema group	No difference in comfort between those with eczema and two other groups with sweating.
BACTERIAL INFECTIONS							
David 1986 UK(David and Cambridge 1986)	Cohort study 21/2 years	190 children with eczema attending outpatient department.	7 weeks to 17 years (median age 3 years)	Bacterial infection as defined by 1.Presence of pustules, purulent discharge, crusting with or without weeping and 2.Response to oral antibiotic or topical antiseptic treatment	Clinical assessment of severity of eczema every 3 months or sooner if unexpected deterioration of eczema	164 episodes of infection and 20 episodes of possible infections in 40% of patients 15% of episodes lead to hospital admissions	Impossible to exclude role of other factors, although response to antibiotics supports role of infection. No clinical severity scoring system used

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
SEASONALITY							
Vocks 2001 Germany (Vocks, Busch et al. 2001)	Observational ecological study 7 years	2,106 participants	16-74y	Meteorological data (15 variables)	Daily average itch score	Inverse correlation of group daily average itch score with temperature (r=-0.235)	Group score used. Participants contributing to group changed over time
Krämer 2005 Germany (Kramer, Weidinger et al. 2005)	Panel study 6 months	39 children with eczema (17 excluded due to poor diary completion or absence of eczema)	8.7-9.7 years	Patient daily record of exposure including twice daily household temperature and humidity levels. Outdoor temperature and humidity, pollen count and radiation	Daily itch and extent of eczema	Winter (improved itch by 22% and extent by 65% per 15°C temperature rise) (n=21) and summer types (increased itch by16% and extent by 19% correlated with grass pollen) identified (n=18). The correlation for pollen existed when grass pollen counts were higher than 46 per m^3. There was no association with birch pollen levels	Subtypes identified in *post-hoc* analysis. Study did not include winter period (March to September)

Author/ year/ country	Study type	Number of participants	Age range	Measures of exposure	Outcome measures	Results	Comments
STRESS							
Gil 1987 USA (Gil, Keefe et al. 1987)	Case series	44 eczema	2-21 years	Life events checklist, AD problem total and eczema distress scores	Symptoms score sheet, % BSA	Pearson correlation coefficients: Relation AD distress and symptoms (r=0.5) and life events (r=0.03). Relationship between family environment characteristics and eczema severity (less severity in independent/ organised vs. moral/religious).	Once-off evaluation of all measures in selected group
King 1991 (King and Wilson 1991) Australia	Prospective case-control study	50 eczema, 30 controls	Mean age eczema 30.6 years, controls 27.6 years	Diary completed for two weeks recording daily emotional states and skin condition.	Eczema subjectively scored daily (1-3). Depression and stress recorded daily.	Relation stress and self-rated severity (r=0.2), anxiety and tension (r=0.3). Relation between stress and skin condition on the following day (r=0.28, p=0.04) (reciprocal). Depression was predicted by the skin condition on the previous day (p=0.0005	Volunteers included. Control group were psychology students

Abbreviations for appendix 3

SCORAD: SCORing atopic dermatitis score
AD: atopic dermatitis
OPT: oral provocation tests
DBPCFC: double blind placebo controlled food challenges
HDM: house dust mite
Dp: Dermatophagoides pteronyssinus
SASSAD: Six area six sign atopic dermatitis severity score
FEV1: Forced expiratory volume in 1 minute
FICH: Food immediate-contact hypersensitivity
SPT: Skin prick tests
RAST: Radio-allergosorbent test
APT: Atopy patch test
PBMC: Peripheral blood

Appendix 4 Psychometric properties and scale quality criteria considered in the systematic review of outcome measures in eczema

Name of quality item	Definition of item	Measurement of quality item	Criteria for "adequate" rating	Criteria for "acceptable" rating
Construct validity: (a) convergent (b) divergent	Does the scale measure the hypothetical construct (objective severity of eczema) it should?			
	(a) Are 2 outcome measurements that are presumed to measure the same construct correlated?	(a) and (b) Confirmatory factor analysis, Structural equations modeling (correlation of coefficients)	(a) Correlation coefficient >0.70	(a) Correlation coefficient 0.60-0.69
	(b) Are 2 outcome measurements that are presumed to measure different constructs not related?		(b) Correlation coefficient ≤0.70	(b) Correlation coefficient 0.71-0.85
Content validity	Can the domains measure the construct in question? Are the items representative of the domain they are supposed to measure?	Rating by experts and consumers	Expert/consumer says yes for at least 90% of all items	Expert/consumer says yes for 70% to 89% of all items
Internal consistency	Are the different domains/items of the scale interrelated?	Cronbach α*	≥0.90 (individual patients)	0.70-0.89 (individual patients)
			≥0.70 (groups)	0.60-0.69 (groups)
Interobserver reliability	Do 2 or more independent investigators achieve the same result?	(a) Correlation coefficient	(a) >0.80	(a) 0.60-0.80
		(b) κ†	(b) >0.60	(b) 0.41-0.60
		(c) Coefficient of variation	(c) <20%	(c) 20% to 30%
		(d) ANOVA (% variance explained by	(d) <10%)	(d) 10% to 20%

Name of quality item	Definition of item	Measurement of quality item	Criteria for "adequate" rating	Criteria for "acceptable" rating
		observer)		
Test-retest reliability	Do 2 assessments by one investigator in the same patient yield the same result?	(a) Correlation coefficient	(a) 0.90	(a) 0.80-0.90
		(b) Percentage variation	(b) <5%	(b) 5% to 10%
		(c) Coefficient of variation	(c) <10%	(c) 10% to 20%
Sensitivity to change	Can clinically relevant changes be detected by this measurement?	Correlation of changes in 2 or more outcome measurements of the same construct	>0.80	0.60-0.80
Acceptability	Is the measurement practical enough to be applied in:	Time to administer		
	(a) everyday clinical practice		(a) <3 min	(a) 3-5 min
	(b) clinical trials		(b) <7 min	(b) 7-10 min

*The Cronbach α value assesses the extent to which the items and domains of an outcome can be treated as measuring a single latent variable (range, $-\infty$ to 1.0; higher values reflect better internal consistency) (Kline 2005)

† The κ value is the chance-corrected agreement between 2 observers (range, −1.0 to 1.0; higher values reflect higher interobserver reliability) (Rosner 2000)

Appendix 5 Table of references for systematic review of outcome measures in eczema

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Bahmer, Schafer *et al.* 1991
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Hanifin, Thurston *et al.* 2001
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Silny, Czarnecka-Operacz *et al.* 2005
Sowden, Berth-Jones *et al.* 1991
Sprikkelman, Tupker *et al.* 1997
Staab, Kaufmann *et al.* 2005
Sugarman, Fluhr *et al.* 2003
Tofte 1998;
Van Leent, Graber *et al.* 1998
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Appendix 6 Characteristics of validation studies on outcome measures in eczema included in the systematic review

		Study characteristics				
				Study population		
				No. of participants		
Outcome measure	**No. of validation studies**	**Geographic location**	**Setting - Community/primary care - Secondary/tertiary care**	**Total**	**Per study (range)**	**Age (range)**
ADAM	1	Australia	Secondary/tertiary care	171	171	0-16 y
ADASI	1	Germany	Secondary/tertiary care	16	NS	1-34 y
ADSI	0	—	—	—	—	—
BCSS	1	The Netherlands	Secondary/tertiary care	82	NS	0-67 y
EASI	5	Australia, United States, Europe, South America	All secondary/tertiary care	1801	20-1550	0-43 y
FSSS	0	—	—	—	—	—
IGADA	2	Australia, United States, Europe, South America	All secondary/tertiary care	1751	201-1550	0-17 y
Leicester index	1	United Kingdom	Secondary/tertiary care	123	NS	0-60 y
NESS	5	United Kingdom, China	Community, n = 2; secondary/tertiary care, n = 3	651	70-290	1-63 y
OSAAD	2	Europe, United States	All secondary/tertiary care	70	32-38	0-38 y
POEM	1	United Kingdom	Primary and secondary care	453	NA	1-62 y
RL score	3	Europe	All secondary/tertiary care	52	6-30	1-54 y

		Study characteristics				
				Study population		
				No. of participants		
Outcome measure	No. of validation studies	Geographic location	Setting - Community/primary care - Secondary/tertiary care	Total	Per study (range)	Age (range)
SA-EASI	2	United States	All secondary/tertiary care	96	47-49	0-12 y
SASSAD	3	United Kingdom, Australia	Primary, n = 1); secondary/tertiary, n = 2	124	6-85	3-63 y
SCORAD	14	Europe, China, Canada	Community, n = 4; secondary/tertiary care, n = 11	1346	19-201	0-67 y
SIS	0	—	—	—	—	—
SSS	4	Europe	All secondary/tertiary care	235	14-123	0-67 y
TBSA	0	—	—	—	—	—
TISS	2	Europe	Primary and secondary care	306	126-180	0-67 y
WAZ-S	0	—	—	—	—	—

ADAM, Atopic Dermatitis Assessment Measure; *ADASI*, Atopic Dermatitis Area and Severity Index; *NA*, not applicable; *ADSI*, Atopic Dermatitis Severity Index; *BCSS*, Basic Clinical Scoring System; *SIS*, Skin Intensity Score; *TBSA*, Six-area Total Body Severity Assessment.

Appendix 7 Summary of psychometric properties of objective disease severity measures in eczema

Outcome	Content validity-expert	Content validity-consumer	Construct validity-convergent	Construct validity-divergent	Internal consistency	Interobserver reliability	Test-retest reliability	Sensitivity to change	Time to perform (mins.)	Mean score	Recommendation
ADAM	•	•	•	X	X	o	X	X	-	44%	Not recommended
ADASI	•	•	o	X	X	o	X	X	2-10	38%	Not recommended
ADSI	•	•	X	X	X	X	X	X	-	25%	Not acceptable
BCSS	•	•	o	X	X	•	X	X	-	44%	Not recommended
EASI	•	•	•	•	o	o	o	•	-	81%	Recommended
FSSS	•	•	X	X	X	X	X	X	-	25%	Not acceptable
IGADA	•	•	•	X	X	X	X	•	-	50%	Acceptable
Leicester index	•	•	X	X	X	X	X	o	-	31%	Not recommended
NESS	•	•	o	•	X	•	X	X	1	56%	Acceptable

OSAAD	X	X	○	●	X	●	X	○	5	25%	Not acceptable
POEM	X	●	●	○	●	N/A	●	○	1-2	71%	Recommended
RL score	●	●	X	X	X	○	X	X	<1-4	31%	Not recommended
SA-EASI	●	●	○	○	●	N/A	X	○	-	57%	Acceptable
SASSAD	●	●	○	X	X	●	○	○	<2-10	56%	Acceptable
SCORAD	●	●	●	●	X	●	○	●	≤10	81%	Recommended
SIS	●	●	X	X	X	X	X	X	-	25%	Not acceptable
SSS	●	●	○	X	X	○	X	○	1-5	44%	Not recommended
TBSA	●	●	X	X	X	X	X	X	-	25%	Not acceptable
TISS	●	●	●	●	X	○	X	X	-	56%	Acceptable
WAZ-S	X	●	X	X	X	X	X	X	-	13%	Not acceptable

ADAM, Atopic Dermatitis Assessment Measure; *ADASI*, Atopic Dermatitis Area and Severity Index; *ADSI*, Atopic Dermatitis Severity Index; *BCSS*, Basic Clinical Scoring System; *NA*, not applicable; *SIS*, Skin Intensity Score; *TBSA*, Six-area Total Body Severity Assessment.

Guide to appendix 7

•, Criterion is adequately met (100%); ○, criterion is acceptably met (50%); X criterion is inadequately met (0%).

* Recommendations are based on all items except time needed to perform measurement: Highly recommended, score greater than 90%, measurement is valid and reliable; recommended, score of 70% to 90%—measurement meets most validity criteria; acceptable, score of 50% to 69%, but not recommended—validity criteria only partly met; not recommended, score of 30% to 49%—significant validity criteria are not met or have not been evaluated"; not acceptable, score of less than 30%—measurement is invalid or has not been validated.

† Weighted mean (weighted by the number of study participants) if psychometric property was assessed in more than one study; criterion judged as inadequately met if no studies identified on a psychometric property.

Appendix 8 Eczema study questionnaire

Child's date of birth: / / (dd/mm/yy)

Sex: Boy ☐ Girl ☐

Ethnicity:	1	White	2	Black-Caribbean
	3	Black-African	4	Black-other
	5	Indian	6	Pakistani
	7	Bangladeshi	8	Chinese
	9	Other - please specify:		

Your child's eczema

1. How long has your child had eczema for? _____

2. What kind of moisturiser does your child normally use?

1) _____ 2) _____

3) _____ 4) _____

3. What topical steroids does your child use?

1) _____ 2) _____

4. How do you normally treat your child's eczema every day? (Name creams and how often use you use them)

_____

_____

5. When your child's eczema gets worse, what treatments do you usually use?

_____

---

6. How long do you use them for?

_____

7. Does your child use any other treatments (other than topical steroids/ emollients) for their eczema (e.g. wet wraps, tacrolimus, and antihistamines)?

Yes No

If yes, please say what: _____

_____

8. Has your child been on any of the following treatments for their eczema?

Phototherapy/light treatment ☐

Cyclosporine, *Neoral* ☐

Azathioprine, *Imuran* ☐

Steroids taken by mouth ☐

9. Has your child ever had asthma? Yes ☐ No ☐

10. Has your child ever had hay fever? Yes ☐ No ☐

Environmental factors

11. Are you avoiding any types of clothes because of your child's eczema?

Yes ☐ No ☐

If yes, which type(s) of clothes?

_____

12. Are you avoiding any cleansing products (shampoo, shower gel etc) because of your child's eczema?

Yes ☐ No ☐

If yes, which ones? _____

13. Do you avoid contact with animals because of your child's eczema?

Yes ☐ No ☐

If yes, proceed to q14

14. Which types of animals do you avoid? _____

15. Are there pets at home? Yes ☐ No ☐

If yes, specify type and

number_____

16. Is there carpet in your/ your child's bedroom? Yes ☐ No ☐

17. Are there furry toys in your/ your child's bedroom? Yes ☐ No ☐

18. How often do you dust and Hoover your child's room each month?

Daily ☐

Every few days ☐

Weekly ☐

Every few weeks ☐

Once a month or less ☐

19. Does the eczema get worse in summer (June, July, and August)?

Yes ☐ No ☐

20. Does the eczema get worse in winter (November, December, and January)?

Yes ☐ No ☐

21. How does cold weather affect you/ your child's eczema?

Not at all ☐

Makes it better ☐

Makes it worse ☐

22. How does hot weather affect you/ your child's eczema?

Not at all ☐

Makes it better ☐

Makes it worse ☐

Home details:

23. Does your child regularly share a bedroom? Yes ☐ No ☐

If yes, proceed to q24

24. How many people does your child share his/ her bedroom with?

_____

25. Does your child regularly share a bed? Yes ☐ No ☐

26. How many brothers and sisters does your child have? _____

27. How many people live in your house? _____

Main household earner's occupation

28. What is your occupation? _____

29. If you have a partner, what is your partner's occupation?

_____

Your occupation	Your partner's occupation
Present occupation _____	Present occupation _____
Previous occupation _____	Previous occupation _____
Never employed ☐	Never employed ☐

30. What is the highest educational qualification of the main care giver?

None ☐

GCSE, O level or equivalent ☐

A-level or equivalent ☐

Higher education below degree ☐

Degree/ higher degree ☐

Other: _____

Thank you very much for completing this questionnaire.

Appendix 9 Diary questions

Daily questions			
No	**Question**	**Next step**	**Notes**
0	WELCOME SCREEN Please enter your data for <day/month/year>. Press tick to continue	**Proceed to Q1**	
1	How much did you (your child) scratch today? Please give a number from 0 to 10 (0= not scratched at all; 10= scratched all of the time)	**Proceed to Q2**	
2	How much bother did your (your child's) eczema cause today? Please give a number from 0 to 10 (0= no bother at all; 10= the most bother you can imagine)	**Proceed to Q3**	
3	Where did your (your child's) eczema get worse? (can pick more than one) 1) Hands 2) Face 3) Arms or legs 4) Some of your trunk (back and tummy)	**Proceed to Q4**	**Need to be able to select more than one choice**
4	How much time did you (your child) spend outdoors today? 1) Less than 15 minutes 2) Between 15 and 30 minutes 3) Between 30 minutes and 2 hours 4) More than 2 hours?	**Proceed to Q5**	
5	What parts of your (your child's) skin were not covered by clothes during this time? (can pick more than one) 1) Hands and face 2) Face only 3) Arms or legs 4) Some of your trunk (back and tummy)	**Proceed to Q6**	**Need to be able to select more than one choice**
6	What was the most you (your child) sweated today? 1) Not at all 2) A little 3) Damp forehead and/or underarms only 4) Wet hair and damp underarms 5) Dripping with sweat	**Proceed to Q7**	
7	Did you (your child) sweat because of playing sport? 1) Yes 2) No	**Proceed to Q8**	
8	Did you (your child) wear woollen clothes today? 1) Yes 2) No	**If Yes proceed to Q9. If No proceed to Q11**	
9	Did you (your child) wear it next to the skin? 1) Yes 2) No	**If Yes proceed to Q10. If No proceed to Q11**	
10	How long did you (your child) wear it for? 1) Less than one hour 2) More than one hour, up to a half day 3) More than a half day, up to a full day	**Proceed to Q11**	
11	Did you (your child) wear nylon or synthetic clothes today? 1) Yes 2) No	**If Yes proceed to Q12. If No proceed to**	

		Q13	
12	Did you (your child) wear it next to the skin? 1) Yes 2) No	**If Yes proceed to Q13. If No proceed to Q14**	
13	How long did you (your child) wear it for? 1) Less than one hour 2) More than one hour, up to a half day 3) More than a half day, up to a full day	**Proceed to Q14**	
14	Were you (your child) in close contact with any animals today? 1) Yes 2) No	**If Yes proceed to Q15. If No proceed to Q18**	
15	What type of animal was it? (can pick more than one) 1) Cat 2) Dog 3) Hamster, guinea pig or gerbil 4) Rabbit 5) Horse 6) Other	**Proceed to Q16**	**Need to be able to select more than one choice**
16	How long for? 1) Less than one hour 2) More than one hour up to two hours 3) More than two hours	**Proceed to Q17**	
17	Was it your own pet? 1) Yes 2) No	**Proceed to Q18**	
18	Were you (your child) in a very obviously dusty place today? 1) Yes 2) No	**If Yes proceed to Q19. If No proceed to Q20**	
19	How long for? 1) Less than one hour 2) More than one hour up to two hours 3) More than two hours	**Proceed to Q20**	
20	Did you (your child) go swimming today? 1) Yes 2) No	**Proceed Q21**	
21	Have you had to ***step up*** your treatment today because your (your child's) eczema was worse? 1) Yes 2) No	**Proceed Q22**	
22	Did you wash your (your child's) hair today? 1) Yes 2) No	**If yes, proceed to Q23. If no, proceed to 24**	
23	Did you wash it at the same time as your bath or shower? 1) Yes 2) No	**Proceed to Q24**	

24	Thank you for entering your data. Are you happy with your answers? Yes	**If Yes, proceed to Q25 and data**	

	No	**is saved. If No, return back to Q0 and Data is not saved**	
25	Your data has been submitted. You need to enter your data again on <date>	**Finish.**	