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Investigating International Time Trends in the Incidence and Prevalence of Atopic Eczema 1990–2010: A Systematic Review of Epidemiological Studies

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Abstract

The prevalence of atopic eczema has been found to have increased greatly in some parts of the world. Building on a systematic review of global disease trends in asthma, our objective was to study trends in incidence and prevalence of atopic eczema. Disease trends are important for health service planning and for generating hypotheses regarding the aetiology of chronic disorders. We conducted a systematic search for high quality reports of cohort, repeated cross-sectional and routine healthcare database-based studies in seven electronic databases. Studies were required to report on at least two measures of the incidence and/or prevalence of atopic eczema between 1990 and 2010 and needed to use comparable methods at all assessment points. We retrieved 2,464 citations, from which we included 69 reports. Assessing global trends was complicated by the use of a range of outcome measures across studies and possible changes in diagnostic criteria over time. Notwithstanding these difficulties, there was evidence suggesting that the prevalence of atopic eczema was increasing in Africa, eastern Asia, western Europe and parts of northern Europe (i.e. the UK). No clear trends were identified in other regions. There was inadequate study coverage worldwide, particularly for repeated measures of atopic eczema incidence. Further epidemiological work is needed to investigate trends in what is now one of the most common long-term disorders globally. A range of relevant measures of incidence and prevalence, careful use of definitions and description of diagnostic criteria, improved study design, more comprehensive reporting and appropriate interpretation of these data are all essential to ensure that this important field of epidemiological enquiry progresses in a scientifically robust manner.

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Introduction

Atopic eczema is a very common inflammatory skin disorder [1]. Its prevalence appears to vary across the world as noted in key international epidemiological studies [2–5]. Such variation has been found in both children and adults and points to the likely importance of environmental risk factors. In addition, atopic eczema has been shown to cluster in families and there is growing evidence that it is an herald condition in many people who go on to develop allergic problems affecting other organ systems (e.g. food allergy) [6,7]. Genetics are important in the aetiology of atopic eczema: in particular, recent genetic epidemiological studies found a strong association between filaggrin gene defects (present in 1 in 10 Europeans and North Americans), and atopic eczema [7]. Filaggrin plays a role in maintaining the epidermal skin barrier function, whereby it helps to retain moisture in the skin and limits penetration by allergens. These functions can be impaired in filaggrin loss-of-function mutations, thus resulting in dry, scaly skin, which increases the risk of allergic sensitisation and disease [7–9].

Monitoring disease trends over time aids aetiological understanding and helps with the planning of health services nationally

and internationally. Building on our previous work on asthma, we sought to describe international trends in the incidence and prevalence of atopic eczema [10]. We aimed to draw preferentially on high quality studies using appropriate study designs and, in particular, studies using validated instruments [such as the International Study of Asthma and Allergies in Childhood (ISAAC) or the European Community Respiratory Health Survey (ECRHS)] [11,12].

Methods

This review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guide (see Appendix S1) [13]. The methods for this review were specified in advance and documented in a study protocol.

Our full search strategy is given in Appendix S2. In short, we searched seven electronic databases, namely Medline, CINAHL, Embase, Global Health, Global Health Library, Google Scholar and Web of Knowledge, from 1 January 1990 to 19 May 2010 (date of last search). We used both Medical Subject Headings (MeSH) and free text terms of the following concepts: (atopic

Table 1. Inclusion criteria.

- | |
|---|
| 1. Epidemiological design (e.g. cohort, repeated cross-sectional or routine health care) |
| 2. Estimates of eczema incidence and/or prevalence at least twice within the period 1990–2010 |
| 3. Use of a comparable approach and instrument to measure eczema at each time point. |

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eczema OR atopic dermatitis) AND (cohort studies OR cross-sectional studies OR ISAAC OR ECRHS) AND (incidence OR prevalence OR trend). The searches were not limited by age, sex, ethnicity or language. Furthermore, bibliographies of key reports were scanned and a citation search was conducted for any additional papers of interest. We only included full-text reports of cohort studies, repeated cross-sectional surveys or analyses of routine healthcare datasets, as we considered these appropriate designs for the assessment of disease trends. Studies were required to present at least two estimates of atopic eczema incidence and/or prevalence within the period 1990 to 2010 and, at each assessment time point, they needed to use a similar approach and instrument (see Table 1). The screening of titles and abstracts and the eligibility assessment of full-text reports was independently performed by two reviewers. Disagreements were resolved by discussion or by a third reviewer if agreement could not be reached. Similarly, to establish the methodological quality of each study, the internal and external validity was examined using the Critical Appraisal Skills Programme (CASP) tool [14] and scored as 'good', 'moderate' or 'poor'. This methodological assessment included for example an appraisal of whether validated instruments were used [i.e. at least one of the ISAAC key questions (see Table 2)]. Reviewers were not masked when assessing study quality. Incidence and/or prevalence data as well as study and participant characteristics were extracted onto a customised data extraction sheet by one reviewer and thoroughly checked by the second reviewer.

To compare disease trends, our primary outcome measure was the lifetime prevalence of symptoms suggestive of atopic eczema or the incidence of atopic eczema (see Table 3). We also collected data on the secondary outcomes, such as the lifetime prevalence of physician-diagnosed eczema or 12-month prevalence measures. There was too much heterogeneity of populations studied and methods employed to undertake meta-analysis.

Results

Our searches retrieved 2,464 titles from which we identified 70 papers that satisfied our inclusion criteria (see Figure 1). We

excluded one of these studies because the full-text paper was only available in Korean [15] and we were unable to procure a translation; there were therefore 69 papers in our final dataset. Data from included studies judged to be of moderate or good quality are summarised in Table 4 and explored descriptively by region (see Tables 5, 6, 7, 8 and 9) [16]. Data from the primary outcomes are additionally represented on a map (see Figure 2). Data from studies judged to be at greater risk of bias are available from the corresponding author [17–22]. Nearly all studies had prevalence data, while incidence data were only reported in three European studies [23–25]. Prevalence data are described using lifetime prevalence of atopic eczema symptoms.

Africa

As presented in Table 4, we found four studies on atopic eczema trends for Africa [26–29]. Incidence was not measured in any of these studies. Prevalence was measured based on parental- or self-report as assessed by ISAAC-based questions (see Table 5). Data were mainly from 13–14 year old children and in these children the general trend in Africa (Kenya, Morocco and South Africa) for the prevalence of atopic eczema was increasing [25,27,28] [26,27,29]. In these children, an approximate doubling of the lifetime prevalence of atopic eczema symptoms was found for Morocco [e.g. flexural rash in Marrakech, Morocco – from 9.9% (1995) to 20.9% (2001–02)] [26], for South Africa [e.g. flexural rash – from 10.2% (1995) to 16.5% (2002)] [29] and for Kenya [e.g. itchy recurrent rash in flexural areas – from 11.4% (1995) to 19.8% (2001)] [27]. In Nigeria in children of this age group, the lifetime prevalence of itchy rash decreased from a high baseline prevalence [from 26.1% (1995) to 18.0% (2001–02)] [28]. Prevalence estimates in 2001–02 were, however, comparable for all countries. An approximate doubling was also seen in the lifetime prevalence of physician-diagnosed atopic eczema in 13–14 year olds in South Africa and Kenya [27,29]. In contrast, the prevalence of physician-diagnosed atopic eczema in Nigeria considerably decreased over a 5-year period from 1995 to 2001 in 6–7 year olds [from 9.4% to 6.8%] and in 13–14 year olds [from 38.4% to 19.4%] [28]. The baseline estimate for 13–14 year

Table 2. Key question for atopic eczema from the ISAAC questionnaire.

Have you ever had an itchy rash which was coming and going for at least six months?
--

Have you had this itchy rash at any time in the last 12 months?
--

Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?

At what age did this itchy rash first occur; under 2 years, age 2–4 years or age 5 or more?

Has this rash cleared completely at any time during the last 12 months?
--

In the last 12 months , how often, on average, have you been kept awake at night by this itchy rash; never in the last 12 months, less than one night per week or one or more nights per week?

Have you ever had eczema?

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Table 3. Primary and secondary outcomes measures.

Primary outcomes	Lifetime prevalence of atopic eczema symptoms
	Incidence of atopic eczema
Secondary outcomes	Lifetime prevalence of physician diagnosis of atopic eczema
	12-month prevalence of atopic eczema symptoms
	12-month prevalence of physician diagnosis of atopic eczema

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olds was again extremely high. In other African countries, single estimates of atopic eczema prevalence may have been reported, but we were unable to locate any serial data on trends.

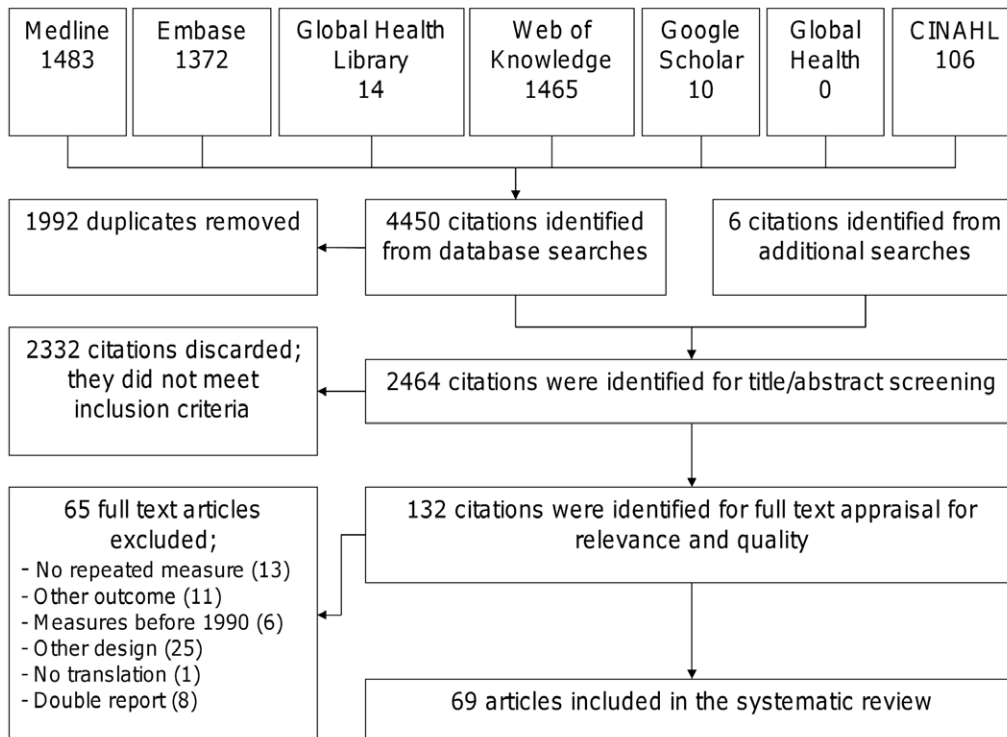
Asia

For Asia, we summarised 20 papers representing 61 measures of trends in Table 4. The majority of data came from eastern Asia [30–39], whereas south-eastern Asia [40–43] and western Asia [44–49] were represented to a lesser extent. For other regions in Asia, we found no relevant data. Here too no study assessed trends in incidence; rather, each study measured prevalence as based on parental- or self-report by questionnaires (see Tables 6). Trends were found for different age groups in 12 different countries and showed no overall pattern.

In eastern Asia, the general trend for atopic eczema prevalence was mainly increasing across different age groups. Lee et al. (2007) reported an increase in the sex- and age-standardised lifetime prevalence of ISAAC-based parental-report of atopic eczema symptoms in Taiwan among 12–15 year olds [from 2.4% (1995–96) to 4.0% (2001)] [32]. The lifetime prevalence of atopic eczema symptoms also increased in Korea in the same age group [from

7.2% (1995) to 9.3% (2000)] [36], in China (Guangzhou city) in a similar age group 13–14 [from 1.7% (1994–95) to 3.0% (2001)] [37] and in Japan in a wider-ranged age group 7–15 [from 10.1% (1996) to 13.6% (2006)] [39]. Moreover, baseline prevalences were low, but considerably higher in Korea and Japan, compared to Taiwan and China. In a slightly younger age group 6–12 in Korea, atopic eczema symptoms showed a modest increase from a substantially higher baseline prevalence [from 15.3% (1995) to 17.0% (2000)] [36]. In the youngest children aged 6–7, the prevalence of atopic eczema symptoms was stable in Hong Kong [e.g. chronic rash – from 5.7% (1995) to 5.4% (2001)] [31], whilst a modest increase was seen in a later study in Taiwan in a similar age group 6–8 [e.g. chronic rash - from 5.8% (2002) to 7.7% (2007)] [34]. Trends in the lifetime prevalence of physician-diagnosed atopic eczema followed nearly the same pattern as the lifetime prevalence of atopic eczema symptoms; trends were increasing in most countries among different age groups with only few exceptions.

In south-eastern Asia, the prevalence of different atopic eczema symptoms showed mixed trends. For chronic rash, the lifetime prevalence was stable in 6–7 year olds in Singapore [10.5% (1994) and 12.5% (2001)] [42] and in north-eastern Thailand [18.0%

**Figure 1. PRISMA flow diagram.**

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Table 4. Summary of trends in different atopic eczema outcomes between 1990 and 2010 by region*.

Region	Papers (n)	Trends (n)	Incidence			Lifetime prevalence						12-month prevalence					
			↑	↔	↓	symptoms			diagnosis			symptoms			diagnosis		
						↑	↔	↓	↑	↔	↓	↑	↔	↓	↑	↔	↓
Africa	4	20	0	0	0	9	0	1	2	0	2	4	1	1	0	0	0
Asia	20	61															
eastern	10	27	0	0	0	7	2	0	7	1	1	7	1	0	0	0	1
south-eastern	4	20	0	0	0	2	4	0	1	3	0	4	6	0	0	0	0
western	6	14	0	0	0	1	0	3	0	3	2	0	2	2	0	0	1
Americas	5	21															
North	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Central	1	6	0	0	0	0	0	2	2	0	0	0	0	2	0	0	0
South	4	15	0	0	0	0	5	0	0	1	3	0	5	1	0	0	0
Europe	31	101															
western	10	42	1	1	0	4	2	0	12	5	0	4	9	0	0	0	4
southern	4	15	0	0	0	1	1	0	4	1	0	5	1	0	2	0	0
northern	15	41	1	1	0	9	1	1	15	1	0	8	2	1	0	1	0
eastern	2	3	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0
Oceania	3	4	0	0	0	1	0	0	1	1	0	1	0	0	0	0	0

*Based on UN classification [16].

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(1998–99) and 17.2% (2003) [41]. Moreover, this prevalence also remained stable in older children (aged 12–15) in Singapore and, even though the baseline prevalence was appreciably lower, in 13–14 year olds in north-eastern Thailand. For chronic rash with a typical distribution, however, the lifetime prevalence was increasing in Singapore in children of both age groups [e.g. in 6–7 year olds – from 6.1% (1994) to 9.8% (2001)] [43]. In Malaysia and two specific geographical areas in Thailand (Chiang Mai and Bangkok) only data regarding the 12-month prevalence of atopic eczema symptoms were available [40,41]. In Malaysia and Chiang Mai, the 12-month prevalence of atopic eczema symptoms increased in 6–7 year olds, but was stable in 13–14 year olds, whereas the opposite was seen in Bangkok.

In western Asia, data were found for Georgia, Kuwait, Turkey and Israel [44–49]. In Georgia, the lifetime prevalence of atopic eczema symptoms was found to be decreasing in two different geographical areas among 6–7 year olds: in Tbilisi [from 4.5% (1996) to 3.4% (2003)] and in Kutaisi [from 5.2% (1996) to 2.4% (2003)] [44]. This trend was additionally apparent in the lifetime prevalence of physician-diagnosed atopic eczema in these children. There was also a decrease in the prevalence of atopic eczema symptoms in 13–14 year old children from Kuwait [from 17.5% (1995–96) to 10.6% (2001–02)], but the baseline prevalence was much higher [48]. In Israel, the lifetime prevalence of itchy rash in a distribution suggestive of atopic eczema was found to be increasing [from 5.9% (1997) to 8.7% (2003)] [49]. In Turkey, two measures of the prevalence of physician-diagnosed atopic eczema were reported. The lifetime prevalence was stable in 6–13 year old children [6.1% (1992) and 6.5% (2007)] [47], whilst the 12-month prevalence was reported to have decreased over a 15-year period in 7–12 year old children [from 4.0% (1992) to 1.2% (2007)] [46].

The Americas

We found no studies on atopic eczema trends for North America, one study for Central America [50] and four studies for

South America [51–54] (see Table 4). No studies reported an incidence trend. The study from Central America, which was conducted in Mexico in 6–8 and 11–14 year old children (see Table 7) [50]. This study showed a sharply decreasing lifetime (and 12-month) prevalence of itchy rash in both age groups [e.g. in 6–8 year olds – from 15.0% (1995) to 7.3% (2002)] and, conversely, a from low baseline increasing lifetime prevalence of physician-diagnosed atopic eczema in both age groups [e.g. in 6–8 year olds – from 3.9% (1995) to 6.1% (2002)].

All four studies from South America were from Brazil and each study included only trends in prevalence as based on parental- or self-report by questionnaires (see Table 7) [51–54]. Two studies measured the lifetime prevalence of atopic eczema symptoms and showed a stable trend among 6–7 and 13–14 year olds [e.g. itchy rash in São Paulo in 6–7 year olds - 13.6% (1996) and 15.0% (1999)] [51,52]. In another study, the 12-month prevalence of itchy rash remained stable in children aged 13–14 years old [6.3% (1995) and 6.0% (2001)] [53], whereas in the last study both the lifetime prevalence of physician-diagnosed atopic eczema and the 12-month prevalence of atopic eczema symptoms were decreasing in 13–14 year olds across five centres [e.g. physician-diagnosed atopic eczema - from 5.3% (1994–95) to 4.5% (2001–03)] [54].

Europe

The largest set of reports (n = 31) on atopic eczema trends is for Europe. The majority of all trends were increasing, although decreasing and stable trends were found in some areas (see Table 4).

Incidence. Three studies reported on incidence trends in atopic eczema in Europe [23–25]. In Denmark, the adjusted cumulative incidence of the UK Working Party-based parental-report of physician-diagnosed atopic eczema in 7 year olds was 18.9% in 1993 and 19.6% in 1998 (see Table 8). Compared to the survey of 1993 the sample size was over nine times larger in the survey of 1998 [23]. Further, the cumulative incidence of parental-

Table 5. Good and moderate quality studies reporting the prevalence of parental- or self-report of atopic eczema between 1990 and 2010 in Africa.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
<i>Measures of symptoms of atopic eczema</i>											
Falade et al. (2009) [28]	Nigeria (Ibadan)	6–7	ISAAC-based parental-report of: lifetime prevalence of itchy rash	1995/ 2001–02	1,696	7.7 (0.7)	2,396	10.2 (0.6)	% change (S.E.) 2.5 (0.9), P = 0.007	Increase	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	13–14	ISAAC-based parental-report of: lifetime prevalence of itchy rash	1995/ 2001–02	3,057	4.5 (0.5)	3,142	5.0 (0.5)	0.5 (0.7), P = 0.437 % change (S.E.)	Stable	Moderate
Bouayad et al. (2006) [26]	Morocco (Casablanca)	13–14	ISAAC-based self-report of: lifetime prevalence of rash	1995/ 2001–02	3,178	17.7 (0.7)	1,744	7.7 (0.5)	% change per year – 10.0 (0.8), P < 0.001	Decrease	Moderate
Bouayad et al. (2006) [26]	Morocco (Marrakech)	13–14	ISAAC-based self-report of: lifetime prevalence of rash	1995/ 2001–02	2,896	26.1 (0.8)	1,677	18.0 (0.7)	– 8.1 (1.0), P < 0.001	Decrease	Moderate
Esamai et al. (2002) [27]	Kenya (Uasin Gishu)	13–14	ISAAC-based self-report of: lifetime prevalence of rash	1995/2001	3,018	14.2	3,258	26.1 (25.3–26.8)	1.98, P < 0.001	Increase	Moderate
Zar et al. (2007) [29]	South Africa (Cape Town)	13–14	ISAAC-based self-report of: lifetime prevalence of itchy recurrent rash	1995/2002	5,161	23.8	5,019	28.5	P = 0.001	Increase	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	6–7	ISAAC-based parental-report of: lifetime prevalence of itchy recurrent rash in flexural areas	1995/ 2001–02	1,696	11.4	2,396	19.8	P = 0.001	Increase	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	13–14	ISAAC-based self-report of: lifetime prevalence of itchy recurrent rash	1995/ 2001–02	3,057	14.4	3,142	21.3	P = 0.001	Increase	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	6–7	ISAAC-based self-report of: lifetime prevalence of itchy recurrent rash	1995/ 2001–02	1,696	15.5	2,396	26.2	OR (95%CI) 1.93 (1.75–2.14), P < 0.001	Increase	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	13–14	ISAAC-based self-report of: lifetime prevalence of itchy recurrent rash	1995/ 2001–02	3,057	10.2	3,142	16.5	1.75 (1.56–1.97), P < 0.001	Increase	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	13–14	ISAAC-based self-report of: lifetime prevalence of itchy recurrent rash	1995/ 2001–02	3,057	11.8	3,142	19.4	1.77 (1.56–1.97), P < 0.001	Increase	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	6–7	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995/ 2001–02	1,696	9.4 (0.7)	2,396	6.8 (0.5)	– 2.6 (0.9), P = 0.003	Decrease	Moderate
Falade et al. (2009) [28]	Nigeria (Ibadan)	13–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995/ 2001–02	3,057	9.4 (0.7)	3,142	6.8 (0.5)	– 2.6 (0.9), P = 0.003	Decrease	Moderate

Table 5. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
			lifetime prevalence of physician-diagnosed atopic eczema		38.4 (0.9)	19.4 (0.7)			-19.0 (1.1), P<0.001	Decrease	
Esamai et al. (2002) [27]	Kenya (Uasin Gishu)	13–14	ISAAC-based self-report of:	1995/2001	3,018	3,258					Moderate
Zar et al. (2007) [29]	South Africa (Cape Town)	13–14	ISAAC-based self-report of:	1995/2002	5,161	5,019	28.5		P = 0.001 OR (95% CI)	Increase	Moderate
			lifetime prevalence of physician-diagnosed atopic eczema		9.6	16.7			1.88 (1.67–2.12), P<0.001	Increase	

Abbreviations – CI: confidence intervals, SE: standard error, OR: odds ratio.

*Based on UN classification [16].

**95% CI and SE are only reported if included in original report.

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report of history of physician-diagnosed atopic eczema in 5–6 year olds was stable in West Germany [12.5% (1991) and 12.8% (1997)], whilst it increased sharply in East Germany [from 9.6% (1991) to 23.4% (1997)] [24]. Finally, the age- and sex-standardised incidence of physicians' recorded atopic eczema diagnosis as based on secondary analysis of QRESEARCH, a large primary care dataset (n = 333,294) in England, increased from 9.6% (2001) to 13.6% (2005) per 1000 patient-years [25].

Prevalence. Prevalence data on trends in atopic eczema for western Europe are shown in Table 9 [24,55–63]. Parental- and self-report of atopic eczema symptoms were reported in five countries [55,56,59,60,62,63]. The lifetime prevalence of atopic eczema symptoms increased in 5–7 year old children in Switzerland [from 11.7% (1992) to 17.4% (2001)] [56] and in slightly older children (aged 6–9) in Austria, but from a lower baseline [from 9.2% (1995–97) to 11.0% (2001–03)] [63]. This lifetime prevalence of atopic eczema symptoms also increased in Belgium, both in boys and girls aged 6–7 [e.g. in boys - from 12.9% (1995–96) to 18.4% (2002)], whilst in 13–14 year old boys and girls it remained stable [e.g. in boys - 15.7% (1995–96) and 13.3% (2002)] [62]. We found no data on the lifetime prevalence of atopic eczema symptoms for Germany and France. In France, the lifetime prevalence of physician-diagnosed atopic eczema increased in 13–14 year olds [from 25.8% (1995) to 30.4% (2002)] [55]. In Germany (Münster), this prevalence also increased in 13–14 year olds [e.g. in boys - from 8.2% (1994–95) to 10.9% (1999–2000)], whilst it showed a stable trend in 6–7 year olds [e.g. in boys - 14.3% (1994–95) and 13.6% (1999–2000)] [60].

In southern Europe, the lifetime prevalence of atopic eczema symptoms remained stable in the Maltese Islands in 5–8 year olds [7.0% (1994–95) and 6.7% (2001–02)] [64] and increased in Greece in older children (aged 8–10) [from 4.5% (1991) to 9.5% (2003)] [65]. Here, the trend was measured over a longer time period and started at a lower baseline level. In Italy and Portugal, no lifetime prevalence trends for atopic eczema symptoms were reported. The lifetime prevalence of physician-diagnosed atopic eczema showed an increasing trend in 6–7 year olds in Italy [from 14.3% (1994–95) to 17.0% (2002)] [66] and in the same age group in Portugal [from 18.6% (1993–94) to 21.0% (2002)] [67]. Compared to Italy and Portugal, the increase of physician-diagnosed atopic eczema in the Maltese Islands in a similar age group of 5–8 year olds was considerably larger and more than doubled over a 7-year period, as it originated from a low baseline [from 4.4% (1994–95) to 11.2% (2001–02)] [64].

For northern Europe, 15 papers reported on trends in atopic eczema [23,25,68–80]. The prevalence of rash and rash with a typical distribution was overall increasing in boys and girls and in 6–7 and 13–14 year olds in the UK [e.g. in 6–7 year old boys - from 17.8% (1995–96) to 21.0% (2001–02)], although not all trends reached significance [80]. Several other studies, which measured the lifetime prevalence of physician-diagnosed atopic eczema [68,71,75–77] or the lifetime prevalence of physicians' recorded atopic eczema diagnosis [25,73] in the UK, also showed increasing trends confirming patterns of atopic eczema prevalence in the UK in children and across all age-groups over time. An increasing trend for atopic eczema symptoms was also found in Estonia in 6–7 year olds [from 16.9% (1993–94) to 22.0% (2001–02)] [69]. However, in Sweden in slightly older children (aged 7–8), the lifetime prevalence of atopic eczema symptoms was decreasing [from 29.3% (1996) to 26.5% (2006)] [78]. Despite this decrease, prevalence estimates remained higher as compared to Estonia. There was no data on the lifetime prevalence of atopic eczema symptoms available in Lithuania and Norway. In Lithuania in 6–7 year olds, the prevalence of physician-diagnosed

Table 6. Good and moderate quality studies reporting the prevalence of parental- or self-report of atopic eczema between 1990 and 2010 in Asia.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Eastern Asia*											
<i>Measures of symptoms of atopic eczema</i>											
Liao MF et al. (2009) [34]	Central Taiwan (Changhwa County)	6–8	ISAAC-based parental-report of:	2002/2007	7,040		4,622		POR (95% CI)		Good
			lifetime prevalence of chronic rash			5.8	7.7		1.39 (1.20–1.61), P<0.001	Increase	
			lifetime prevalence of chronic rash with typical distribution			5.9	8.9		1.56 (1.34–1.83), P<0.001	Increase	
Liao PF et al. (2009) [35]	Taiwan	6–15	ISAAC-based parental-report of:	1994/2002	75,960		11,580		1.45 (1.25–1.67), P<0.001	Increase	Moderate
			12-month prevalence of chronic rash			7.0	9.7		No formal test		
			12-month prevalence of current atopic eczema symptoms			1.5	2.8		–	Increase	
Lee et al. (2007) [32]	Taiwan	12–15	ISAAC-based parental-report of:	1995–96/2001	42,919		10,215		Adjusted PR (95% CI)		Good
			Sex- and age-standardised lifetime prevalence of atopic eczema symptoms			2.4	4.0		1.61 (1.42–1.81), P<0.001	Increase	
Yan et al. (2005) [38]	Taiwan (Taipei)	13–14	ISAAC-based self-report of:	1994–95/2001–02	11,400		6,303				Moderate
			12-month prevalence of recurrent itchy rash in a typical distribution			1.4 (1.1–1.6)	4.1 (3.6–4.6)		P<0.001	Increase	
Lee et al. (2004) [31]	China (Hong Kong)	6–7	ISAAC-based parental-report of:	1995/2001	3,618		4,448		OR (95% CI)		Moderate
			lifetime prevalence of chronic rash			5.7	5.4		0.95 (0.79–1.15), P=0.56	Stable	
			lifetime prevalence of chronic rash at typical areas			4.2	3.6		0.85 (0.68–1.07), P=0.18	Stable	
Wang et al. (2006) [37]	China (Guangzhou city)	13–14	ISAAC-based self-report of:	1994–95/2001	3,855		3,516				Moderate
			lifetime prevalence of flexural atopic eczema symptoms			1.7 (1.3–2.1)	3.0 (2.4–3.6)		P<0.05	Increase	
			12-month prevalence of flexural atopic eczema symptoms			1.3 (0.9–1.7)	2.2 (1.7–2.7)		P=0.002	Increase	
Oh et al. (2004) [36]	Korea	6–12	ISAAC-based parental-report of:	1995/2000	25,361		27,425		No formal test		Moderate
			lifetime prevalence of itchy atopic eczema symptoms			15.3 (14.9–15.8)	17.0 (16.5–17.4)			Increase	
			12-month prevalence of itchy flexural atopic eczema symptoms			7.3 (7.0–7.6)	10.7 (10.4–11.1)			Increase	

Table 6. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Oh et al. (2004) [36]	Korea	12–15	ISAAC-based parental-report of: lifetime prevalence of itchy atopic eczema symptoms	1995/2000	15,068	7.2 (6.8–7.7)	14,777	9.3 (8.8–9.8)	No formal test	Increase	Moderate
Kusunoki et al. (2009) [30]	Japan (Kyoto)	7–15	Parental-report of: lifetime prevalence of symptoms of atopic dermatitis	1996/2006	16,176	3.9 (3.6–4.3)	13,215	6.1 (5.7–6.5)	P<0.0001	Increase	Moderate
<i>Measures of physician-diagnosed atopic eczema</i>											
Liao MF et al. (2009) [34]	Taiwan (Changhwa County)	6–8	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	2002/2007	7,040	10.1	4,622	13.6	POR (95% CI)	Increase	Good
Liao PF et al. (2009) [35]	Taiwan	6–15	ISAAC-based parental-report of: lifetime prevalence of atopic eczema	1994/2002	75,960	4.2	11,580	5.6	P<0.0001	Increase	Moderate
Lee et al. (2005) [33]	Taiwan	12–15	ISAAC-based parental-report of: lifetime prevalence of atopic eczema	1995–96/2001	44,104	1.9	11,048	3.4	No formal test	Increase	Moderate
Yan et al. (2005) [38]	Taiwan (Taipei)	13–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1994–95/2001–02	11,400	1.6	6,303	2.8	No formal test	Increase	Moderate
Lee et al. (2004) [31]	China (Hong Kong)	6–7	ISAAC-based parental-report of: lifetime prevalence of atopic eczema	1995/2001	3,618	11.8 (11.2–12.4)	4,448	17.4 (16.4–18.3)	P<0.001	Increase	Moderate
Wang et al. (2006) [37]	China (Guangzhou city)	13–14	ISAAC-based self-report of: lifetime prevalence of atopic eczema	1994–95/2001	3,855	28.1	3,516	30.7	1.13 (1.03–1.25), P=0.01	Increase	Moderate
Oh et al. (2004) [36]	Korea	6–12	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995/2000	25,361	18.3 (17.1–19.5)	27,425	17.6 (16.3–18.9)	P=0.462	Stable	Moderate
			lifetime prevalence of physician-diagnosed atopic eczema			16.6 (16.2–17.1)		24.9 (24.4–25.4)	No formal test	Increase	Moderate

Table 6. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Oh et al. (2004) [36]	Korea	12–15	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995/2000	15,068	7.3 (6.9–7.7)	14,777	12.8 (12.3–13.3)	No formal test	Increase	Moderate
Yura et al. (2001) [39]	Japan (Osaka Prefecture)	7–12	Parental-report of: lifetime prevalence of physician-diagnosed atopic dermatitis	1993/1997	514,656	24.1	458,284	22.9	No formal test	Decrease	Moderate
South-eastern Asia*											
<i>Measures of symptoms of atopic eczema</i>											
Wang et al. (2004) [43]	Singapore	6–7	ISAAC-based parental-report of: lifetime prevalence of chronic rash	1994/2001	2,030	10.5 (1.2)	5,305	12.5 (0.5)	% Change (S.E.)	Stable	Good
			lifetime prevalence of chronic rash with typical distribution			6.1 (0.9)		9.8 (0.4)	2.0 (1.3), P = 0.194	Increase	
Wang et al. (2004) [43]	Singapore	12–15	ISAAC-based parental-report of: lifetime prevalence of chronic rash	1994/2001	4,208	8.9 (1.1)	4,058	11.0 (0.4)	3.7 (1.0), P = 0.028	Stable	Good
			lifetime prevalence of chronic rash			12.3 (0.5)		14.9 (0.6)	2.1 (1.2), P = 0.155	Increase	
Quah et al. (2005) [40]	Malaysia (Kota Bharu)	6–7	ISAAC-based parental-report of: lifetime prevalence of chronic rash with typical distribution	1995/2001	3,939	7.0 (0.4)	3,157	10.2 (0.5)	% Change (95% CI)	Stable	Good
			12-month prevalence of chronic rash			9.5 (0.5)		11.6 (0.5)	2.1 (0.7), P = 0.034	Increase	
Quah et al. (2005) [40]	Malaysia (Kota Bharu)	13–14	ISAAC-based parental-report of: 12-month prevalence of flexural itchy rash	1995/2001	3,116	14.0	3,004	17.6	3.6 (1.3–5.9), P = 0.004	Increase	Good
Trakultivakorn et al. (2007) [42]	Thailand (Chiang Mai)	6–7	ISAAC-based parental-report of: 12-month prevalence of atopic eczema symptoms	1995/2001	3,828	12.1	3,106	13.4	% Change (95% CI)	Stable	Moderate
			12-month prevalence of atopic eczema symptoms			11.4		16.3	1.3 (–4.6–7.1), P = 0.11	Increase	
Trakultivakorn et al. (2007) [42]	Thailand (Bangkok)	6–7	ISAAC-based parental-report of: 12-month prevalence of atopic eczema symptoms	1995/2001	3,628	12.5	3,430	13.3	P < 0.01	Stable	Moderate
			12-month prevalence of atopic eczema symptoms			12.5		13.3	P = 0.33	Stable	

Table 6. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Teeratakulpisarn et al. (2004) [41]	Thailand (Northeast)	6–7	parental-report of: lifetime prevalence of rash	1998–99/ 2003	2,658	18.0	2,119	17.2	No formal test	Stable	Moderate
Trakulivakorn et al. (2007) [41]	Thailand (Chiang Mai)	13–14	12-month prevalence of rash ISAAC-based parental-report of:	1995/2001	3,927	15.2	3,538	14.7		Stable	Moderate
Trakulivakorn et al. (2007) [41]	Thailand (Bangkok)	13–14	12-month prevalence of atopic eczema symptoms ISAAC-based parental-report of:	1995/2001	3,713	9.6	4,669	8.6	P=0.63	Stable	Moderate
Teeratakulpisarn et al. (2004) [41]	Thailand (Northeast)	13–14	12-month prevalence of atopic eczema symptoms parental-report of:	1998–99/ 2003	3,410	6.8	2,956	10.4	P<0.01	Increase	Moderate
			lifetime prevalence of rash			9.9		10.9		Stable	
			12-month prevalence of rash			7.4		8.7		Stable	
<i>Measures of physician-diagnosed atopic eczema</i>											
Wang et al. (2004) [43]	Singapore	6–7	ISAAC-based parental-report of:	1994/2001	2,030		5,305		% Change (S.E.)		Good
			lifetime prevalence of physician-diagnosed atopic eczema			3.0 (0.7)		8.8 (0.4)	5.8 (0.8), P<0.001	Increase	
Wang et al. (2004) [43]	Singapore	12–15	ISAAC-based parental-report of:	1994/2001	4,208		4,058		% Change (S.E.)		Good
			lifetime prevalence of physician-diagnosed atopic eczema			4.1 (0.3)		5.8 (0.4)	1.7 (0.5), P=0.810	Stable	
Teeratakulpisarn et al. (2004) [41]	Thailand (Northeast)	6–7	Parental-report of:	1998–99/ 2003	2,658		2,119		No formal test		Moderate
Teeratakulpisarn et al. (2004) [41]	Thailand (Northeast)	13–14	lifetime prevalence of atopic eczema Self-report of:	1998–99/ 2003	3,410	30.5	2,956	29.2	No formal test	Stable	Moderate
			lifetime prevalence of atopic eczema			24.4		26.8		Stable	
Western Asia*											
<i>Measures of symptoms of atopic eczema</i>											
Abramidze et al. (2006) [44]	Georgia (Tbilisi)	6–7	ISAAC-based parental-report of: lifetime prevalence of symptoms of flexural dermatitis current prevalence of itchy rash	1996/2003	6,770	4.5	6,002	3.4	% Change –1.1, P<0.05	Decrease	Moderate
						5.3		5.8	0.5, P=not significant	Stable	

Table 6. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Abramidze et al. (2006) [44]	Georgia (Kutaisi)	6–7	ISAAC-based parental-report of: lifetime prevalence of symptoms of flexural dermatitis	1996/2003		5.2	2.4	% Change –2.8, P<0.05	Decrease	Moderate	
Abramidze et al. (2007) [45]	Georgia (Tbilisi and Kutaisi)	13–14	ISAAC-based self-report of: current prevalence of itchy rash	1996/2003	6,746	6.1	3.4	% Change –2.7, P<0.05	Decrease	Moderate	
Owayed et al. (2008) [48]	Kuwait	13–14	ISAAC-based self-report of: current prevalence of itchy rash	1995–96/2001–02	3,110	4.1	4.3	0.2, P=not significant	Stable	Moderate	
Romano-Zelekha et al. (2007) [49]	Israel	13–14	12-month prevalence of itchy rash	1997/2003	10,057	17.5 (16.2–18.8)	10.6 (9.5–11.7)	P<0.001	Decrease	Moderate	
			ISAAC-based self-report of: lifetime prevalence of itchy rash in a typical distribution			12.6 (11.4–13.8)	8.3 (7.3–9.3)	P<0.001	Decrease	Moderate	
<i>Measures of physician-diagnosed atopic eczema</i>											
Abramidze et al. (2006) [44]	Georgia (Tbilisi)	6–7	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1996/2003	6,770	11.6	3.6	% Change –8, P<0.05	Decrease	Moderate	
Abramidze et al. (2006) [44]	Georgia (Kutaisi)	6–7	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1996/2003		4.7	1.8	% Change –2.9, P<0.05	Decrease	Moderate	
Abramidze et al. (2007) [45]	Georgia (Tbilisi and Kutaisi)	13–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1996/2003	6,746	3.0	2.6	% Change –0.4, P=not significant	Stable	Moderate	
Owayed et al. (2008) [48]	Kuwait	13–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995–96/2001–02	3,110	11.3 (10.2–12.4)	12.8 (11.6–14)	P=0.101	Stable	Moderate	
Kalyoncu et al. (1999) [47]	Turkey (Ankara)	6–13	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic dermatitis	1992/1997	1,036	6.1 (4.7–7.7)	6.5 (4.8–8.5)	P=not significant	Stable	Moderate	
Demir et al. (2010) [46]	Turkey (Ankara)	7–12	Parental-report of: lifetime prevalence of physician-diagnosed atopic dermatitis	1992/2007	1,036		4.2	Adjusted POR		Moderate	

Table 6. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate	Final estimate	Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**	
			current prevalence of atopic eczema			4.0 (2.8–5.2)		1.2 (0.2–2.2)	
								0.4 (0.2–1.0), P trend = 0.004	Decrease

Abbreviations – CI: confidence intervals, SE: standard error, OR: odds ratio, POR: prevalence odds ratio, PR: prevalence ratio.

*Based on UN classification [16].

**95% CI or SE are only reported if included in original report.

##Point estimate extracted from graph or chart.

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atopic eczema was increasing from an extremely low baseline [from 1.4% (1994–95) to 3.5% (2002–03)] [72]. In Norway, this prevalence was stable in 9–11 year olds [21.1% (1995) and 20.8% (2000)] [79].

Two studies yielded relevant data in relation to eastern Europe. In Poland, the lifetime prevalence of parental-reported physician-diagnosed atopic eczema increase over a decade in children aged 7–10 [from 2.3% (1993) to 8.1% (2002)] [81]. Later, this same prevalence, measured with a different questionnaire in both 7–9 and 7–14 year olds, remained stable in Hungary over a relatively short time period [e.g. for 7–9 year olds –15.1% (2002) and 17.1% (2005)] [82]. In Europe, there were many other countries with single measurements of any atopic eczema outcome, but serial data were not yet available.

Oceania

For Oceania, we found three papers from Australia with prevalence data on atopic eczema trends (see Table 4) [83–85]. As shown in Table 10, the lifetime prevalence of atopic eczema symptoms was measured in Melbourne in 6–7 year olds, where it markedly increased from 22.6% in 1993 to 32.3% in 2002 [84]. Two other studies measured trends in lifetime prevalence of atopic eczema diagnosis. In one study this was increasing in 4–6 year olds, even though the baseline prevalence was high [from 31.0% (2000) to 37.0% (2005)] [83] and in another study, using a non-validated questionnaire, it was stable in 8–11 year olds [85].

Discussion

The considerable body of international literature identified by this systematic review was heterogeneous in many respects rendering it difficult to directly compare different regions. That said, there was no obvious consistent overall global trend in the incidence or prevalence of atopic eczema symptoms and diagnosis. Nevertheless, in Africa and eastern Asia there was an increasing trend for both the lifetime prevalence of parental- and self-reported atopic eczema symptoms and physician-diagnosed atopic eczema. In western Europe and parts of northern Europe (i.e. the UK), these trends were also mainly increasing. There were extremely diverse trends among different age groups and countries in south-eastern Asia, western Asia and southern Europe. In addition, data for the Americas, eastern Europe and Oceania were limited. The heterogeneous findings in some regions and the limited data available for other regions have precluded conclusions regarding a global atopic eczema trend and atopic eczema trends in major parts of the world.

We found that many outcome measures are used across studies to determine changes in atopic eczema prevalence. Although we found that trends of all outcomes generally pointed in the same direction, we considered the lifetime prevalence of parental- or self-report of atopic eczema symptoms the optimal outcome for the purpose of comparing disease trends between regions within our highly heterogeneous dataset. As atopic eczema occurs in episodes and may be season-related it is particularly difficult to compare studies measuring current or 12-month symptomatology or if patient- and/or study- characteristics, such as age group, do not match. Furthermore, there are marked differences per region in current medical practice, including prevention strategies, national guidelines and physician’s awareness of the problem, that make prevalence estimates and trends of physician-diagnosed atopic eczema difficult to compare across the globe. Even though the diagnostic process of a physician is overall likely to be standardised, there is no objective gold standard. This is highlighted in the ENRIECO project which shows that different countries use

Table 7. Good and moderate quality studies reporting the prevalence of parental- or self-report of atopic eczema between 1990 and 2010 in the Americas.

Study	Geographic area	Age range	Outcome	Time period	Baseline estimate (SE)** N	Final estimate N	Summary measures % (95%CI)/(SE)**	Conclusion	Quality
Central America *									
<i>Measures of symptoms of atopic eczema</i>									
Barraza-villareal et al. (2007) [50]	Mexico (Cuernavaca)	6–8	ISAAC-based parental-report of: lifetime prevalence of dry itchy skin spots	1995/2002	2,770 15.0 (13.8–16.4)	2,633 7.3 (6.3–8.4)	P = 0.000	Decrease	Good
			12-month prevalence of dry itchy skin spots		10.1 (9.1–11.3)	5.8 (4.9–6.8)	P = 0.000	Decrease	
Barraza-villareal et al. (2007) [50]	Mexico (Cuernavaca)	11–14	ISAAC-based parental-report of: lifetime prevalence of dry itchy skin spots	1995/2002	2,795 17.0 (15.6–18.4)	2,605 7.0 (6.0–8.1)	P = 0.000	Decrease	Good
			12-month prevalence of dry itchy skin spots		10.5 (9.5–11.7)	5.4 (4.5–6.3)	P = 0.000	Decrease	
<i>Measures of physician-diagnosed atopic eczema</i>									
Barraza-villareal et al. (2007) [50]	Mexico (Cuernavaca)	6–8	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995/2002	2,770 3.9 (3.2–4.7)	2,633 6.1 (5.2–7.2)	P = 0.000	Increase	Good
Barraza-villareal et al. (2007) [50]	Mexico (Cuernavaca)	11–14	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995/2002	2,795 4.2 (3.5–5.0)	2,605 6.9 (6.0–8.0)	P = 0.000	Increase	Good
South America *									
<i>Measures of symptoms of atopic eczema</i>									
Camelo-Nunes et al. (2004) [52]	Brazil (São Paulo)	6–7	ISAAC-based parental-report of: lifetime prevalence of itchy rash	1996/1999	3,005 13.6	3,033 15.0	P = not significant	Stable	Moderate
			lifetime prevalence of lesions in skin-folds		7.5	6.6	P = not significant	Stable	
Camelo-Nunes et al. (2004) [52]	Brazil (São Paulo)	13–14	ISAAC-based self-report of: lifetime prevalence of itchy rash	1996/1999	3,008 10.6	3,487 9.9	P = not significant	Stable	Moderate
			lifetime prevalence of itchy rash		12.6	14.0	P = not significant	Stable	
			lifetime prevalence of lesions in skin-folds		4.8	4.6	P = not significant	Stable	
Borges et al. (2008) [51]	Brazil (Federal district of Brasilia)	13–14	ISAAC-based self-report of: lifetime prevalence of itchy rash	1996/2002	3,254 8.1	3,009 8.8	P = not significant	Stable	Moderate
			lifetime prevalence of itchy rash		15.5	16.8	P = 0.185	Stable	

Table 7. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Solé et al (2007) [54]	Brazil (5 centres)	13–14	12-month prevalence of itchy rash ISAAC-based self-report of:	1994–95/ 2001–03	15,419	9.2	10.2	15,684	P = 0.202 OR (95% CI)	Stable	Moderate
Riedi et al. (2005) [53]	Brazil (Curitiba)	13–14	12-month prevalence of itchy rash ISAAC-based self-report of:	1995/2001	3,008	10.3	8.4	3,628	0.80 (0.74–0.86), P<0.05	Decrease, not uniform among centres	Moderate
			12-month prevalence of itchy rash intermittent itchy rash in skin creases			6.3	6.0		P = not significant	Stable	
						3.7	3.7		P = not significant	Stable	
<i>Measures of physician-diagnosed atopic eczema</i>											
Camelo-Nunes et al. (2004) [52]	Brazil (São Paulo)	6–7	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1996/1999	3,005	13.2	11.4	3,033	P<0.05	Decrease	Moderate
Camelo-Nunes et al. (2004) [52]	Brazil (São Paulo)	13–14	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1996/1999	3,008	14.0	15.0	3,487	P = not significant	Stable	Moderate
Borges et al. (2008) [51]	Brazil (Federal district of Brasilia)	13–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1996/2002	3,254	9.8	13.6	3,009	P = 0.0002	Decrease	Moderate
Solé et al (2007) [54]	Brazil (5 centres)	13–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1994–95/ 2001–03	15,419	5.3	4.5	15,684	OR (95% CI) 0.84 (0.76–0.93), P<0.05	Decrease, not uniform among centres	Moderate

Abbreviations – CI: confidence intervals, SE: standard error, OR: odds ratio.

**Based on UN classification [16].

**95% CI and SE are only reported if included in original report.

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Table 8. Good and moderate quality studies reporting the incidence of parental- or self-report of atopic eczema between 1990 and 2010 in Europe.

Study	Geographic area	Age range	Outcome	Time period	Baseline estimate % (95%CI)/ (SE)**	N	Final estimate % (95%CI)/ (SE)**	N	Summary measures	Conclusion	Quality
Schäfer et al. (2000) [24]	Germany (west)	5–6	Parental-report of: cumulative incidence of history of physician-diagnosed atopic eczema	1991/1997	12.5	4,001	12.8	4,001	No formal test	Stable	Moderate
Schäfer et al. (2000) [24]	Germany (east)	5–6	Parental-report of: cumulative incidence of history of physician-diagnosed atopic eczema	1991/1997	16.0		23.4		No formal test	Increase	Moderate
Olesen et al. (2005) [23]	Denmark	7	UK working party-based parental-report of: adjusted cumulative incidence of physician-diagnosed atopic dermatitis	1993/1998	18.9	1,060	19.6	9,744	No formal test	Stable	Moderate
Simpson et al. (2009) [25]	UK	all	QRESEARCH-based physicians' recorded: age- and sex-standardised incidence of atopic eczema diagnosis (per 1000 patient years (py))	2001–05	9.6 (9.5–9.7)	>30 million py	13.6 (13.5–13.7)	>30 million py	Relative % Change 41.8, P<0.001	Increase	Moderate

Abbreviations – CI: confidence intervals, SE: standard error.

*Based on UN classification [16].

**95% CI and SE are only reported if included in original report.

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Table 9. Good and moderate quality studies reporting the incidence and prevalence of parental- or self-report of atopic eczema between 1990 and 2010 in Europe.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Western Europe*											
<i>Measures of symptoms of atopic eczema</i>											
Grize et al. (2006) [56]	Switzerland	5–7	ISAAC-based parental-report of:	1992/2001	988		1,274				Good
			adjusted lifetime prevalence of skin rash			11.7 (9.7–14.0)		17.4 (15.3–19.7)	P = 0.0014	Increase	
			adjusted 12-month prevalence of atopic eczema specific skin rash			4.6 (3.4–6.2)		7.6 (6.2–9.2)	P = 0.0090	Increase	
Vellinga et al. (2005) [62]	Belgium (Antwerp)	6–7	ISAAC-based parental-report of:	1995–96/2002					POR (95% CI)		Good
			lifetime prevalence of rash in boys		2,313	12.9	2,225	18.4	1.5 (1.3–1.8), P = 0.00	Increase	
			lifetime prevalence of rash in girls		2,359	15.7	2,196	19.8	1.3 (1.1–1.5), P = 0.00	Increase	
			12-month prevalence of rash in boys		2,313	8.5	2,225	11.4	1.4 (1.1–1.7), P = 0.00	Increase	
			12-month prevalence of rash in girls		2,359	11.9	2,196	14.7	1.3 (1.1–1.5), P = 0.01	Increase	
Vellinga et al. (2005) [62]	Belgium (Antwerp)	13–14	ISAAC-based parental-report of:	1995–96/2002					POR (95% CI)		Good
			lifetime prevalence of rash in boys		1,240	15.7	1,215	13.3	0.9 (0.7–1.1), P = 0.17	Stable	
			lifetime prevalence of rash in girls		1,150	19.0	1,318	20.3	1.1 (0.9–1.3), P = 0.30	Stable	
			12-month prevalence of rash in boys		1,240	9.7	1,215	8.5	0.9 (0.7–1.1), P = 0.30	Stable	
			12-month prevalence of rash in girls		1,150	13.3	1,318	13.6	1.0 (0.8–1.3), P = 0.84	Stable	
Krämer et al. (2009) [59]	Germany (west)	6	ISAAC-based parental-report of:	1994–95/1996–2000	4,761		3,654		Area-adjusted trend		Good
			12-month prevalence of itchy skin rash			4.6		4.5	0.89 (0.41–1.92)	Stable	
Krämer et al. (2009) [59]	Germany (east)	6	ISAAC-based parental-report of:	1994–95/1996–2000	114,457		9,031		Area-adjusted trend		Good
			12-month prevalence of itchy skin rash			6.3		6.2	0.96 (0.66–1.39)	Stable	
Maziak et al. (2003) [60]	Germany (Münster)	6–7	ISAAC-based parental-report of:	1994–95/1999–2000					POR (95% CI)		Good
			12-month prevalence of atopic eczema symptoms in boys		1,754	7.3	1,863	6.6	0.9 (0.69–1.17)	Stable	
			12-month prevalence of atopic eczema symptoms in girls		1,713	6.7	1,666	9.8	1.5 (1.18–1.97)	Increase	
Maziak et al. (2003) [60]	Germany (Münster)	13–14	ISAAC-based self-report of:	1994–95/1999–2000					POR (95% CI)		Good
			12-month prevalence of atopic eczema symptoms in boys		1,865	5.0	1,894	4.5	0.9 (0.66–1.22)	Stable	
			12-month prevalence of atopic eczema symptoms in girls		1,892	9.4	1,922	11.1	1.2 (0.98–1.50)	Stable	

Table 9. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Weber et al. (2010) [63]	Austria (Upper)	6–9	ISAAC-based parental-report of:	1995–97/ 2001–03	12,115		11,468		No formal test		Moderate
			lifetime prevalence of rash		9.2		11.0			Increase	
			12-month prevalence of rash		6.0		6.7			Stable	
Annesi-Maesano et al. (2009) [55]	France (Languedoc Roussillon)	13–14	ISAAC-based self-report of:	1995/2002	3,383		1,642		Absolute/relative % Change		Moderate
			12-month prevalence of atopic eczema symptoms		12.5		14.3		1.78/0.14, P = not significant	Stable	
<i>Measures of physician-diagnosed atopic eczema</i>											
Grize et al. (2006) [56]	Switzerland	5–7	ISAAC-based parental-report of:	1992/2001	988		1,274				Good
			adjusted lifetime prevalence of physician-diagnosed atopic eczema		18.4 (15.8–21.2)		15.2 (13.2–17.4)		P trend = 0.1065	Stable	
Vellinga et al. (2005) [62]	Belgium (Antwerp)	6–7	ISAAC-based parental-report of:	1995–96/ 2002					POR (95% CI)		Good
			lifetime prevalence atopic eczema in boys		2,313	18.5	2,225	20.8	1.2(1.0–1.3), P=0.06	Increase	
			lifetime prevalence atopic eczema in girls		2,359	19.1	2,196	22.4	1.2(1.1–1.4), P=0.01	Increase	
Vellinga et al. (2005) [62]	Belgium (Antwerp)	13–14	ISAAC-based parental-report of:	1995–96/ 2002					POR (95% CI)		Good
			lifetime prevalence atopic eczema in boys		1,240	23.4	1,215	21.1	0.9(0.7–1.1), P=0.17	Stable	
			lifetime prevalence atopic eczema in girls		1,150	27.8	1,318	29.7	1.1(0.9–1.3), P=0.30	Stable	
Schäfer et al. (2000) [24]	Germany (west)	5–6	Report of:	1991/1997	801		771		No formal test		Moderate
			current prevalence of physician-diagnosed atopic eczema		11.2		4.5			Decrease	
Schäfer et al. (2000) [24]	Germany (east)	5–6	Report of:	1991/1997	285		633		No formal test		Moderate
			current prevalence of physician-diagnosed atopic eczema		17.5		11.2			Decrease	
Krämer et al. (2009) [59]	Germany (west)	6	Report of:	1991–95/ 1996–2000	4,761		3,654		Area-adjusted trend (10 y)		Good
			current prevalence of physician-diagnosed atopic eczema		10.5		5.2		0.30 (0.17–0.53)	Decrease	
Krämer et al. (2009) [59]	Germany (east)	6	Report of:	1991–1995/ 1996–2000	114,457		9,031		Area-adjusted trend (10 y)		Good
			current prevalence of physician-diagnosed atopic eczema		14.3		10.5		0.36 (0.17–0.61)	Decrease	

Table 9. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Maziak et al. (2003) [60]	Germany (Münster)	6–7	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema in boys	1994–95/ 1999–2000	1,754	14.3	1,863	13.6	POR (95% CI) 0.9 (0.77–1.13)	Stable	Good
			lifetime prevalence of physician-diagnosed atopic eczema in girls		1,713	14.6	1,666	16.9	1.2 (0.99–1.44)	Stable	
Maziak et al. (2003) [60]	Germany (Münster)	13–14	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema in boys	1994–95/ 1999–2000	1,865	8.2	1,894	10.9	POR (95%CI) 1.4 (1.09–1.71)	Increase	Good
			lifetime prevalence of physician-diagnosed atopic eczema in girls		1,892	12.3	1,922	17.4	1.5 (1.22–1.77)	Increase	
Heinrich et al. (2002) [58]	Germany (east)		Parental-report of: adjusted lifetime prevalence of physician-diagnosed atopic eczema	1992–1993/ 1998–1999	2,773		3,092		No formal test		Moderate
		6	adjusted lifetime prevalence of physician-diagnosed atopic eczema			8.6		13.0		Increase	
		9	adjusted lifetime prevalence of physician-diagnosed atopic eczema			8.6		11.8		Increase	
		12	adjusted lifetime prevalence of physician-diagnosed atopic eczema			9.6		10.2		Increase	
Schernhammer et al. (2008) [61]	Austria (Upper)	6–7	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995–97/ 2001–03	13,399		12,784		P<0.001	Increase	Moderate
			lifetime prevalence of physician-diagnosed atopic eczema			10.1		13.8		Increase	
Haidinger et al. (2008) [57]	Austria (Upper)	6–7	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995–97/ 2001–03	35,238		12,541		% Change		Moderate
			lifetime prevalence of physician-diagnosed atopic eczema			9.9		13.6	3.7	Increase	
Weber et al. (2010) [63]	Austria (Upper)	6–9	ISAAC-based parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995–97/ 2001–03	12,115		11,468		No formal test		Moderate
			lifetime prevalence of physician-diagnosed atopic eczema			9.6		13.4		Increase	
Schernhammer et al. (2008) [61]	Austria (Upper)	12–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995–97/ 2001–03	1,516		1,443		P<0.001	Increase	Moderate
			lifetime prevalence of physician-diagnosed atopic eczema			6.3		12.1		Increase	
Annesi-Maesano et al. (2009) [55]	France (Languedoc Roussillon)	13–14	ISAAC-based self-report of: lifetime prevalence of physician-diagnosed atopic eczema	1995/2002	3,383		1,642		Absolute/relative % Change		Moderate
			lifetime prevalence of physician-diagnosed atopic eczema			25.8		30.4	4.56/0.17, P=0.001	Increase	

Table 9. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Southern Europe*											
<i>Measures of symptoms of atopic eczema</i>											
Montefort et al. (2009) [64]	Maltese Islands	5–8	ISAAC-based parental-report of:	1994–95/ 2001–02	4,465		4,761				Moderate
			lifetime prevalence of recurrent rash			7.0	6.7		P = 0.61	Stable	
			12-month prevalence of recurrent rash			5.5	5.4		P = 0.85	Stable	
Galassi et al. (2006) [66]	Italy (North)	6–7	ISAAC-based parental-report of:	1994–95/ 2002	16,115		11,287		Area-adjusted absolute % Change (95% CI)		Good
			12-month prevalence of atopic eczema symptoms			8.3	14.5		6.2 (5.3–7.1)	Increase	
			12-month prevalence of atopic eczema symptoms in flexures			6.0	10.4		4.4 (3.6–5.2)	Increase	
Galassi et al. (2006) [66]	Italy (North)	13–14	ISAAC-based self-report of:	1994–95/ 2002	19,723		10,267		Area-adjusted absolute % Change (95% CI)		Good
			12-month prevalence of atopic eczema symptoms			10.1	11.2		1.2 (0.1–2.4)	Increase	
			12-month prevalence of atopic eczema symptoms in flexures			6.5	8.5		2.1 (1.2–3.0)	Increase	
Anthracopoulos et al. (2009) [65]	Greece (Patras)	8–10	Parental-report of:	1991/2003	2,417		2,725				Moderate
			lifetime prevalence of atopic eczema symptoms			4.5	9.5		P trend <0.001	Increase	
			24-month prevalence of atopic eczema symptoms			2.5	5.0		P trend <0.001	Increase	
<i>Measures of physician-diagnosed atopic eczema</i>											
Montefort et al. (2009) [64]	Maltese Islands	5–8	ISAAC-based parental-report of:	1994–95/ 2001–02	4,465		4,761				Moderate
			lifetime prevalence of physician-diagnosed atopic eczema			4.4	11.2		P <0.0001	Increase	
Galassi et al. (2006) [66]	Italy (North)	6–7	ISAAC-based parental-report of:	1994–95/ 2002	16,115		11,287		Area-adjusted absolute % Change (95% CI)		Good
			lifetime prevalence of atopic eczema			14.3	17		2.5 (1.6–3.5)	Increase	
Galassi et al. (2006) [66]	Italy (North)	13–14	ISAAC-based parental-report of:	1994–95/ 2002	19,723		9,362		Area-adjusted absolute % Change (95% CI)		Good
			lifetime prevalence of atopic eczema			11.0	12.8		1.5 (0.3–2.8)	Increase	
Rosado-Pinto et al. (2006) [67]	Portugal	6–7	ISAAC-based report of:	1993–94/ 2002	5,000		5,350				Moderate

Table 9. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
			lifetime prevalence of atopic eczema		18.6		21.0		P=0.002	Increase	
			12-month prevalence of atopic eczema		13.9		15.6		P=0.013	Increase	
Rosado-Pinto et al. (2006) [67]	Portugal	13-14	ISAAC-based report of:	1993-94/2002	11,400		11,850				Moderate
			lifetime prevalence of atopic eczema		12.8		13.3		P=0.22	Stable	
			12-month prevalence of atopic eczema		7.6		8.7		P=0.002	Increase	
Northern Europe*											
<i>Measures of symptoms of atopic eczema</i>											
Annus et al. (2005) [69]	Estonia (Tallinn)	6-7	ISAAC-based parental-report of:	1993-94/2001-02	3,070		2,383		Sex-adjusted POR (95% CI)		Good
			lifetime prevalence of itchy rash		16.9		22.0		1.40 (1.22-1.61), P<0.001	Increase	
			12-month prevalence of itchy rash		12.6		17.1		1.44 (1.24-1.67), P<0.001	Increase	
			12-month prevalence of flexural rash		12.0		13.5		1.20 (1.02-1.41), P=0.025	Increase	
Annus et al. (2005) [69]	Estonia (Tallinn)	13-14	ISAAC-based parental-report of:	1993-94/2001-02	3,476		3,576		Sex-adjusted POR (95% CI)		Good
			lifetime prevalence of itchy rash		15.2		19.3		1.34 (1.18-1.52), P<0.001	Increase	
			12-month prevalence of itchy rash		10.4		14.9		1.51 (1.31-1.74), P<0.001	Increase	
			12-month prevalence of flexural rash		7.7		9.4		1.26 (1.07-1.50), P=0.006	Increase	
Shamssain et al. (2007) [80]	UK (North-east England)	6-7	ISAAC-based parental-report of:	1995-96/2001-02	3,000		1,843		OR (95% CI)		Good
			lifetime prevalence of rash in boys		17.8		21.0		1.6 (1.29-1.98)	Increase	
			lifetime prevalence of rash in girls		18.7		22.5		1.8(1.35-2.30)	Increase	
			lifetime prevalence of rash with typical distribution in boys		13.2		21.1		1.9 (1.41-3.57)	Increase	
			lifetime prevalence of rash with typical distribution in girls		14.7		23.8		1.8(1.35-2.25)	Increase	
			12-month prevalence of current rash in boys		14.7		23.3		1.4 (1.31-1.61)	Increase	
			12-month prevalence of current rash in girls		16.9		25.0		1.8(1.42-2.28)	Increase	
Shamssain et al. (2007) [80]	UK (North-east England)	13-14	ISAAC-based parental-report of:	1995-96/2001-02	3,000		2,195		OR (95% CI)		Good
			lifetime prevalence of rash in boys		13.9		15.3		1.1 (0.88-1.22)	Stable	
			lifetime prevalence of rash in girls		22.8		17.5		1.6 (1.29-1.98)	Increase	
			lifetime prevalence of rash with typical distribution in boys		8.8		19.6		2.4 (1.81-3.37)	Increase	

Table 9. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
			lifetime prevalence of rash with typical distribution in girls		15.9	19.3		1.5 (1.12–1.98)		Increase	
			12-month prevalence of current rash in boys		11.3	16.8		1.6 (1.30–2.20)		Increase	
			12-month prevalence of current rash in girls		20.5	20.9		1.0 (0.89–1.32)		Stable	
Anderson et al. (2004) [68]	UK (British Isles)	12–14	ISAAC-based self-report of:	1995/2002	15,083	15,755		Absolute/Relative % Change		Moderate	
			12-month prevalence of flexural rash		16.2	11.4		–4.8/–29.6		Decrease	
Bjerg et al. (2010) [70]	Sweden (Kiruna, Luleå, Piteå)	7–8	ISAAC-based parental-report of:	1996/2006	3,430	2,585				Good	
			12-month prevalence of atopic eczema symptoms		27.2	25.8		P = 0.215		Stable	
Rönmark et al. (2009) [78]	Sweden (northern)	7–8	ISAAC-based parental-report of:	1996/2006	2,148	1,700				Moderate	
			lifetime prevalence of atopic eczema symptoms		29.3	26.5		P = 0.048		Decrease	
Kudzytė et al. (2008) [72]	Lithuania (Kaunas)	6–7	ISAAC-based parental-report of:	1994–95/2001–02	1,879	2,772				Moderate	
			12-months prevalence of itchy rash		2.6	3.9		P < 0.05		Increase	
<i>Measures of physician-diagnosed atopic eczema</i>											
Kuehni et al. (2001) [63]	UK (Leicestershire)	1–5	Secondary analysis of:	1990/1998	1,264	2,127		Age- and sex-adjusted OR (95% CI)		Good	
			lifetime prevalence of physicians' recorded atopic eczema diagnosis		29.0	44.0		1.95 (1.68–2.27), P < 0.001		Increase	
Shamssain et al. (2007) [80]	UK (North-east England)	6–7	ISAAC-based parental-report of:	1995–96/2001–02	1,445	918		OR (95% CI)		Good	
			lifetime prevalence of atopic eczema in boys		27.8	37.0		1.9 (1.45–3.55), P = 0.001		Increase	
			lifetime prevalence of atopic eczema in girls		27.0	35.5		1.8 (1.45–2.45), P = 0.001		Increase	
Shamssain et al. (2007) [80]	UK (North-east England)	13–14	ISAAC-based parental-report of:	1995–96/2001–02	1,510	1,000		OR (95% CI)		Good	
			lifetime prevalence of atopic eczema in boys		13.9	27.2		6.13 (3.52–10.79), P = 0.001		Increase	
			lifetime prevalence of atopic eczema in girls		22.8	30.7		1.63 (1.48–1.81), P = 0.001		Increase	
Ng Man Kwong et al. (2001) [76]	UK (Sheffield)	8–9	ISAAC-based parental-report of:	1991/1999	4,523	4,809		Absolute % Change (95% CI)		Moderate	

Table 9. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Anderson et al. (2004) [68]	UK (British Isles)	12–14	lifetime prevalence of atopic eczema ISAAC-based self-report of:	1995/2002	15,083	18.1	31.1	13.0 (11.27–14.72), P<0.001	Absolute/Relative % Change	Increase	Moderate
Simpson et al. (2009) [25]	UK	all	lifetime prevalence of atopic eczema Secondary analysis of:	2001–2005	>9 million	21.1	24.3	3.3/15.4	Relative % Change	Increase	Moderate
McNeill et al. (2009) [75]	Scotland (Aberdeen)	7–9	age- and sex-standardised lifetime prevalence of physicians' recorded atopic eczema diagnosis ISAAC-based parental-report of:	1999/2004	2,340	24.0 (22.3–25.7)	34.6 (32.3–36.9)	48.2, P<0.001	No formal test	Increase	Moderate
Osman et al. (2007) [77]	Scotland (Aberdeen)	9–11	lifetime prevalence of atopic eczema ISAAC-based parental-report of:	1994/2004							Moderate
McNeill et al. (2009) [75]	Scotland (Aberdeen)	9–12	lifetime prevalence of atopic eczema in boys lifetime prevalence of atopic eczema in girls ISAAC-based parental-report of:	1999/2004	3,280	17.9	23.6	P trend<0.0001		Increase	Moderate
Devenny et al. (2004) [71]	Scotland (Aberdeen)	9–12	lifetime prevalence of atopic eczema ISAAC-based parental-report of:	1994/1999	4,047	21.1 (19.7–22.5)	34.2 (31.8–36.6)	RR (95% CI)		Increase	Moderate
Kudzyteet al. (2008) [72]	Lithuania (Kaunas)	6–7	lifetime prevalence of atopic eczema ISAAC-based parental-report of:	1994–95/ 2001–02	1,879	18.0	21.0	1.2 (1.10–1.33)		Increase	Moderate
Selnes et al. (2005) [79]	Norway (subarctic)	9–11	lifetime prevalence of physician-diagnosed atopic eczema ISAAC-based self-report of:	1995/2000	1,432	1.4	3.5	P<0.05		Increase	Moderate
Bjerg et al. (2010) [70]	Sweden (Kiruna, Luleå, Piteå)	7–8	lifetime prevalence of atopic eczema ISAAC-based parental-report of:	1996/2006	3,430	21.1	20.8	0.99 (0.88–1.11)		Stable	Moderate
Latvala et al. (2005) [74]	Finland	18–19	lifetime prevalence of physician-diagnosed atopic eczema Report of:	1990–2000	–	13.4	15.2	P = 0.048	No formal test	Increase	Moderate
			12-month prevalence of physician-diagnosed atopic eczema			1.2 [#]	1.2 [#]			Stable	

Table 9. Cont.

Study	Geographic area	Age range (y)	Outcome	Time period	Baseline estimate		Final estimate		Summary measures	Conclusion	Quality
					N	% (95%CI)/(SE)**	N	% (95%CI)/(SE)**			
Eastern Europe*											
<i>Measures of physician-diagnosed atopic eczema</i>											
Harangi et al. (2007) [82]	Hungary (Baranya County)	7–9	Hanifin-Rajka criteria-based of: parental-report	2002/2005	587		574		No formal test		Moderate
Harangi et al. (2007) [82]	Hungary (Baranya County)	7–14	physician-diagnosed atopic dermatitis Hanifin-Rajka criteria-based of: parental-report	2002/2005	1,454	17.0	1,454	17.1	No formal test	Stable	Moderate
Brożek et al. (2004) [81]	Poland (Chorzów)	7–10	physician-diagnosed atopic dermatitis Parental-report of: lifetime prevalence of physician-diagnosed atopic eczema	1993/2002	1,130	15.1	1,451	16.1	P<0.001	Stable Increase	Moderate

Abbreviations – CI: confidence intervals, SE: standard error, POR: prevalence odds ratio, OR: odds ratio.

*Based on UN classification [16].

**95% CI and SE are only reported if included in original report.

#Point estimate extracted from graph or chart.

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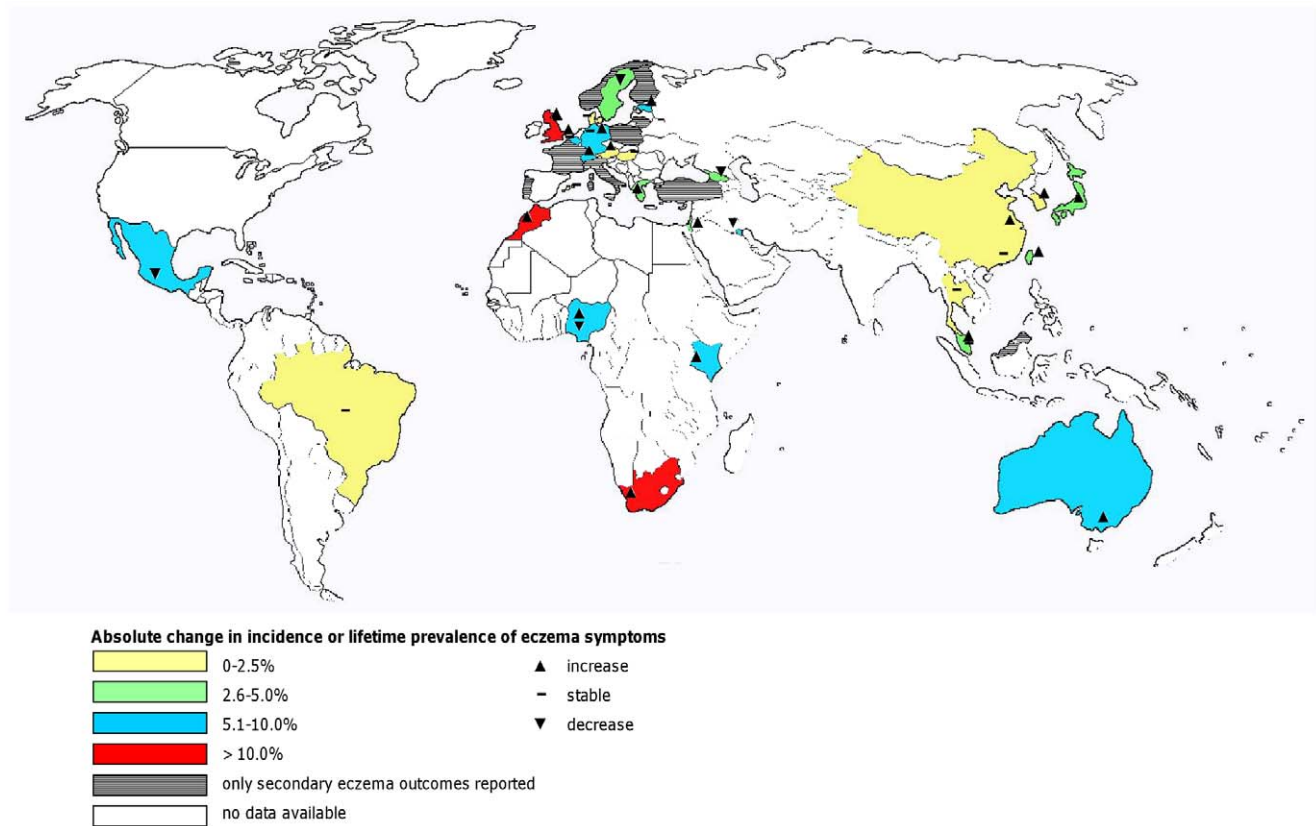


Figure 2. World map of the incidence and lifetime prevalence of atopic eczema symptoms (1990–2010). Overview of absolute changes in the incidence of atopic eczema and lifetime prevalence of atopic eczema symptoms between 1990 and 2010. doi:10.1371/journal.pone.0039803.g002

different terms to describe atopic eczema [86]. In addition, not every language has disease labels, nor are they understood in the same way. This means that a diagnostic label may be influenced by region-specific guidelines for the diagnosis of atopic eczema and this may therefore render it difficult to compare estimates of physician-diagnosed atopic eczema prevalence between regions. We thus judged that the lifetime prevalence of atopic eczema symptoms was most likely to prove useful in relation to yielding comparative data on trends in atopic eczema.

Strengths and limitations. To our knowledge, no systematic review on international disease trends in the incidence and prevalence of atopic eczema has been published. We searched a large amount of potential relevant literature using seven electronic databases and included 69 papers which reported on trends in atopic eczema. These should represent a good coverage of published literature. Furthermore, we searched systematically, according to a protocol and used stipulated inclusion criteria. To ensure that included studies are above a specific quality threshold, the studies were independently quality-filtered by two reviewers. Where a consensus could not be obtained a third reviewer provided arbitration guidance. In contrast with earlier work into this field, we included all reports on atopic eczema trends, whereas previously papers have limited themselves to single estimates of atopic eczema [4,5], or to original data from the ISAAC study [2,87].

There are gaps in the literature. We could include particularly few reports from the Americas, eastern Europe and Oceania. In general, studies are available on the prevalence of atopic eczema in these regions. However, information from these studies will not be

relevant until they are repeated over time. This perhaps somewhat surprising gap for North America is likely to be, at least in part, due to the fact that the ISAAC programme had difficulty identifying a regional coordinator for this region [88]. We were unable to obtain the full-text translation of one Korean paper. Nevertheless, we are reasonably confident that this report or any other additional reports would be unlikely to undermine our overall findings – that there is no clear trend in the worldwide incidence and prevalence of atopic eczema. For nearly all regions information on atopic eczema is questionnaire-based. Questionnaires are non-specific and the measured symptoms suggestive of atopic eczema may overlap with symptoms of other conditions, such as contact dermatitis. The ISAAC questionnaire stipulates the typical distribution and the onset of the itchy rash (see Table 2), which helps to enhance its specificity. At the population level and particularly for the purpose of between-population comparison, ISAAC questions are therefore likely to provide adequate symptom-derived prevalence estimates [89]. That said there is inevitably some loss of ability to differentiate between atopic eczema and other differential diagnoses such as allergic contact dermatitis. This problem may have been more pronounced had we also identified studies using the ECRHS; in the event however, no such relevant studies were found to be eligible.

Future work. Further research in this area should firstly address methodological issues to help inform the optimum design, execution and reporting of future epidemiological studies of trends in atopic eczema. In our dataset various outcome measures were reported and various assessment tools were used, data were analysed differently across studies and results were reported in

Table 10. Good and moderate quality studies reporting the prevalence of parental- or self-report of atopic eczema between 1990 and 2010 in Oceania.

Study	Geographic area	Age range	Outcome	Time period	Baseline estimate % (95%CI)/ (SE)**	N	Final estimate % (95%CI)/(SE)**	N	Summary measures	Conclusion	Quality
<i>Measures of symptoms of atopic eczema</i>											
Robertson et al. (2004)[84]	Australia (Melbourne)	6–7	ISAAC-based parental-report of: lifetime prevalence of atopic eczema symptoms	1993/2002	22.6 (20.8–24.6)	2,843	32.3 (30.4–34.2)	2,968	No formal test	Increase	Moderate
<i>Measures of physician-diagnosed atopic eczema</i>											
Ponsonby et al. (2008) [83]	Australia (Australian Capital Territory)	4–6	Annual school entry-based and ISAAC-based parental-report of: lifetime prevalence of atopic eczema	2000–05	11.1 (10.0–12.3)	3,873	17.2 (15.7–18.8)	3,849	Adjusted OR (95% CI) per year 1.05 (1.03–1.07) P<0.001 % Change (95%CI)	Increase	Good
Toelle et al. (2004) [85]	Australia (Belmont)	8–11	ISAAC-based parental-report of: lifetime prevalence of atopic eczema	1992/2002	31.0#	908	37.0#	800	0.4 (–3.7–4.5), P = not significant	Stable	Moderate

Abbreviations – CI: confidence intervals, SE: standard error, OR: odds ratio.

*Based on UN classification [16].

**95% CI and SE are only reported if included in original report.

#Point estimate extracted from graph or chart.

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different formats (e.g. with and without confidence intervals (CI)), age groups did not match and studies were inconsistently stratified for sex. All of these factors enhance the incomparability of studies. In view of the above, we suggest full and elaborate reporting of the results (including CI) of all of the outcomes obtained. We recommend that the above gaps be addressed using the complete ISAAC tool (and, where possible, also include detailed clinical assessment to allow atopic eczema to be differentiated from allergic contact dermatitis) and be reported according to a standardised format, so that comparisons to other reports on trends are possible. However, even if studies are comparable the prevalence of atopic eczema may still be difficult to compare across countries, without a universal definition. Thus, we need a range of relevant measures of incidence and prevalence as well as a careful description of the diagnostic criteria used together with appropriate interpretation of these data in order to ensure that this important field of epidemiological enquiry progresses in a scientifically robust manner.

Interpretation. Although there is no consistent overall global trend in atopic eczema incidence and prevalence, there are some specific trends which are worth remarking upon further, as they may be of interest for research into the aetiology of atopic eczema. Firstly, there was a stable incidence of atopic eczema in 5–6 year olds in West Germany [12.5% (1991) and 12.8% (1997)] and a sharply increasing incidence in East Germany [from 9.6% (1991) to 23.4% (1997)] [24]. This coincides with the adoption of a “Western” lifestyle in East Germany as a result of political change. A consequence of changed lifestyle and increased socio-economic wealth may be an increased frequency of bathing and a greater availability of soaps and bubble baths, which may remove the skin’s natural barrier oils and make atopic eczema more prevalent [90]. This is a biologically credible mechanism to explain an increase in incidence – in particular of mild disease. Nevertheless, Schafer et al. (2000) found that, after adjustment for potential confounders, including socio-economic status, the difference in incidence between East and West Germany remained [24]. Other factors, such as nutritional factors, allergens and irritants or infections may therefore be important in the aetiology of atopic eczema. Political changes resulting in, for example, improved access to physicians in East Germany after reunification or due to changes in disease labelling could also have impacted on measures of the incidence of atopic eczema, as has been noted in relation to asthma diagnosis and prescribing [91]. If this were the case, this would reflect an increase in reporting behaviour rather than any true change in the epidemiology of eczema.

Other trends of interest regarding aetiological hypotheses include diverging trends between neighbouring regions. For example, there are marked increases in lifetime prevalence of atopic eczema symptoms in most countries in Africa [e.g. in South

Africa – from 15.5% (1995) to 26.2% (2002)] [29], whereas there is a large decrease in Nigeria [from 26.1% (1995) to 18.0% (2001–02)] [27]. This anomalous decrease is most likely a consequence of the extremely high baseline prevalence, as prevalence estimates in 2001–02 are largely comparable for all African countries. Rather than a true prevalence, this high baseline estimate may be a reflection of the presence of another skin condition, such as another rash, perhaps caused by parasites, which are common in these regions. In addition, in our dataset there were also marked baseline differences between neighbouring countries. This is indicated by the low baseline prevalence of atopic eczema symptoms in 12–15 year olds in Taiwan [2.4% (1995–96)] [32] and the much higher baseline prevalence in Korea [7.2% (1995)] [36]. In these countries too, cultural, social and diagnostic differences may potentially explain this pattern. In contrast, large changes in prevalence estimates within one country in a short space of time are of interest as such changes are likely to represent a true change. For example the doubling in lifetime prevalence of both atopic eczema diagnosis [from 13.9% (1995–96) to 27.2% (2001–02)] and atopic eczema symptoms [from 8.8% (1995–96) to 19.6% (2001–02)] in boys aged 13–14 in England [80] is likely to represent a true change and we must consider environmental explanations for this.

In conclusion, we have found no overall trend for the incidence or prevalence of atopic eczema worldwide. However, in Africa, eastern Asia, western Europe and parts of northern Europe (i.e. the UK) trends in atopic eczema prevalence were mainly increasing. There are gaps in the literature, particularly in the Americas and Oceania and for measures of atopic eczema incidence. Future research should investigate trends in what is now one of the most prevalent disorders in Europe and other regions in a scientifically robust manner. In order to do so, the careful use of key definitions, improved study design and more comprehensive reporting are essential.

Supporting Information

Appendix S1 PRISMA checklist. PRISMA checklist with 27 reporting items used for the systematic review. (DOC)

Appendix S2 Search terms. Search terms and limitations used for the systematic review. (DOC)

Author Contributions

Conceived and designed the experiments: ID SM MM CvS AS. Analyzed the data: ID SM SL. Wrote the paper: ID SM SL MM CvS AS.

References

- Gupta R, Sheikh A, Strachan DP, Anderson HR (2004) Burden of allergic disease in the UK: secondary analyses of national databases. *Clin Exp Allergy* 34: 520–526.
- Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, et al. (2006) Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 368: 733–743.
- Gupta R, Sheikh A, Strachan DP, Anderson HR (2007) Time trends in allergic disorders in the UK. *Thorax* 62: 91–96.
- Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI, et al. (2009) Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 124: 1251–1258.e1223.
- Warner JO (1999) Worldwide variations in the prevalence of atopic symptoms: what does it all mean? *Thorax* 54 Suppl 2: S46–51.
- Punekar YS, Sheikh A (2009) Establishing the incidence and prevalence of clinician-diagnosed allergic conditions in children and adolescents using routinely collected data from general practices. *Clin Exp Allergy*: 1–8.
- van den Oord RA, Sheikh A (2009) Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *Bmj* 339: b2433.
- Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, et al. (2006) Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 38: 441–446.
- Sandilands A, Sutherland C, Irvine AD, McLean WH (2009) Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci* 122: 1285–1294.
- Anandan C, Nurmatov U, van Schayck OC, Sheikh A (2009) Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 65: 152–167.
- ISAAC steering Committee (1998) Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC.

- The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 351: 1225–1232.
12. The European Community Respiratory Health Survey II steering committee (2002) The European Community Respiratory Health Survey II. *Eur Respir J* 20: 1071–1079.
 13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 62: e1–34.
 14. Public Health Resource Unit England (2006) Critical Appraisal Skills Programme (CASP) Available: <http://www.sph.nhs.uk/sph-files/casp-appraisal-tools/Case%20Control%2011%20Questions.pdf>. Accessed 18 July 2011.
 15. Choi HS, Yun SK, Kim HU, Ihm CW (2005) A statistical study of dermatoses in the Jeonbuk Province (1979–1980, 1987–2002). *Korean Journal of Dermatology* 43: 606–618.
 16. United Nations (2010) Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings Available: <http://unstats.un.org/unsd/methods/m49/m49regin.htm>. Accessed 26 Aug 2011.
 17. Al Frayh AR, Shakoor Z, Fakhri SAM, Koshak EA, Al Nameem S, et al. (2004) A 17-year trend for the prevalence of asthma and allergic diseases among children in Saudi Arabia. *Current Pediatric Research* 8: 1–5.
 18. Dörner T, Lawrence K, Rieder A, Kunze M (2007) Epidemiology of allergies in Austria. Results of the first Austrian allergy report. *Wiener Medizinische Wochenschrift* 157: 235–242.
 19. Ellsäßer G, Diepgen TL (2002) Atopic diseases and social status of school beginners in the federal state of Brandenburg, Germany. *Trend analysis 1994–2000. Monatsschrift Kinderheilkunde* 150: 839–847.
 20. Nishima S, Chisaka H, Fujiwara T, Furusho K, Hayashi S, et al. (2009) Surveys on the prevalence of pediatric bronchial asthma in Japan: A comparison between the 1982, 1992, and 2002 surveys conducted in the same region using the same methodology. *Allergy International* 58: 37–53.
 21. Riikjarv MA, Annus T, Braback L, Rahu K, Björkstén B (2000) Similar prevalence of respiratory symptoms and atopy in Estonian schoolchildren with changing lifestyle over 4 yrs. *Eur Resp J* 16: 86–90.
 22. Saeeki H, Oiso N, Honma M, Odajima H, Izuka H, et al. (2009) Comparison of prevalence of atopic dermatitis in Japanese elementary schoolchildren between 2001/2002 and 2007/2008. *The Journal of Dermatology* 36: 512–514.
 23. Olesen AB, Bang K, Juul S, Thestrup-Pedersen K (2005) Stable incidence of atopic dermatitis among children in Denmark during the 1990s. *Acta Dermatovenereologica* 85: 244–247.
 24. Schafer T, Kramer U, Vieluf D, Abeck D, Behrendt H, et al. (2000) The excess of atopic eczema in East Germany is related to the intrinsic type. *Br J Dermatol* 143: 992–998.
 25. Simpson CR, Newton J, Hippisley-Cox J, Sheikh A (2009) Trends in the epidemiology and prescribing of medication for eczema in England. *J R Soc Med* 102: 108–117.
 26. Bouayad Z, Aichane A, Afif A, Benouhoud N, Trombati N, et al. (2006) Prevalence and trend of self-reported asthma and other allergic disease symptoms in Morocco: ISAAC phase I and III. *Int J Tuberc Lung Dis* 10: 371–377.
 27. Esamai F, Ayaya S, Nyandiko W (2002) Prevalence of asthma, allergic rhinitis and dermatitis in primary school children in Uasin Gishu district, Kenya. *East Afr Med J* 79: 514–518.
 28. Falade AG, Ige OM, Yusuf BO, Onadeko MO, Onadeko BO (2009) Trends in the prevalence and severity of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. *Journal of the National Medical Association* 101: 414–418.
 29. Zar HJ, Ehrlich RI, Workman L, Weinberg EG (2007) The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Pediatr Allergy Immunol* 18: 560–565.
 30. Kusunoki T, Morimoto T, Nishikomori R, Yasumi T, Heike T, et al. (2009) Changing prevalence and severity of childhood allergic diseases in Kyoto, Japan, from 1996 to 2006. *Allergy International* 58: 543–548.
 31. Lee SL, Wong W, Lau YL (2004) Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). *Pediatr Allergy Immunol* 15: 72–78.
 32. Lee YL, Li CW, Sung FC, Guo YL (2007) Increasing prevalence of atopic eczema in Taiwanese adolescents from 1995 to 2001. *Clin Exp Allergy* 37: 543–551.
 33. Lee YL, Lin YC, Hwang BF, Guo YL (2005) Changing prevalence of asthma among Taiwanese adolescents: Two surveys 6 years apart. *Pediatr Allergy Immunol* 16: 157–164.
 34. Liao MF, Liao MN, Lin SN, Chen JY, Huang JL (2009) Prevalence of Allergic Diseases of Schoolchildren in Central Taiwan. From ISAAC surveys 5 years apart. *Journal of Asthma* 46: 541–545.
 35. Liao PF, Sun HL, Lu KH, Lue KH (2009) Prevalence of Childhood Allergic Diseases in Central Taiwan over the Past 15 Years. *Pediatrics and Neonatology* 50: 18–25.
 36. Oh JW, Pyun BY, Choung JT, Ahn KM, Kim CH, et al. (2004) Epidemiological change of atopic dermatitis and food allergy in school-aged children in Korea between 1995 and 2000. *Journal of Korean Medical Science* 19: 716–723.
 37. Wang HY, Zheng JP, Zhong NS (2006) Time trends in the prevalence of asthma and allergic diseases over 7 years among adolescents in Guangzhou city. *Natl Medical J China* 86: 1014–1020.
 38. Yan DC, Ou LS, Tsai TL, Wu WF, Huang JL (2005) Prevalence and severity of symptoms of asthma, rhinitis, and eczema in 13- to 14-year-old children in Taipei, Taiwan. *Ann Allergy Asthma Immunol* 95: 579–585.
 39. Yura A, Shimizu T (2001) Trends in the prevalence of atopic dermatitis in school children: longitudinal study in Osaka Prefecture, Japan, from 1985 to 1997. *Br J Dermatol* 145: 966–973.
 40. Quah BS, Wan-Pauzi I, Ariffin N, Mazidah AR (2005) Prevalence of asthma, eczema and allergic rhinitis: two surveys, 6 years apart, in Kota Bharu, Malaysia. *Respirology* 10: 244–249.
 41. Teeratakulpisarn J, Wiangnon S, Kosalaraksa P, Heng S (2004) Surveying the prevalence of asthma, allergic rhinitis and eczema in school-children in Khon Kaen, Northeastern Thailand using the ISAAC questionnaire: phase III. *Asian Pacific Journal of Allergy & Immunology* 22: 175–181.
 42. Trakulvivakorn M, Sangsupawanich P, Vichayanond P (2007) Time trends of the prevalence of asthma, rhinitis and eczema in Thai children-ISAAC (International Study of Asthma and Allergies in Childhood) Phase Three. *Journal of Asthma* 44: 609–611.
 43. Wang XS, Tan TN, Shek LPC, Chng SY, Hia CPP, et al. (2004) The prevalence of asthma and allergies in Singapore; data from two ISAAC surveys seven years apart. *Arch Dis Child* 89: 423–426.
 44. Abramidze T, Gotua M, Rukhadze M, Gamkrelidze A (2006) ISAAC I and III in Georgia: time trends in prevalence of asthma and allergies. *Georgian Medical News* 8: 80–82.
 45. Abramidze T, Gotua M, Rukhadze M, Gamkrelidze A (2007) Prevalence of asthma and allergies among adolescents in Georgia: comparison between two surveys. *Georgian Medical News* 3: 38–41.
 46. Demir AU, Celikel S, Karakaya G, Kalyoncu AF (2010) Asthma and allergic diseases in school children from 1992 to 2007 with incidence data. *Journal of Asthma* 47: 1128–1135.
 47. Kalyoncu AF, Selcuk ZT, Enunlu T, Demir AU, Coplu L, et al. (1999) Prevalence of asthma and allergic diseases in primary school children in Ankara, Turkey: two cross-sectional studies, five years apart. *Pediatr Allergy Immunol* 10: 261–265.
 48. Owayed A, Behbehani N, Al-Momen J (2008) Changing prevalence of asthma and allergic diseases among Kuwaiti children: An ISAAC study (phase III). *Med Princ Pract* 17: 284–289.
 49. Romano-Zelekha O, Graif Y, Garty B-Z, Livne I, Green MS, et al. (2007) Trends in the prevalence of asthma symptoms and allergic diseases in Israeli adolescents: results from a national survey 2003 and comparison with 1997. *Journal of Asthma* 44: 365–369.
 50. Barraza-Villarreal A, Hernandez-Cadena L, Moreno-Macias H, Ramirez-Aguilar M, Romieu I (2007) Trends in the prevalence of asthma and other allergic diseases in schoolchildren from Cuernavaca, Mexico. *Allergy & Asthma Proceedings* 28: 368–374.
 51. Borges WG, Burns DAR, Guimarães FATM, Felizola MLBM, Borges VM (2008) Atopic dermatitis among adolescents from Federal District. Comparison between ISAAC phases I and III by socioeconomic status [Portugues]. *Rev bras alergologia imunopatol* 31: 146–150.
 52. Camelo-Nunes IC, Wandalsen GF, Melo KC, Naspitz CK, Solé D (2004) Prevalence of atopic eczema and associated symptoms in school children. *Jornal de Pediatria (Rio J)* 80: 60–64.
 53. Riedi CA, Rosario NA, Ribas LFO, Backes AS, Kleiniibing GF, et al. (2005) Increase in prevalence of rhinoconjunctivitis but not asthma and atopic eczema in teenagers. *J Investig Allergol Clin Immunol* 15: 183–188.
 54. Solé D, Melo KC, Camelo-Nunes IC, Freitas LS, Britto M, et al. (2007) Changes in the prevalence of asthma and allergic diseases among Brazilian schoolchildren (13–14 years old): Comparison between ISAAC phases one and three. *Journal of Tropical Pediatrics* 53: 13–21.
 55. Annesi-Maesano I, Mourad C, Daures JP, Kalaboka S, Godard P (2009) Time trends in prevalence and severity of childhood asthma and allergies from 1995 to 2002 in France. *Allergy* 64: 798–800.
 56. Grize L, Gassner M, Wuthrich B, Bringolf-Isler B, Takken-Sahli K, et al. (2006) Trends in prevalence of asthma, allergic rhinitis and atopic dermatitis in 5–7-year old Swiss children from 1992 to 2001. *Allergy* 61: 556–562.
 57. Haidinger G, Waldhör T, Meusbürger S, Süss G, Vutuc C (2008) The prevalence of childhood asthma and of allergies in 7 districts of Upper Austria - ISAAC III. [German]. *Allergologie* 31: 17–22.
 58. Heinrich J, Hoelscher B, Frye C, Meyer I, Wjst M, et al. (2002) Trends in prevalence of atopic diseases and allergic sensitization in children in Eastern Germany. *Eur Resp J* 19: 1040–1046.
 59. Krämer U, Oppermann H, Ranft U, Schafer T, Ring J, et al. (2009) Differences in allergy trends between East and West Germany and possible explanations. *Clin Exp Allergy* 40: 289–298.
 60. Maziak W, Behrens T, Brasky TM, Duhme H, Rzehak P, et al. (2003) Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Münster, Germany. *Allergy* 58: 572–579.
 61. Schernhammer ES, Vutuc C, Waldhor T, Haidinger G (2008) Time trends of the prevalence of asthma and allergic disease in Austrian children. *Pediatr Allergy Immunol* 19: 125–131.

62. Vellinga A, Droste JHJ, Vermeire PA, Desager K, De Backer WA, et al. (2005) Changes in respiratory and allergic symptoms in schoolchildren from 1996 to 20029 results from the ISAAC surveys in Antwerp (Belgium). *Acta Clinica Belgica* 60: 219–225.
63. Weber AS, Haidinger G (2010) The prevalence of atopic dermatitis in children is influenced by their parents' education: results of two cross-sectional studies conducted in Upper Austria. *Pediatr Allergy Immunol* 21: 1028–1035.
64. Montefort S, Ellul P, Montefort M, Caruana S, Muscat HA (2009) Increasing prevalence of asthma, allergic rhinitis but not eczema in 5- to 8-yr-old Maltese children (ISAAC). *Pediatr Allergy Immunol* 20: 67–71.
65. Anthracopoulos MB, Antonogeorgos G, Liolios E, Triga M, Panagiotopoulou E, et al. (2009) Increase in chronic or recurrent rhinitis, rhinoconjunctivitis and eczema among schoolchildren in Greece: Three surveys during 1991–2003. *Pediatr Allergy Immunol* 20: 180–186.
66. Galassi C, De Sario M, Biggeri A, Bisanti L, Chellini E, et al. (2006) Changes in prevalence of asthma and allergies among children and adolescents in Italy: 1994–2002. *Pediatrics* 117: 34–42.
67. Rosado-pinto J, Gaspar A, Morais-Almeida M (2006) Epidemiology of asthma and allergic diseases in Portuguese speaking regions. *Revue française d'allergologie et d'immunologie clinique* 46: 305–308.
68. Anderson HR, Ruggles R, Strachan DP, Austin JB, Burr M, et al. (2004) Trends in prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds in the British Isles, 1995–2002: questionnaire survey. *Bmj* 328: 1052–1053.
69. Annus T, Riikjarv MA, Rahu K, Bjorksten B (2005) Modest increase in seasonal allergic rhinitis and eczema over 8 years among Estonian schoolchildren. *Pediatr Allergy Immunol* 16: 315–320.
70. Bjerg A, Sandstrom T, Lundback B, Ronmark E (2010) Time trends in asthma and wheeze in Swedish children 1996–2006: Prevalence and risk factors by sex. *Allergy* 65: 48–55.
71. Devenny A, Wassall H, Ninan T, Omran M, Khan SD, et al. (2004) Respiratory symptoms and atopy in children in Aberdeen: questionnaire studies of a defined school population repeated over 35 years. *Bmj* 329: 489–490.
72. Kudzytė J, Griška E, Bojarskas J (2008) Time trends in the prevalence of asthma and allergy among 6-7-year-old children. Results from ISAAC phase I and III studies in Kaunas, Lithuania. *Medicina (Kaunas)* 44: 944–952.
73. Kuchni CE, Davis A, Brooke AM, Silverman M (2001) Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 357: 1821–1825.
74. Latvala J, von Hertzen L, Lindholm H, Haahtela T (2005) Trends in prevalence of asthma and allergy in Finnish young men: nationwide study, 1966–2003. *Bmj* 330: 1186–1187.
75. McNeill G, Tagiyeva N, Aucott L, Russell G, Helms PJ (2009) Changes in the prevalence of asthma, eczema and hay fever in pre-pubertal children: A 40-year perspective. *Paediatric and Perinatal Epidemiology* 23: 506–512.
76. Ng Man Kwong G, Proctor A, Billings C, Duggan R, Das C, et al. (2001) Increasing prevalence of asthma diagnosis and symptoms in children is confined to mild symptoms. *Thorax* 56: 312–314.
77. Osman M, Tagiyeva N, Wassall HJ, Ninan TK, Devenny AM, et al. (2007) Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. *Pediatr Pulmonol* 42: 60–65.
78. Ronmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundback B (2009) Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. *J Allergy Clin Immunol* 124: 357–363.
79. Selnes A, Nystad W, Bolle R, Lund E (2005) Diverging prevalence trends of atopic disorders in Norwegian children. Results from three cross-sectional studies. *Allergy* 60: 894–899.
80. Shamsain M (2007) Trends in the prevalence and severity of asthma, rhinitis and atopic eczema in 6- to 7- and 13- to 14-yr-old children from the north-east of England. *Pediatr Allergy Immunol* 18: 149–153.
81. Brozek GM, Zejda JE (2004) Increase in the frequency of diagnosed allergic diseases in children - Fact or artefact? [Polish]. *Pediatrica Polska* 79: 385–392.
82. Harangi F, Fogarasy A, Muller A, Schneider I, Sebok B (2007) No significant increase within a 3-year interval in the prevalence of atopic dermatitis among schoolchildren in Baranya County, Hungary. *Journal of the European Academy of Dermatology and Venereology* 21: 964–968.
83. Ponsonby A-L, Glasgow N, Pezic A, Dwyer T, Ciszek K, et al. (2008) A temporal decline in asthma but not eczema prevalence from 2000 to 2005 at school entry in the Australian Capital Territory with further consideration of country of birth. *Int J Epidemiol* 37: 559–569.
84. Robertson CF, Roberts MF, Kappers JH (2004) Asthma prevalence in Melbourne schoolchildren: have we reached the peak? *Med J Aust* 180: 273–276.
85. Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, et al. (2004) Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. *Bmj* 328: 386–387.
86. Galassi C, Grabenhenrich L, Hohmann C, Keil T, Thijs C, et al. (2010) Asthma and Allergy. In: Slama R, Charles M, Keil T, Kogevinas M, Sunyer J, editors. *Evaluation of Health Information and Recommendations in European Birth Cohorts The ENRIECO Project: Environmental Health Risks In European Birth Cohorts, work package 3 Report to the European Commission, ENV-FP7–2008–2262852010*.
87. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR, et al. (2008) Is eczema really on the increase worldwide? *J Allergy Clin Immunol* 121: 947–954.e915.
88. ISAAC Steering Committee (2011) The ISAAC story. Available: <http://isaac.auckland.ac.nz/story/centres/regions.php?cen=North%20America>. Accessed 28 Mar 2012.
89. Flohr C, Weinmayr G, Weiland SK, Addo-Yobo E, Annesi-Maesano I, et al. (2009) How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. *Br J Dermatol* 161: 846–853.
90. Cork MJ, Danby S (2009) Skin barrier breakdown: a renaissance in emollient therapy. *Br J Nurs* 18: 872, 874, 876–877.
91. Mommers M, Swaen GM, Weishoff-Houben M, Dott W, van Schayck CP (2005) Differences in asthma diagnosis and medication use in children living in Germany and the Netherlands. *Prim Care Respir J* 14: 31–37.