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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

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Summary

Background Questionnaires are widely used in epidemiological studies to measure eczema symptom prevalence, but there are concerns regarding their accuracy if used as a diagnostic tool.

Objectives To compare the performance of a validated eczema symptom questionnaire and a standardized skin examination protocol employed in the second phase of the International Study of Asthma and Allergies in Childhood (ISAAC).

Methods A total of 30 358 schoolchildren aged 8–12 years from 18 countries were examined for flexural eczema. Parents also completed an eczema symptom questionnaire. We compared prevalence estimates at the population level based on the questionnaire vs. physical examination. We also compared the skin examination and the ISAAC questionnaire in making a diagnosis of flexural eczema.

Results The point prevalences for flexural eczema at centre level based on a single examination were lower than the questionnaire-based 12-month period prevalences (mean centre prevalence 3·9% vs. 9·4%). Correlation between prevalences of both outcome measures was high ($r = 0{\cdot}77$, $P < 0{\cdot}001$). At the individual level, questionnaire-derived symptoms of 'persistent flexural eczema in the past 12 months' missed < 10% of cases of flexural eczema detected on physical examination. However, between 33% and 100% of questionnaire-based symptoms of 'persistent flexural eczema in the past 12 months' were not confirmed on examination.

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Conflicts of interest
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Conclusions ISAAC questionnaire-derived symptom prevalences are sufficiently precise for comparisons between populations. Where diagnostic precision at the individual level is important, questionnaires should be validated and potentially modified in those populations beforehand, or a standardized skin examination protocol should be used.

Many eczema studies use questionnaires to measure disease symptom prevalence. The main advantage of questionnaires is that they are relatively inexpensive to distribute and administer to children and parents, permitting large populations to be sampled. Physical examination on the other hand is resource intensive, requiring trained observers. Questionnaires also permit the measurement of period prevalences, such as eczema symptoms in the past year, whereas skin examination only provides a measure at one point in time, which may be inappropriate for assessing prevalence in a disease that classically relapses and remits over time. Despite the ready availability and widespread use of questionnaire tools for eczema, such as the International Study of Asthma and Allergies in Childhood (ISAAC) eczema symptom questionnaire, there remains concern that the validity of such questionnaire-based data could be compromised by cultural and educational factors, especially where English questionnaires are translated, making comparisons between study populations difficult.[1–5] Diagnostic precision at the individual level is particularly important when eczema risk factors such as allergic sensitization and genetic mutations are examined.

It has been argued that bias associated with the use of questions that directly mention disease labels such as 'asthma' or 'eczema' can be reduced by using validated questionnaire tools that rely on reported symptoms only, such as in the ISAAC questionnaire.[4,5] Indeed, the ISAAC eczema questionnaire is now widely used in population-based eczema studies.

The ISAAC study runs in phases. Phase One and Phase Three were large questionnaire-based prevalence surveys carried out among more than 700 000 schoolchildren from 56 countries to generate the first world map of allergic disease prevalences and to document prevalence changes over time.[6,7] ISAAC Phase Two has been designed to examine risk factors that might explain the variation in eczema prevalences across populations found in ISAAC Phases One and Three and to perform objective measurements relating to exposure and disease. As both a questionnaire and a standardized and validated protocol for physical examination to detect flexural eczema were employed as part of the second phase of ISAAC, we used this opportunity to compare the methods at the population and the individual level (i) to see whether or not questionnaires provide a valid measure of eczema prevalence and (ii) to assess the ISAAC questionnaire's potential suitability as a diagnostic tool in individual patients.

Methods

The rationale and methods of ISAAC Phase Two have been described in detail elsewhere.[8] In brief and with reference to this article, ISAAC Phase Two was conducted among 8–12-year-old schoolchildren to evaluate the prevalence and risk factors of allergic disease between populations. Study centres were required to select randomly at least 10 schools from a complete sampling frame of schools in defined geographical areas, and children attending classes with a majority of 9–11 year olds were invited to participate.

The parental questionnaire on allergy symptoms was identical to the one used for children aged 6–7 years in ISAAC Phases One and Three.[7] Symptom prevalence of 'flexural eczema in the past 12 months' in children was assessed by parents answering 'yes' to the last two of the following three questions: 'Has your child ever had an itchy rash which was coming and going for at least 6 months?', 'Has your child had this itchy rash at any time in the last 12 months?' and 'Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?' (questionnaire-based flexural eczema past 12 months). In addition, parents were asked questions related to the severity of their child's eczema: 'Has this rash cleared completely at any time during the last 12 months?' (a 'no' answer indicating persistent flexural eczema symptoms in the past 12 months), and 'In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?' Possible answers were 'never' (mild), 'less than one night per week' (moderate), or 'one or more nights per week' (severe).

All children were also examined for flexural eczema in the following five body areas: around the eyes, the neck, in front of the elbows, behind the knees, and in front of the ankles. Participants were considered to have flexural eczema if they had a poorly defined erythematous rash with surface change (e.g. fine scaling, vesicles, oozing, crusting or lichenification) in any of the above areas. All fieldworkers were first trained and then formally tested in the recognition of flexural eczema, using a manual and photographic images for training and quality control, specifically developed for this purpose.[9,10]

We performed two separate analyses: (i) a comparison of prevalence estimates generated by the symptom questionnaire and physical examination for each study centre at the population level to ascertain if questionnaires could usefully assess overall population prevalences and differences between countries; and (ii) a comparison of the precision of the questionnaire tool vs. physical examination at the level of individual participants to assess how well such questions might perform in analytical observational studies. As the physical examination is a point prevalence measure and the questionnaire inquired about eczema symptoms within the past year, we were not able to validate one against the other directly. Instead, we investigated the correlation between the two measures at centre level and then used more specific versions of the questionnaire at the individual level such as '*persistent* flexural eczema in the past 12 months' and the severity of questionnaire-based flexural eczema (flexural eczema that kept the child awake at night), on the assumption that prevalence figures based on physical examination would be more strongly related to more persistent or severe disease.

For the centre level analysis, we compared the lowest and highest eczema prevalences based on the questionnaire and skin examination as well as prevalence means. We also plotted the prevalence measurements based on the questionnaire and skin examination against each other, as done in standard correlation analysis. However, rather than fitting a regression line, we inserted a line of equality to show visually how the relation between questionnaire- and examination-derived prevalence estimates changed, depending on disease persistence and severity. Spearman correlation coefficients and P-values were calculated for each of these outcomes.

With regards to analysis at the individual level, we calculated the proportion of children who had eczema on physical examination among those reporting symptoms of persistent flexural eczema based on the questionnaire (on the basis that such persistent cases were more likely to show signs of visible flexural eczema at the time of examination), as well as the proportion of children who had eczema on examination but were not categorized as having persistent flexural eczema symptoms based on the questionnaire. We did not calculate kappa statistics, sensitivities, specificities, or positive and negative predictive values, as these indices require a gold-standard outcome and/or comparison of the same clinical entity by two different diagnostic methods, and these assumptions were not met in ISAAC Phase Two.

Following local data entry, the data were sent to the ISAAC Phase Two coordinating centre in Ulm (Germany) for consistency checks and statistical analysis. The statistical analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC, U.S.A.) and SUDAAN software (version 9.0; RTI, Research Triangle Park, Raleigh, NC, U.S.A). All study centres obtained local ethics committee approval.

Results

A total of 30 358 children from 25 study centres in 18 countries aged 8–12 years (49·9% boys), were surveyed with the ISAAC Phase Two questionnaire and by physical skin examination.

Centre level analysis

Flexural eczema prevalence based on physical examination was lower than questionnaire-derived symptom prevalence estimates for 'flexural eczema in the past 12 months' (mean centre prevalence 3·9% vs. 9·4%; Fig. 1, Tables 1 and 2). There was only one exception, Pichincha (Ecuador), where

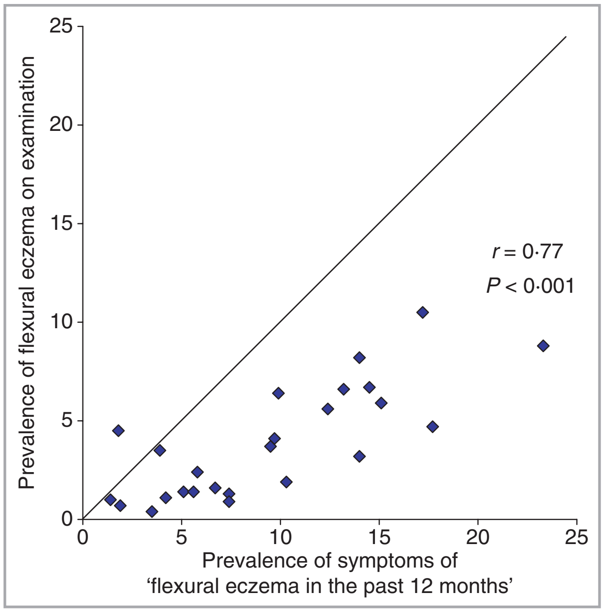

Fig 1. Centre percentage prevalences for symptoms of 'flexural eczema in the past 12 months' vs. flexural eczema on skin examination.

the questionnaire-based prevalence for 'flexural eczema in the past 12 months' was 1·8% compared with a skin examination-based point prevalence of 4·5%. The biggest prevalence estimate differences between questionnaire-based symptoms of 'persistent flexural eczema in the past 12 months' and skin examination-derived flexural eczema were seen for Riga (questionnaire 1·6% vs. skin examination 6·4%), Tromso (questionnaire 5·9% vs. skin examination 10·5%) and Hawkes Bay (questionnaire 4·2% vs. skin examination 8·2%; Table 2). Correlation between skin examination findings and questionnaire-based symptoms of 'flexural eczema in the past 12 months' was high ($r = 0{\cdot}77$, $P < 0{\cdot}001$) and, as would be expected, even higher for '*persistent* flexural eczema in the past 12 months' (0·82, $P < 0{\cdot}001$). This was reflected in a shift closer to the line of equality when plotting skin examination-based centre prevalences against the questionnaire-derived symptom prevalence of 'persistent flexural eczema in the past 12 months' (Fig. 2), with a trend towards lower prevalences based on physical examination (mean prevalences of 2·2% vs. 2·8%; Tables 1 and 2). Plotting physical examination-based prevalence estimates against questionnaire-derived symptom prevalences of mild, moderate and severe 'flexural eczema in the past 12 months', there was a shift in prevalence associations from below to above the line of equality (Fig. 3a–c) as well as a reduction in outcome correlation coefficients from 0·74 ($P < 0{\cdot}001$) to 0·42 ($P = 0{\cdot}05$), suggesting that the questionnaire was sensitive to eczema severity. None of the above results was altered when we included all children with questionnaire data, rather than just those for whom we had information from both skin examination and questionnaires (data not shown).

Table 1 Centre prevalences for all flexural eczema outcomes

Outcome measure	Lowest centre prevalence (%)	Highest centre prevalence (%)	Mean centre prevalence (%)
Flexural eczema (skin examination)	0·4	10·5	3·9
Flexural eczema symptoms in the past 12 months (questionnaire)	1·4	23·3	9·4
Persistent flexural eczema symptoms in the past 12 months (questionnaire)	0·6	7·0	2·8
Mild flexural eczema symptoms in the past 12 months (questionnaire)	0·8	18·1	6·1
Moderate flexural eczema symptoms in the past 12 months (questionnaire)	0·1	5·6	2·5
Severe flexural eczema symptoms in the past 12 months (questionnaire)	0·1	2·0	0·9

Table 2 Individual centre prevalences of flexural eczema based on skin examination and ISAAC Phase Two questionnaire

Country	Centre	Number of participants	Flexural eczema on skin examination % prevalence (95% CI)	Flexural eczema symptoms in the past 12 months (questionnaire) % prevalence (95% CI)	Persistent flexural eczema symptoms in the past 12 months (questionnaire) % prevalence (95% CI)
Albania	Tirana	963	2·4 (1·5–3·4)	5·8 (4·3–7·2)	1·6 (0·8–2·4)
China	Beijing	1044	1·0 (0·4–1·5)	1·4 (0·7–2·2)	0·7 (0·2–1·2)
	Guangzhou	1078	0·7 (0·2–1·3)	1·9 (1·1–2·7)	0·6 (0·1–1·0)
	Hong Kong	1323	3·5 (2·5–4·5)	3·9 (2·8–4·9)	2·9 (2·0–3·9)
Ecuador	Pichincha	894	4·5 (3·1–5·8)	1·8 (0·9–2·7)	1·8 (0·9–2·7)
Estonia	Tallinn	633	4·7 (3·0–6·3)	17·7 (14·7–20·7)	2·4 (1·2–3·6)
France	Creteil	1257	6·6 (5·4–7·9)	13·2 (11·3–15·2)	3·5 (2·4–4·5)
Germany	Dresden	2418	5·9 (5·0–6·9)	15·1 (13·7–16·6)	7·0 (6·0–8·1)
	Munich	2484	4·1 (3·3–4·8)	9·7 (8·5–10·9)	3·6 (2·9–4·4)
Ghana	Kintampo	1325	0·4 (0–0·7)	3·5 (2·5–4·5)	0·8 (0·3–1·3)
Greece	Athens	985	1·3 (0·6–2·0)	7·4 (5·8–9·1)	1·5 (0·8–2·3)
	Thessaloniki	1018	1·4 (0·7–2·1)	5·1 (3·8–6·5)	1·0 (0·4–1·6)
India	Mumbai	1637	1·1 (0·6–1·6)	4·2 (3·2–5·2)	0·7 (0·3–1·1)
Iceland	Reykjavik	628	8·8 (6·6–11·1)	23·3 (20·0–26·6)	6·5 (4·5–8·4)
Italy	Rome	1347	1·6 (1·0–2·3)	6·7 (5·3–8·0)	0·8 (0·3–1·3)
Latvia	Riga	500	6·4 (4·2–8·5)	9·9 (7·3–12·6)	1·6 (0·5–2·7)
Netherlands	Utrecht	1260	5·6 (4·3–6·9)	12·4 (10·6–14·2)	5·4 (4·1–6·6)
New Zealand	Hawkes Bay	1294	8·2 (6·7–9·7)	14·0 (12·1–15·9)	4·2 (3·1–5·3)
Norway	Tromso	665	10·5 (8·2–12·9)	17·2 (14·3–20·1)	5·9 (4·1–7·7)
Spain	Almeria	1061	1·9 (1·1–2·7)	10·3 (8·4–12·1)	2·1 91·2–3·0)
	Cartagena	1148	0·9 (0·4–1·5)	7·4 (5·9–8·9)	2·0 (1·2–2·9)
	Madrid	635	3·2 (1·8–4·5)	14·0 (11·2–16·7)	3·8 (2·3–5·4)
	Valencia	1131	3·7 (2·6–4·7)	9·5 (7·8–11·2)	2·1 (1·2–2·9)
Turkey	Ankara	2661	1·4 (1·0–1·9)	5·6 (4·7–6·5)	2·0 (1·5–2·5)
U.K.	West Sussex	969	6·7 (5·1–8·3)	14·5 (12·2–16·7)	4·9 (3·5–6·3)

ISAAC, International Study of Asthma and Allergies in Childhood; CI, confidence interval.

Individual level analysis

Only between 0·3% and 4·9% of cases of flexural eczema on skin examination were not captured by the question relating to symptoms of ‘flexural eczema in the past 12 months’. Similarly, only between 0·3% and 7·9% of cases of skin examination-diagnosed flexural eczema were not detected with the question inquiring about symptoms of ‘persistent flexural eczema in the past 12 months’ (Table 3, Fig. 4). However, the proportion of skin examination positives among the questionnaire positives for ‘persistent flexural eczema’ ranged from 66·7% and 53·2% in the two English-speaking study centres Hawkes Bay (New Zealand) and West Sussex (U.K.) to only 6·7% in Athens (Greece) and even 0% in Rome, Cartagena, Ankara and Guangzhou. In other words, up to 100% of questionnaire-derived symptoms of persistent flexural eczema were not diagnosed as flexural eczema on skin examination. Other study centres where a high proportion of questionnaire-based symptoms of ‘persistent flexural eczema in the past 12 months’ were not detected on skin examination included Mumbai (91·7%), Kintampo (90·9%), Pichincha (87·5%), Tirana (86·7%) and the other Spanish study centres (66·7–

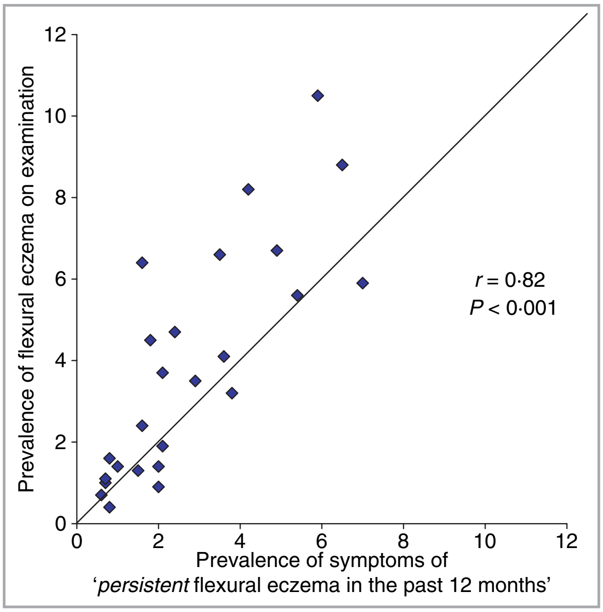

Fig 2. Centre percentage prevalences for symptoms of 'persistent flexural eczema in the past 12 months' vs. flexural eczema on skin examination.

91·3%, Table 3, Fig. 5), all of which were centres in countries where people tend to have darker skin.

Discussion

As expected, skin examination-derived prevalences, being a point prevalence measure, were lower than questionnaire-based symptom estimates for 'flexural eczema in the past 12 months'. The correlation between the ISAAC Phase Two questionnaire and examined eczema was high and was sensitive to changes in eczema severity and persistence. At the individual level, < 8% of cases of flexural eczema diagnosed on skin examination were not detected by questionnaire. However, children with questionnaire-derived symptoms of 'persistent flexural eczema in the past 12 months' should by definition be more likely to also have flexural eczema on skin examination, yet a significant number of cases of questionnaire-based persistent flexural eczema was not confirmed on skin examination. This raises concerns about the use of the ISAAC questionnaire tool in making a diagnosis of flexural eczema.

Strengths of the study include its size and population base, with questionnaire and skin examination data from more than 30 000 schoolchildren. We avoided using skin examination findings as the 'gold standard', as questionnaires measure symptoms over a 12-month period and skin examination is

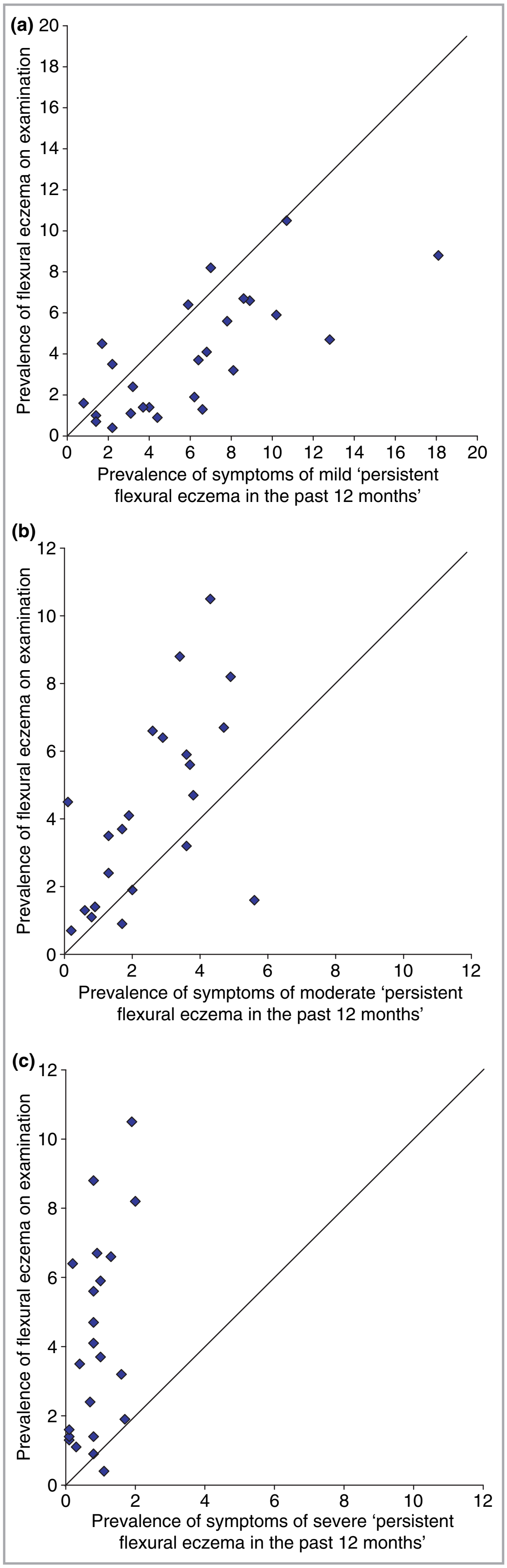

Fig 3. Centre percentage prevalences for symptoms of (a) mild 'flexural eczema in the past 12 months' vs. flexural eczema on skin examination, (b) moderate 'flexural eczema in the past 12 months' vs. flexural eczema on skin examination, and (c) severe 'flexural eczema in the past 12 months' vs. flexural eczema on skin examination.

Table 3 Individual level analysis

			Flexural eczema symptoms in the past 12 months (questionnaire)						Persistent flexural eczema symptoms in the past 12 months (questionnaire)					
Country	Centre	Number of participants	a	b	c	d	Questionnaire negative + examination positive (%)	Examination positive among questionnaire positives (%)	a	b	c	d	Questionnaire negative + examination positive (%)	Examination positive among questionnaire positives (%)
Albania	Tirana	963	881	52	19	3	2·1	5·5	920	13	20	2	2·1	13·3
China	Beijing	1044	1022	12	7	3	0·7	20·0	1029	5	8	2	0·8	28·6
	Guangzhou	1078	1044	20	8	0	0·8	0·0	1058	6	8	0	0·8	0·0
	Hong Kong	1323	1243	34	29	17	2·3	33·3	1249	28	35	11	2·7	28·2
Ecuador	Pichincha	894	840	14	38	2	4·3	12·5	840	14	38	2	4·3	12·5
Estonia	Tallinn	633	508	91	9	20	1·7	18·0	590	11	24	4	3·9	26·7
France	Creteil	1257	1009	114	39	46	3·7	28·8	1101	24	66	18	5·7	42·9
Germany	Dresden	2418	1985	266	47	96	2·3	26·5	2133	117	90	51	4·1	30·4
	Munich	2484	2168	184	48	54	2·2	22·7	2292	61	74	28	3·1	31·5
Ghana	Kintampo	1325	1275	45	4	1	0·3	2·2	1309	10	4	1	0·3	9·1
Greece	Athens	985	899	69	9	4	1·0	5·5	955	14	12	1	1·2	6·7
	Thessaloniki	1018	950	47	9	5	1·0	9·6	989	6	10	4	1·0	40·0
Iceland	Reykjavik	628	454	113	23	32	4·8	22·1	543	22	36	18	6·2	45·0
India	Mumbai	1637	1558	59	8	10	0·5	14·5	1606	11	17	1	1·1	8·3
Italy	Rome	1347	1216	80	11	8	0·9	9·1	1286	11	19	0	1·5	0·0
Latvia	Riga	500	423	40	22	9	4·9	18·4	459	5	27	3	5·6	37·5
Netherlands	Utrecht	1260	1081	101	16	54	1·5	34·8	1143	39	41	28	3·5	41·8
New Zealand	**Hawkes Bay**	**1294**	**1075**	**113**	**37**	**68**	**3·3**	**37·6**	**1170**	**18**	**69**	**36**	**5·6**	**66·7**
Norway	Tromso	665	511	68	24	43	4·5	38·7	561	20	48	18	7·9	47·4
Spain	Almeria	1061	916	97	10	9	1·1	8·5	998	19	17	3	1·7	13·6
	Cartagena	1148	1034	81	7	2	0·7	2·4	1098	23	10	0	0·9	0·0
	Madrid	635	532	70	4	17	0·8	19·5	587	16	13	8	2·2	33·3
	Valencia	1131	969	95	32	10	3·2	9·5	1053	21	40	2	3·7	8·7
Turkey	Ankara	2661	2421	140	32	6	1·3	4·1	2517	52	38	0	1·5	0·0
U.K.	**West Sussex**	**969**	**796**	**95**	**21**	**43**	**2·6**	**31·2**	**870**	**22**	**39**	**25**	**4·3**	**53·2**

a, Both skin examination and questionnaire negative; b, skin examination negative and questionnaire positive; c, skin examination positive and questionnaire negative; d, skin examination and questionnaire both positive; bold indicates centres which used the English version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.

performed only once. Although great care was taken in the translation process and the ISAAC protocol requires independent back translation of questionnaires into English, the most likely reasons for the discrepancies between questionnaire-derived persistent flexural eczema and skin examination are factors related to translation and cultural differences in question interpretation. In fact, three smaller studies, one from Germany, one from Hong Kong, and a survey from Ethiopia, showed similar findings.[3,4,11] In addition to language- and culture-related issues, darker skin colour is likely to make detection of flexural eczema on examination more difficult, and this has probably contributed to the fact that in a number of centres questionnaire-derived symptoms of persistent flexural eczema were not confirmed when examining the child. Further unknown factors must be involved given that considerable over-reporting of symptoms of persistent flexural eczema was seen in the two centres where English is the main language, West Sussex (U.K.) and Hawkes Bay (New Zealand). Another factor might have been that skin examinations were done by field workers trained in the detection of flexural eczema rather than dermatologists or paediatricians, and a future validation study directly comparing the diagnosis of flexural eczema by dermatologists with the performance of trained fieldworkers would be informative. In addition, a proportion of questionnaire-derived symptoms of persistent flexural eczema might in fact have been scabies and other pruritic infectious skin diseases, especially in the centres in developing countries. However, this is equally unlikely to be a full explanation in view of the discrepancies between skin examination and questionnaire findings in developed countries, such as New Zealand and the U.K., where pruritic skin infections are rare. Finally, ears and buttocks were included as flexural areas in the questionnaire but were not part of the skin examination protocol, as the latter is based on the U.K. diagnostic criteria for atopic eczema, which were finalized after the ISAAC eczema symptom questionnaire. However, subsequent careful validation studies of the U.K. diagnostic criteria did not find eczema around the ears and in the infragluteal folds to be an important discriminator in making a diagnosis of eczema.[12,13] This small difference between the ISAAC questionnaire and the

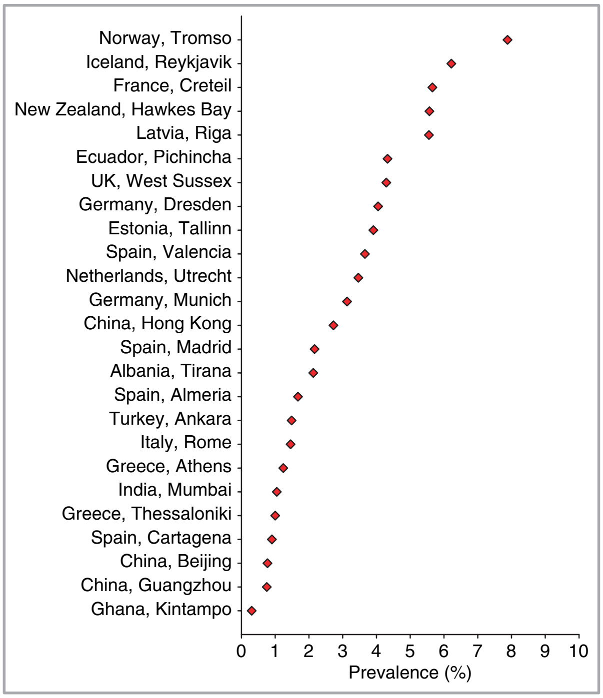

Fig 4. Proportion of questionnaire negatives for symptoms of 'persistent flexural eczema in the past 12 months' among those with a positive skin examination.

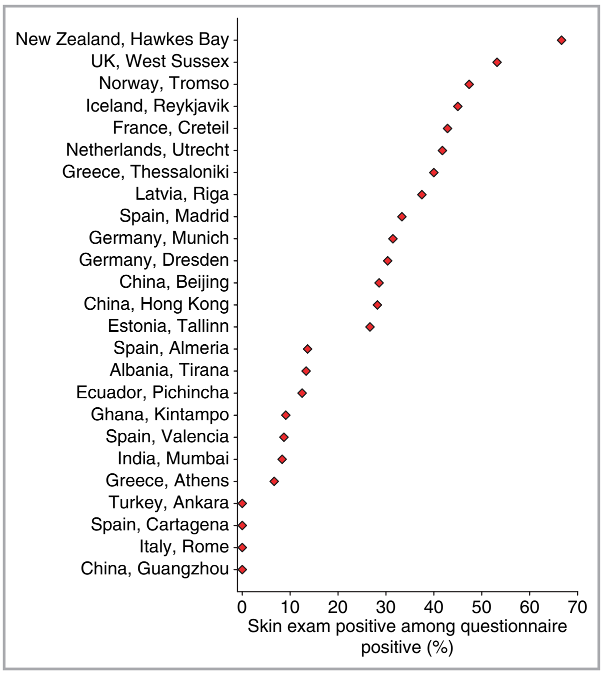

Fig 5. Questionnaire positive symptoms of 'persistent flexural eczema in the past 12 months' and skin examination positives.

skin examination protocol is therefore not an explanation for the significant discrepancies between the questionnaire and skin examination findings in individual patients.

In conclusion, the ISAAC Phase Two eczema questions provide adequate prevalence estimates at the population level, confirming the validity of the eczema world map generated in ISAAC Phases One and Three, and as such will prove very important for assessing the burden of eczema in and between populations. However, we suggest that physical examination for flexural eczema is used as an outcome measure for risk factor analyses, in particular because physical examination is less likely to be susceptible to culture- and language-related problems associated with translation and interpretation than questionnaire tools. However, if physical examination is only performed once, then this is likely to exclude milder and transient cases of eczema and repeat observations should be considered.

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